Australian Government

Department of Health and Ageing

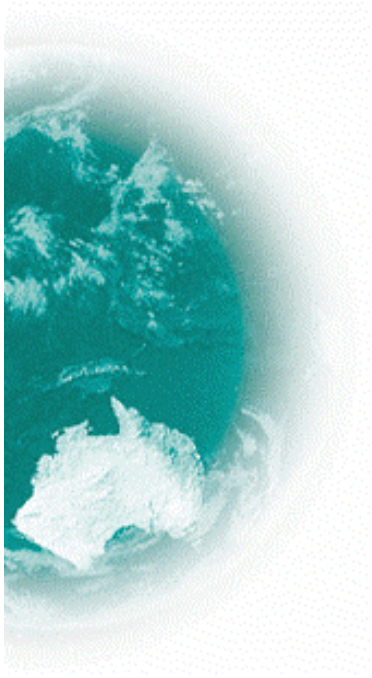
Therapeutic Goods Administration

Australian Public Assessment Report for Saxagliptin Hydrochloride

Proprietary Product Name: Onglyza

Submission No: PM-2008-03469-3-5

Sponsor: Bristol-Myers Squibb Australia Pty Ltd



April 2011

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I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	5 mg tablet: Approved 2.5 mg tablet: Withdrawn
Date of Decision	7 March 2011
Active ingredient(s):	Saxagliptin hydrochloride
Product Name(s):	Onglyza
Sponsor's Name and Address	Bristol-Myers Squibb Pty Ltd 556 Princes Highway Noble Park Victoria 3174
Dose form(s):	Film coated tablets
Strength(s):	5 mg
Container(s):	Blister pack
Pack size(s):	7 and 28
Approved Therapeutic use:	**Add-on combination** - Onglyza is indicated in patients with type 2 diabetes mellitus, to improve glycaemic control, in combination with metformin, a sulfonylurea, or a thiazolidinedione, as an adjunct to diet and exercise, when the single agent alone does not provide adequate glycaemic control. **Initial combination** - Onglyza is indicated for use as initial combination therapy with metformin, in patients with type 2 diabetes mellitus, to improve glycaemic control as an adjunct to diet and exercise, when dual saxagliptin and metformin therapy is appropriate (that is, high initial HbA1c levels and poor prospects for response to monotherapy).
Route(s) of administration:	Oral
Dosage:	5 mg daily
ARTG Number:	157907

Product Background

This AusPAR describes the evaluation of a submission by the sponsor, Bristol-Myers Squibb Australia Pty Ltd, through its agent AstraZeneca Pty Ltd, for the registration of the new chemical entity saxagliptin (Onglyza) for the treatment of type 2 diabetes mellitus.

The sponsor noted that the prevalence of type 2 diabetes mellitus (T2DM) and the complications associated with T2DM make this condition a critical public health issue. Improved treatment of T2DM is vital. The Australian Bureau of Statistics' National Health Survey (NHS) states that:[1]

[1] Australian Bureau of Statistics. National Health Survey (NHS): summary of results. 2007-8. http://www.ausstats.abs.gov.au/ausstats/subscriber.nsf/0/48061B1C977096A6CA2575B000139E2D/$File/43640_2007-08.pdf.

"An estimated 818,200 persons (4% of the population) in 2007–08 had diabetes mellitus that had been medically diagnosed (excluding those with gestational diabetes), an increase from the proportion reported in the 2004–05 NHS (3.5%). A further 35,500 people reported that they currently had high sugar levels in the blood or urine, but had not been diagnosed with diabetes. The estimates for diabetes and high sugar levels understate the true prevalence of these conditions in the community, as they exclude those cases which have remained undetected. The majority of people with diabetes reported that they had Type 2 (adult onset) diabetes (88%), 10% reported Type 1 (sometimes referred to as insulin dependent diabetes) while 2% reported diabetes, but did not know which type. The proportions of males and females reporting diabetes mellitus were different at 5% and 3% respectively."

T2DM is a complex disorder of decreased β-cell function, peripheral insulin resistance and abnormal hepatic glucose metabolism. It is difficult to control hyperglycaemia over the long term in this condition. In T2DM, oral hypoglycaemic agents are not necessarily first line treatments. Major efforts should be made to influence diet and exercise patterns. If treatment targets have not been reached after a period of time (for example 2-3 months) spent attempting to change diet and exercise patterns, then is it reasonable to introduce oral hypoglycaemic agents (unless diabetic symptoms are significant, in which case oral agents may be needed earlier). Treatment of T2DM (as opposed to treatment of hyperglycaemia) is not only a matter of controlling blood glucose. To prevent complications, other risk factors must be addressed. For example, to prevent symptomatic cardiovascular disease, it is vital to address smoking, blood pressure and lipid levels.

Where oral hypoglycaemic agents are required, there is a variety to choose from in the Australian market. Insulin sensitisers include biguanides (for example metformin) and thiazolidinediones. Insulin secretagogues include sulfonylureas (first to third generation), meglitinides (for example. repaglinide), glucagon-like peptide-1 (GLP-1) analogues (for example exanatide, liraglutide) and dipeptidyl peptidase-4 (DPP4) inhibitors (for example sitagliptin). Acarbose is an a-glucosidase inhibitor. One approach to choice of 'first oral hypoglycaemic agent' is to consider the patient's weight, with overweight patients commenced on metformin (since this enhances weight loss and lowers triglyceride levels) (Therapeutic Guidelines, 2009).[2] Another approach is to use metformin as the initial choice in all subjects (Davis, 2008).[3]

Dipeptidyl peptidase 4 (DPP4), also known as CD26, is the founding member of a family of 'DPP4 activity and / or structural homolog' (DASH) proteins, which also includes 'quiescent cell proline dipeptidase' (QPP), DPP8, DPP9, fibroblast activation protein (FAP), attractin and DPP4-b (Ohnuma et al, 2008).[4] Thus, the specificity of saxagliptin for DPP4 (relative to other DASH proteins) is of interest in predicting 'off-target' effects, as is the tissue expression and function of any DASH (or other) protein for which saxagliptin shows specificity.

DPP4 is a cell surface peptidase of 766 amino acids that selectively cleaves dipeptides from the N-terminus of oligopeptides with proline or alanine in the penultimate position. While the enzyme has a range of substrates, the sponsor emphasises the DPP4 substrates glucagon-like peptide-1 (GLP-1) and GIP, both incretins.[5]

Other substrates for DPP4's enzymatic activity include chemokines (for example, CXCL12, CCL22 [macrophage-derived chemokine], CCL5 [RANTES], CCL11 [eotaxin]), neuropeptides such as

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[2] Therapeutic Guidelines: Endocrinology (2009). Online version.

[3] Davis TME. Contemporary management of type 2 diabetes: blood glucose-lowering therapies and glycaemic targets. Med J Aust 2008; 189: 246-248.

[4] Ohnuma K, Dang NH, Morimoto C. Revisiting an old acquaintance: CD26 and its molecular mechanisms in T cell function. Trends in Immunology 2008; 29: 295-301.

[5] Incretins are a group of gastrointestinal hormones that cause an increase in the amount of insulin released from the beta cells of the islets of Langerhans after eating, even before blood glucose levels become elevated.

neuropeptide Y and substance P, endomorphin and vasoactive peptides. The significance of inhibiting cleavage of these substrates is unclear.

In addition to enzymatic activity, DPP4 is reported to interact non-enzymatically with some molecules (adenosine deaminase; fibronectin; collagen [see. Jost et al, 2009]; CXCR4; CD45).[6]

DPP4 is widely distributed, being expressed on some T lymphocytes and natural killer cells, and on lymphatic, endothelial and epithelial cells of a variety of tissues (intestine, liver, lung, kidney and placenta). It is strongly up-regulated in activated B cells. Also, a soluble form lacking the membrane-bound form's transmembrane domain is present in plasma and other body fluids.

Given that DPP4 acts enzymatically to cleave GLP-1 and GIP into inactive forms, inhibitors of DPP4 increase endogenous intact (active) GLP-1 and GIP concentrations.

GLP-1 and GIP are post-prandially secreted from enteroendocrine L- and K-cells (although there may be low level secretion in the fasting state). In the circulation, GLP-1 regulates blood glucose via stimulation of glucose-dependent insulin secretion, inhibition of gastric emptying and inhibition of glucagon secretion. GLP-1 is rapidly cleaved (half-life [$t_{½}$] = 1-2 minutes) by DPP4.

The sponsor states that saxagliptin's inhibition of DPP4 will augment postprandial insulin secretion, and emphasises that DPP4 inhibitors "stimulate insulin secretion in a glucose-dependent manner". The sponsor further states that "this mechanism of action is expected to present low risk of hypoglycaemia and may not lead to weight gain".

DPP4's role in the immune system is reported to be mediated via a combination of peptidase activity and non-enzymatic interactions. DPP4 is reported to influence T cell activity and to modulate chemotaxis. DPP4 is also implicated in HIV-1 entry, malignant transformation and tumour invasion. Ohnuma et al (2008) report that due to their inhibitory effect on T cell activation and function, DPP4 inhibitors have been successfully evaluated as immunosuppressive therapies in *in vivo* animal models of human diseases.[4] DPP4 inhibitors have been reviewed from a medicinal chemistry standpoint by Havale and Pal (2009).[7]

Proposed indications were:

Monotherapy

Onglyza is indicated in patients with type 2 diabetes mellitus, to improve glycaemic control, as an adjunct to diet and exercise.

Add-on combination

Onglyza is indicated in patients with type 2 diabetes mellitus, to improve glycaemic control, in combination with metformin, a sulfonylurea, or a thiazolidinedione, as an adjunct to diet and exercise, when the single agent alone does not provide adequate glycaemic control.

Initial combination

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

Regulatory Status

A similar application was approved in Canada (14 September 2009), the European Union (EU) (1 October 2009) and United States (31 July 2009).

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[6] Jost MM, Lamerz J, Tammen H et al. In vivo profiling of DPP4 inhibitors reveals alterations in collagen metabolism and accumulation of an amyloid peptide in rat plasma. Biochem Pharmacol 2009; 77: 228-237.

[7] Havale SH, Pal M. Medicinal chemistry approaches to the inhibition of dipeptidyl peptidase for the treatment of type 2 diabetes. Bioorg Medicin Chem 2009; doi:10.1016/j.bmc.2009.01.061.

The Australian submission includes a '4-month Safety update', not included in other submissions.

The Canadian submission included additional information, including additional analyses of (a) Study CV181013 (combined use of saxagliptin and pioglitazone), (b) all Phase III studies (summary of exposures ≥52 weeks) and (c) adverse drug reactions. The Canadian version also contains subject data listings and case report forms.

The proposed Canadian indication included monotherapy (wording essentially the same as in the proposed Australian PI) and add-on combination but monotherapy and combination treatment with pioglitazone were withdrawn. Health Canada deemed that there was limited clinical data to support the use of 2.5 mg dose in patients with moderate to severe renal impairment and patients with end-stage renal disease and only 5 mg was approved. The Canadian indication does not include initial combination therapy with metformin.

The proposed European indication did not include a monotherapy claim. Otherwise, the proposed European indication was essentially the same as the proposed Australian indication. The indication for initial combination therapy with metformin was withdrawn as well as the use of saxagliptin for the treatment of patients with moderate, severe and end-stage renal impairment. The European Medicines Agency (EMA) deemed that there were limited clinical data to support the use of 2.5 mg dose in patients with moderate to severe renal impairment and patients with end-stage renal disease and only 5 mg was approved.

The approved US indication is as follows:

Monotherapy and combination therapy: ONGLYZA is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

The approved combination therapies include add-on combination therapy with metformin, sulfonylurea, and thiazolidinedione as well as initial combination treatment with metformin in treatment naïve patients and approved strengths of 2.5 mg and 5 mg.

Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Saxagliptin is a new chemical entity which is an inhibitor of dipeptidyl-peptidase 4 (DPP-4). The drug substance is saxagliptin monohydrate (that is, the monohydrate of saxagliptin free base).[8]

Saxagliptin drug substance is a white to light yellow or light brown, non-hygroscopic, crystalline powder.

Saxagliptin is chiral, with four stereogenic centres; it is presented as a single enantiomer.

Nomenclature

Chemical Name (CAS):

(1*S*,3*S*,5*S*)-2-[(2*S*)-2-Amino-2-(3-hydroxytricyclo-[3.3.1.13,7]dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate

IUPAC Name:

(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

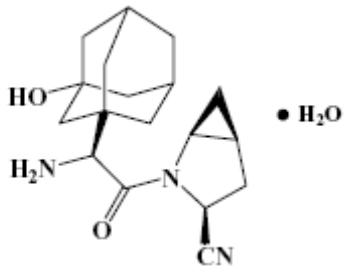
[8] Saxagliptin monohydrate will be referred to as saxagliptin for the remainder of this AusPAR.

Generic Name (USAN, INN): Saxagliptin

CAS Registry Number: 945667-22-1

Molecular Formula: $C_{18}H_{25}N_3O_2 \bullet H_2O$

Molecular Weight: 333.43 (or 315.41 anhydrous)



Manufacture

The synthesis is performed in five reactions carried out as three steps with isolation of two intermediates. Details of the in-process test methods have been provided.

Four versions of the synthesis are described for the manufacture of saxagliptin from the final synthetic intermediate. These aspects are well described.

Saxagliptin is synthetic. There are three specified impurities.

Drug Product

Saxagliptin is somewhat susceptible to degradation when formulated conventionally, with an internal rearrangement forming impurity BMS-537679. Degradation is slower in an acidic environment. Thus Onglyza film coated tablets are made by a film-coating process over inert cores

The 2.5 mg and 5 mg tablets have identical formulations, but with different amounts of drug and difference in outer coat colour and markings. The tablets are thus the same size, but distinguished by colour and printed markings (2.5 mg yellow with '2.5' and '4214' printed in blue; 5 mg pink with '5' and '4215' printed in blue).

The data submitted are sufficient to support a shelf life of 24 months when stored below 30ºC in Al/Al blister packs.

Bioavailability

No absolute bioavailability study had been conducted at the time of the initial submission, although it appears that an intravenous solution could be formulated. Instead, the sponsor referred to the mass balance and metabolism study CV181004 in which a 50 mg oral solution of saxagliptin labelled with ^{14}C (91.5 µCi) was given to six healthy subjects. Urine was collected over 168 hours. Urinary excretion of radioactivity was 70.9, 72.7, 70.2, 81.0, 79.6 and 33.9% of the dose (mean 68%); the sponsor considered it likely that the low result for one subject was due to incomplete initial urine collection. About 22% of the radioactivity was recovered in faeces, mainly as oxidative metabolites.

The sponsor thus concluded that human absorption from a high dose of an *oral solution* is high. This does not provide information on absorption from the proposed tablets. An estimate is only possible from cross-trial comparison with a saxagliptin benzoate capsule formulation, which is separately linked to the tablets. An absolute bioavailability study (CV181128) was completed subsequent to the consideration of the application by the Pharmaceutical Subcommittee (PSC) and the Australian Drug Evaluation Committee (ADEC).

Clinical Trial Formulations

The first clinical trials used 2.5, 5 and 10 mg capsules containing saxagliptin benzoate (studies up to the end of Phase IIb: CV181001, CV181002, CV181008, CV181010). Saxagliptin benzoate was unsuitable for making tablets.

"Early clinical tablets" were 5 and 40 mg tablets made with saxagliptin free base monohydrate, although the drug was actually present as the hydrochloride salt in the tablets after acidic spray coating. "Early clinical tablets" were used in studies CV181005, CV181017, CV181018,

CV181019, CV181020, CV181022, CV181026, CV181027, CV181028, CV181033 and CV181052.

The tablet formulation was modified slightly to give the "clinical tablet" or "Phase III clinical tablet" formulations (2.5, 5, 10 and 20 mg) which were used in Studies CV181031, CV181032, CV181034, CV181035, CV181036, CV181037 and CV181053.

The 2.5 and 5 mg tablets proposed for registration have the same formulation as the "Phase III clinical tablets" except for a different outer film coat colour and the addition of printed tablet strength and product code. These changes are unlikely to affect bioavailability and the final formulation has not been used in any bioequivalence studies. Dissolution data are very similar.

Bioequivalence

The bioavailabilities of saxagliptin from the 20 mg capsule and 40 mg "early clinical tablet" formulations were equivalent.

The bioavailabilities of saxagliptin from the 5 mg capsule and 5 mg "early clinical tablet" formulations were compared and were equivalent with respect to the area under the serum concentration versus time curve (AUC) but not the maximal serum concentration (C_{max}).

The bioavailabilities of saxagliptin from the 5 mg capsule and 5 mg "clinical tablet/Phase III" formulation were compared and were bioequivalent with respect to AUC but again not with respect to C_{max}.

The relative bioavailabilities of saxagliptin from two 5 mg vs one 10 mg "clinical tablet/Phase III" tablet were compared and were bioequivalent

Food Effects

Study **CV181034** investigated the effect of a high fat on the absorption of saxagliptin from 10 mg tablets in healthy subjects (n=14). This study was reviewed in detail by the quality evaluator. Food slightly delayed absorption but mean C_{max} was higher (7.7%) and the extent of exposure was markedly higher with fed dosing (AUC 27%, higher; 90% CI 1.19-1.36). Fed and fasting doses were thus not within standard bioequivalence limits. The sponsor suggested that increased splanchnic blood flow may reduce first pass metabolism of saxagliptin when dosed with food. It is, however, claimed that the difference is not clinically important and saxagliptin can be administered without regard to food.

Advisory Committee Considerations

The submission was considered at the 129th meeting of the PSC.

The PSC was unable to recommend approval for registration on pharmaceutic and biopharmaceutic grounds. In particular, the Committee considered that the absence of an absolute bioavailability study, a bioavailability study comparing the formulation proposed for marketing with that used in pivotal clinical studies and a food effect study on the formulation proposed for marketing made it difficult to fully characterise both the drug substance and the proposed formulations.

The PSC considered the available data on systemic absorption poor, with the key study using an undefined radiolabel and a very high oral dose.

The PSC was concerned about possible degradation *in vivo* and queried the toxicity of such degradation products.

The PSC considered that the sponsor should be asked to provide a bioavailability study comparing the formulation proposed for marketing with that used in pivotal clinical studies and a food effect study on the proposed formulation.

The PSC questioned the rationale of dosing with or without food as stipulated in the proposed Product Information (PI) in view of the fact that the dosing occurred prior to morning meals in the pivotal clinical studies. The Committee therefore recommended that the attention of the Delegate be drawn to this issue.

The PSC recommended that tablet dissolution should be controlled at expiry.

PSC reconsidered the application at its the 130th meeting but indicated the previous concerns remained unresolved (that is, a lack of an absolute bioavailability study, a comparative bioavailability study on the clinical and commercial formulations and food effect study on the proposed tablet formulation).

Post PSC Response from Sponsor

Radiolabeled absorption disposition, metabolism, excretion (ADME) study

The saxagliptin dose used in the ADME study of 50 mg was well within the linear range for oral saxagliptin and the results were considered applicable to the proposed doses of saxagliptin 2.5 and 5 mg. In addition, the relatively high dose in the human ADME study optimized the opportunity to identify minor metabolites and thus to fully characterize the metabolic fate of saxagliptin. Nevertheless, the sponsor has thoroughly characterized the pharmacokinetics of saxagliptin and its active metabolite in the development program over a wide dose range and in relevant specific populations when it is administered via the intended clinical (oral) route. In particular, the results of the radiolabeled absorption, disposition, metabolism, excretion (ADME) study [CV181004] have sufficiently characterized the fate of saxagliptin. The majority of the dose is absorbed following oral administration (at least 75% based on urinary recovery of total radioactivity and up to 97% based on urinary recovery and faecal metabolic profiling). [^{14}C]saxagliptin with the same radiolabeling scheme was used in the rat, dog and monkey ADME studies (details of which were provided in the nonclinical documents).

Degradation in vivo

Saxagliptin is known to undergo an intramolecular cyclisation when in solution to form the cyclic amidine BMS-537679. The major metabolite BMS-510849 also undergoes a similar cyclisation reaction to form BMS-743894. Degradation products BMS-537679 and BMS-743894 were the only degradants derived from saxagliptin found in the human ADME study. These degradants each represented only a small portion (≤1.8%) of the circulating radioactivity of the human plasma samples and were well-represented in the animal species used in toxicology studies. Since BMS-537679 is also a known impurity and degradant in the drug product, it was further evaluated in a series of *in vitro* and *in vivo* toxicology studies; lots of saxagliptin with this impurity had similar toxicity as saxagliptin alone. The sponsor therefore considered that the degradation products are not toxic *in vivo*. Additionally, the clinical program showed that saxagliptin was safe and well tolerated, indicating that any chemical degradants were unlikely to result in any clinical adverse effects.

Bioavailability Study between Phase III Clinical and Commercial Formulation

The two formulations are essentially identical utilizing the same granulation method. The differences are the colour of the film coat and the printing on the tablets. In addition, the dissolution profiles of the two formulations are similar. The differences between the commercial tablet and the Phase III tablet can reasonably be considered non-functional and will have no effect on the *in vivo* performance of the commercial tablet, relative to the tablets used in the pivotal safety and efficacy assessments. Furthermore, since saxagliptin is considered highly soluble in aqueous media, and has a high extent of oral absorption, *in vitro* dissolution testing is considered reflective of the *in vivo* performance of this immediate release formulation. Consistent with the *in vitro* dissolution results, saxagliptin was rapidly absorbed upon oral administration, and peak plasma concentrations were

usually observed within 0.5-0.75 hours following administration in the fasted state. As discussed above, the Phase III and proposed commercial tablets have essentially the same composition and both have been shown to rapidly release saxagliptin (>85% released in 15 minutes) with highly similar *in vitro* dissolution profiles (that is, they have the same rate and extent of release of saxagliptin). Thus, an appropriate link has been made between the proposed commercial tablets and the Phase III formulations.

Formulation Used in the Food Effect Study (CV181034)

As discussed above, there are only minor differences between the two formulations, which are expected to have no effect on the product performance. Saxagliptin also has a high aqueous solubility across a wide pH range relative to the proposed dose and for the 10 mg dose used in the definitive food effect study. The *in vivo* absorption of saxagliptin from the gastrointestinal tract in humans is extensive and systemic exposure is linear up to 400 mg daily. The *in vitro* dissolution of the 2.5, 5 and 10 mg film-coated tablet is rapid and the dissolution profiles of the formulations are similar. The clinical experience gathered to date supports a wide therapeutic index for saxagliptin. In light of this a food effect bioavailability study on the commercial formulation was not required. Reference has been made by the PSC to statements in the Product Information concerning the dosing of saxagliptin with or without food. This was raised separately in the clinical evaluation report and the Product Information had been amended to include the following statements "*Based on food effects studies, Onglyza may be administered with or without food. However, in pivotal efficacy and safety studies Onglyza was generally taken prior to the morning meal*."

Absolute Bioavailability study

Subsequent to the PSC recommendations an absolute bioavailability study was conducted (CV181128). The results of this study showed the mean absolute oral bioavailability (BA) of saxagliptin was 50% (individual absolute BA values ranged from 48% to 52% and 90% confidence interval of 48% to 53%). As expected, the plasma saxagliptin terminal elimination phases from the intravenous and oral routes were similar, indicating that the results were not confounded by non-linear pharmacokinetics of the micro-tracer dose. In addition, the mean total body clearance of saxagliptin was 504 mL/min (a combination of metabolic and active renal clearance), which shows that saxagliptin is not a high clearance drug. The mean volume of distribution was 123 L, which indicates that saxagliptin has some degree of tissue penetration. Together with the results of the human ADME study (CV181004), these new data support the conclusion that saxagliptin is well-absorbed after oral administration and undergoes a modest degree of first pass metabolism. Furthermore, if all of the highest proposed dose of 5 mg oral saxagliptin were available to the systemic circulation, the exposures achieved would not exceed those of the 10 mg dose. The 10 mg dose of saxagliptin was studied extensively and shown to be safe in the Phase III development program.

Additional Advisory Committee Considerations

PSC reconsidered the application at its 136th meeting and reviewed additional data notably the new absolute bioavailability study and comments provided by the sponsor and the TGA. The PSC agreed all issues of concern previously raised had been resolved to the satisfaction of the TGA.

The PSC therefore concluded that there should be no objection to the approval of this application.

Quality Summary and Conclusions

Registration was recommended with respect to chemistry and quality control and bioavailability aspects.

III. Non-Clinical Findings

Introduction

The overall quality of the submitted dossier was high, with all pivotal toxicity studies conducted under GLP conditions using the proposed clinical route (oral).

Pharmacology

Primary pharmacodynamics

Dipeptidyl peptidase IV (DPP-4) is a ubiquitous enzyme that catalyses the removal of the N-terminal dipeptide of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). These incretin hormones stimulate glucose-dependent insulin secretion by pancreatic β-cells and stimulate pancreatic β-cell proliferation. GLP-1 also stimulates insulin biosynthesis by pancreatic β-cells, inhibits glucagon secretion from pancreatic α-cells and inhibits gastric emptying. Saxagliptin is a DPP-4 inhibitor, envisaged to improve glycaemic control in patients with type 2 diabetes by enhancing the levels of the active forms of GLP-1 and GIP.

Saxagliptin displayed comparable potency against rat, pig and monkey DPP-4 compared with the human isoform.

In vivo, orally administered saxagliptin decreased plasma DPP-4 activity, increased the levels of the active form of GLP-1, improved plasma glucose clearance and increased plasma insulin levels in diabetic rats, consistent with the proposed pharmacological action. Plasma concentrations of saxagliptin of≥200 nM (63 ng/mL) were effective in reducing plasma glucose levels in rats. In monkeys, maximum inhibition of plasma DPP-4 activity was achieved with≥0.1 mg/kg saxagliptin for up to 8 h ($AUC_{0–24h}$ 0.017 µg.h/mL saxagliptin, 0.12 µg.h/mL BMS-510849 [active metabolite]; about1.7–4.3-fold lower than exposure levels in humans at the standard dose of 5 mg/day).

Saxagliptin had greater effects on plasma glucose clearance in diabetic rats than healthy rats. Chronic studies in a rat model of diabetes demonstrated that after 14 days, saxagliptin reduced fasting plasma glucose levels by 17%. However, by 35 days, there were no differences between control animals and those receiving saxagliptin, suggesting the animals responded well to saxagliptin in the early stages of diabetes development but as the rats reached a severely diabetic state, their response was diminished.

The major metabolite of saxagliptin in mice, rats, dogs, monkeys and humans, the monohydroxylate, BMS-510849, also inhibited DPP-4 with slow binding kinetics but was about2-fold less potent than saxagliptin *in vitro*. However, *in vivo*, BMS-510849 was 5–25 fold less potent than saxagliptin at lowering peak plasma glucose in diabetic rats due to its restricted volume of distribution. In humans, exposure to BMS-510849 is more than 2.5-times greater than to saxagliptin and this metabolite is therefore expected to contribute clinically to the pharmacological action of saxagliptin.

Secondary pharmacodynamics

There was no significant inhibition of 19 non-DPP-4-related proteases, 42 receptors and/or ion channels at concentrations up to 30 µM of saxagliptin or BMS-510849 (>200-times the clinical C_{max}). Saxagliptin showed limited inhibition of the related peptidase, fibroblast activation protein (FAP), and more significant inhibition of DPP-8 and DPP-9 (respective K_i values of 508 nM and 98 nM; about400- and 75-times greater than at DPP-4). BMS-510849 also inhibited DPP-8 and DPP-9 (K_i 2495 and 423 nM, respectively; that is, about 4–5 times more weakly than saxagliptin). Unlike at DPP-4, saxagliptin and BMS-510849 did not show slow binding kinetics at DPP-8 and DPP-9. Based on clinical C_{max} values of 72 nM (=24 ng/mL) for saxagliptin and 135 nM (=47 ng/mL) for BMS-510849, some inhibition of DPP-9 by saxagliptin is expected in patients.

Safety pharmacology

Specialised safety pharmacology studies were restricted to the cardiovascular system. Central nervous system (CNS), gastrointestinal (GI) tract and renal safety were assessed in either the general toxicity studies or additional targeted studies. Not all of the safety pharmacology studies were GLP-compliant but the design and conduct of the studies were mostly adequate to reveal any treatment-related effects. The lack of positive controls in some of the studies is a deficiency but the data are adequate considering the high doses of saxagliptin used.

In vitro, saxagliptin and BMS-510849 demonstrated dose-dependent inhibition of hERG K^+ channels with <12% inhibition at 30 µM. As this inhibition occurred at >200-fold the clinical C_{max}, it is considered not to be clinically relevant. *In vivo*, no effects on electrocardiogram, (ECG) parameters were observed in dogs treated with a single dose of saxagliptin at 10 mg/kg orally (yielding plasma concentrations of saxagliptin and BMS-510849 32- to 33-fold the clinical C_{max}); nor in repeat-dose studies (≤50 mg/kg/day orally). No ECG findings were observed in monkeys given saxagliptin at 25 mg/kg orally (yielding plasma concentrations of saxagliptin and BMS-510849 >100-fold the clinical C_{max}).

Decreased blood pressure (down to <40 mmHg) and increased heart rates were observed in a number of monkeys given≥3.4 mg/kg intravenous (IV) saxagliptin (at plasma levels of saxagliptin and BMS-510849 >29-fold the clinical C_{max}). These effects were not consistently observed and were not associated with increased immune factors, such as histamine; blood pressure and heart rate were unaffected in dogs given 10 mg/kg orally saxagliptin, yielding similar exposure levels as in monkeys (32–33-times the clinical C_{max}).

GLP-1 receptors are found in the heart and vasculature and GLP-1 is known to have a role in vasodilation (reviewed in Jax, 2009).[9] The vasodilatory activity of GLP-1 appears to be complex and may involve two pathways – *via* GLP-1 through the GLP-1 receptor and *via* the DPP-4 generated inactive form, GLP-1(9–36), independent of the GLP-1 receptor (Ban *et al.*, 2008).[10] The administration of a DPP-4 inhibitor may have affected the balance of these two pathways, thereby resulting in inconsistent effects on blood pressure and heart rate. Given that the effects of saxagliptin on blood pressure and heart rate were only observed at high exposure ratios based on C_{max}, the findings are expected to be of limited clinical significance.

Pharmacokinetics

Saxagliptin was rapidly absorbed by the oral route in all species (mouse, rat, dog, cynomolgus monkey and human) with the time to maximal serum concentration (t_{max})values ranging from 0.5–2 hours and oral bioavailabilities ranging from 51–76% in laboratory animal species, compared with a clinical absorption of 75%. Exposure to saxagliptin was dose-proportional in all species and there were no gender differences except in the case of rats, where exposures to saxagliptin with males were approximately half those in females at the same dose. Elimination half-lives of saxagliptin in nonclinical species were similar to those observed in humans (2–4 hours). There was no significant accumulation with repeated dosing, except in monkeys at relatively high doses (≥2 mg/kg/day).

The pharmacokinetic profile of the active metabolite, BMS-510849, was also monitored. Plasma AUC and C_{max} values for BMS-510849 were dose-proportional in the laboratory animal species, except in mice, where the C_{max} was less than dose-proportional, probably due to a saturation of

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[9] Jax, T. Treatment of patients with diabetes with GLP-1 analogues or DPP-4-inhibitors: a hot topic for cardiologists? Clin Res Cardiol 2009; 98: 75–79.

[10] Ban K, Noyan-Ashouraf MH, Hoefer J, Bolz S-S, Drucker DJ, Husain M. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor dependent and independent pathways. Circulation 2008; 117: 2340–2350.

metabolism (restricting formation of BMS-510849). Based on AUC, exposure to BMS-510849 was significant compared with the parent compound; 30–70% saxagliptin levels in rats, up to 600% in mice and monkeys, approximately equivalent in dogs and 270% in humans. Based on these data, BMS-510849 is likely to contribute to the pharmacological action of saxagliptin in all species.

Plasma protein binding of saxagliptin and BMS-510849 was low in mouse, rat, dog, monkey and human sera with almost 100% in the free fraction in humans and dogs and≥73% free in the other species. The volume of distribution of saxagliptin was high and after oral administration of ^{14}C-saxagliptin to rats, rapid and widespread tissue distribution was observed. The kidneys, liver, small intestine, bladder, large intestine, thyroid and eyes had the greatest exposure. The exposure (AUC) in pigmented skin was more than double that in non-pigmented skin. The elimination half-lives for radioactivity from tissues were mostly longer than the plasma half-life (about 2 hours), particularly in tissues involved in excretion and pigmented skin and eyes (55 hours, 39 hours and 93 hours, respectively). There was limited penetration of the blood-brain barrier (concentrations about 10% plasma concentrations). BMS-510849 showed a qualitatively similar tissue distribution profile compared with saxagliptin but was quantitatively different with less extravascular distribution and a lower (by 80%) volume of distribution.

In all species, saxagliptin was extensively metabolised through both oxidative and conjugative pathways. All metabolites found in human plasma were found in dog and monkey plasma, with most identified in plasma from rodents. The major pathway of metabolism in all species was *via* cytochrome P-450 (CYP) 3A monohydroxylation to form the pharmacologically-active metabolite BMS-510849, which underwent limited metabolism. Minor pathways of metabolism included other monohydroxylations, direct sulfation, glucuronide conjugation of saxagliptin or monohydroxylate metabolites, imidazoline formation or de-cyanation to form a keto-imidazolidine structure. The latter pathway occurred predominantly in male rats *via* the CYP2C11 enzyme and is not clinically-relevant (humans do not express this CYP isoform).

Saxagliptin was excreted via both the urine (75% of the administered dose in humans and 36–58% in animals) and the faeces. Unchanged saxagliptin was the dominant species in urine, while a minor one in faeces. Biliary excretion was demonstrated in rats. Renal excretion was the primary elimination pathway for BMS-510849 in rats, consistent with findings for humans. Overall, the pharmacokinetic profile of saxagliptin was qualitatively similar across animals and humans.

Pharmacokinetic drug interactions

There was no significant inhibition of the human CYP450 isozymes, CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4 by saxagliptin or BMS-510849, with median inhibitory concentration (IC_{50}) values >50 and >200 μM, respectively (>690-fold the clinical C_{max}). A moderate increase (up to 4-fold) in CYP2C9 mRNA in cultured human hepatocytes was observed with saxagliptin (0.2–100 μM) but without dose-dependence nor a corresponding increase in enzymatic activity, suggesting this is not of particular concern.

Saxagliptin is proposed to be used in combination with metformin, a thiazolidinedione or a sulfonylurea. No pharmacokinetic interaction studies have been conducted with saxagliptin in laboratory animals, however. As saxagliptin is metabolised predominantly by the CYP3A4 and CYP3A5 enzymes, inhibitors or inducers of these enzymes are likely to affect the pharmacokinetic profile of saxagliptin. In the clinical studies, it was reported that co-administration with the CYP3A4/5 inhibitor, ketoconazole, increased the C_{max} and AUC of saxagliptin by 62% and 2.5-times, respectively, and the C_{max} and AUC of BMS-510849 decreased by 95% and 88%, respectively (Clinical Study CV181005). A clinical study involving co-administration of saxagliptin with a CYP3A4 inducer has not been conducted; it is expected that this would reduce systemic exposure to saxagliptin. Saxagliptin was only a weak substrate for P-glycoprotein and not a substrate for OATP1B1 (OATP-C), OATP1B3 (OATP8), OCT1, OCT2, OAT1, OAT3, PEPT1 or

PEPT2. Inhibitors/substrates of P-glycoprotein and these other transporters are not expected to affect the pharmacokinetic profile of saxagliptin.

Toxicology

Acute toxicity

Acute toxicity studies were conducted in mice, rats and monkeys and only the clinical route (oral) was used. Only males were used in the rat study, but this is not considered to be a significant deficiency. Maximum non-lethal doses were 2000 mg/kg for mice and rats and 25 mg/kg for monkeys, indicating low toxicity for saxagliptin when taken orally. Target organs for toxicity were not identified in acute studies. Dedicated acute toxicity studies using the IV route were not submitted, but there were some data from single dose investigative IV studies in monkeys, in which inconsistent effects on heart rate and blood pressure were observed (see *Safety Pharmacology*).

Repeat-dose toxicity

Repeat-dose toxicity studies of up to 3 months duration were performed in mice, 6 months in rats, 12 months in dogs and 3 months in monkeys; all used the clinical route (orally). The duration of the pivotal studies, the species used (rats and dogs), group sizes and the use of both sexes were consistent with ICH guidelines. Toxicokinetic analyses were performed in all studies and exposure ratios based on animal:human area under the plasma concentration time curve from time zero to 24 hours ($AUC_{0–24h}$) values were calculated. Very high multiples of the anticipated clinical exposures to saxagliptin and BMS-510849 were achieved in the submitted toxicity studies. Exposure ratios (ER_{AUC}) quoted for doses or No Observable Effect Levels (NOELs) for given toxicological findings are based on either saxagliptin or BMS-510849, whichever is lower.

Drug-related brain lesions in the corpus callosum, thalamus and caudate putamen were observed in male rats treated at ≥600 mg/kg/day orally for up to 3 months and ≥150 mg/kg/day orally for 68 weeks (ER_{AUC} ≥397; [NOEL, 75 mg/kg/day; ER_{AUC} = 192][11]) and were generally a cause of death in male rats. Clinical signs of decreased activity, ataxia and laboured respiration, and clinical chemistry findings of increased serum glucose, decreased bicarbonate and increased reticulocytes, as well as the location and nature of brain lesions, were consistent with cyanide toxicity (Brierley *et al.*, 1976; Levine and Stypulkowski, 1959).[12,13] There were no gender differences in the brain penetration of saxagliptin or BMS-510849 in rats, which was low (concentrations <10% plasma concentrations), nor in serum levels of thiocyanate, suggesting toxicity was not directly due to saxagliptin, BMS-510849 or metabolically-derived thiocyanate. Mechanistic studies using castrated male rats and specific enzyme inhibitors demonstrated that the neurotoxicity in male rats was attributable to cyanide release from saxagliptin *via* the androgenically controlled CYP2C11 enzyme. The only other CYP2C enzymes that produced cyanide from saxagliptin *in vitro* were the dog CYP2C21 (5-fold less) and human CYP2C8 and 2C9 (about 28-fold less). Cyanide was not released from BMS-510849. The descyano metabolite (M4) of saxagliptin was not observed in either the plasma or excreta of monkeys or humans and cyanide could not be detected in the blood of treated monkeys.

CNS signs—but not histopathological changes—were observed in other species. These included decreased activity, ataxia, hunched posture and/or transient lameness, and were present in mice treated with ≥1000 mg/kg/day orally (ER_{Cmax} >1100; ER_{AUC} >1600), dogs at 50 mg/kg/day orally (ER_{Cmax} = 1500; ER_{AUC} >1380) and monkeys at ≥30 mg/kg/day orally (ER_{Cmax} = 208; ER_{AUC} = 123).

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[11] Based on exposure to saxagliptin. Although exposure ratios are lower for BMS-510849, studies implicate the involvement of saxagliptin, and not this particular metabolite, in the brain lesions.

[12] Brierley JB, Brown AW, Calverley J. Cyanide intoxication in the rat: physiological and neuropathological aspects. J Neurol Neurosurg Psych 1976; 39: 129–140.

[13] Levine S, Stypulkowski W. Experimental cyanide encephalopathy. Arch Pathol 1959; 67: 306–323.

Similar clinical signs were observed with vildagliptin; that is, lameness in monkeys at≥60 mg/kg/day orally. Lameness was observed in monkeys treated with 100 mg/kg/day orally sitagliptin too, suggesting these CNS effects may be related to pharmacological action. DPP-4 has a large number of endogenous peptide substrates (Drucker, 2007) including neuropeptide Y (NPY), a circulating peptide that exerts effects on vasomotor activity as well as anxiolytic and sedative-like effects (Karl *et al.*, 2003a); rats with reduced DPP-4 activity display neurophysiological changes, such as reduced motor activity (Karl *et al.*, 2003b).[14,15,16] DPP-4 inhibitors may affect the circulating levels of NPY, thereby resulting in the observed CNS effects. Though these effects are possibly pharmacologically mediated, they were only observed at high exposures of the DPP-4 inhibitors, suggesting compensatory mechanisms may exist to maintain NPY levels, and therefore these effects are unlikely to be clinically relevant.

Other findings in the repeat-dose studies included thrombocytopenia in rats (NOEL, 100 mg/kg/day; $ER_{AUC} \geq 54$) and monkeys (NOEL, 3 mg/kg/day; $ER_{AUC} = 19$); and anaemia in mice (NOEL, 1000 mg/kg/day; $ER_{AUC} > 1600$), rats (NOEL 100 mg/kg/day; $ER_{AUC} \geq 54$) and monkeys (NOEL, 3 mg/kg/day; $ER_{AUC} = 19$). Effects on lymphoid organs, comprising splenomegaly and lymphoid hyperplasia (in spleen, bone marrow and/or thymus; mostly minimal in severity, and at most mild), were observed in mice (NOEL, 600 mg/kg/day; $ER_{AUC} = 849$), rats (NOEL 2 mg/kg/day; $ER_{AUC} \geq 0.4$) and monkeys (NOEL, 0.3 mg/kg/day; $ER_{AUC} = 1.4$). Treatment with saxagliptin was associated with pulmonary histiocytosis (minimal in severity) in mice (NOEL, 600 mg/kg/day; $ER_{AUC} = 690$) and rats (NOEL, 100 mg/kg/day; $ER_{AUC} \geq 54$).

Saxagliptin produced GI tract toxicity in dogs, evident as villous atrophy, necrosis of the mucosal epithelium, subacute inflammation and mucus-cell depletion, with loose, red faeces and emesis (NOEL, 10 mg/kg/day; $ER_{AUC} = 39$). Foot pad cracking and sores were observed in dogs treated at ≥5 mg/kg/day in the 12-month study (NOEL, 1 mg/kg/day; $ER_{AUC} = 3$); this was associated with erosion of the epidermis/keratin layer, characterised by vacuolation, parakeratosis, sloughing of keratin and/or haemorrhage. Multifocal inflammatory skin lesions were observed in monkeys; these were associated with erosion, ulceration, oedema and necrosis, and were present on the hands/feet and tail at 3 mg/kg/day, and additionally the dorsal and abdominal surfaces, nose, face and scrotum at ≥10 mg/kg/day (NOEL 0.3 mg/kg/day; $ER_{AUC} = 1.4$).

Increased liver weights, without histopathological or clinical chemistry correlates, were observed in rodents at high exposures ($ER_{AUC} \geq 35$ in rats and 2600 in mice) and can be attributed to increased metabolic load. Inflammation and/or mononuclear cell infiltrates were observed in multiple organs (pituitary gland, pancreas, reproductive organs, liver, kidneys, skeletal muscle and brain (choroid plexus)) at ≥10 mg/kg/day in monkeys ($ER_{AUC} = 25$). It is notable these organs either have GLP-1 receptors or express DPP-4 (Holst and Deacon, 1998; Jax, 2009); inflammation of these organs have been observed with other DPP-4 inhibitors.[17,9]

These findings suggest that the toxicity of saxagliptin and vildagliptin is not directly mediated by inhibition of DPP-4. Lankas *et al.* (2005) provided evidence that anaemia, thrombocytopenia, splenomegaly and pulmonary histiocytosis in rodents and GI tract toxicity in dogs were associated with DPP-8 or DPP-9 inhibition, though inhibition of an as yet unidentified target cannot be ruled

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[14] Drucker DJ. Dipeptidyl peptidase-4 inhibition and the treatment of type 2 diabetes. Preclinical biology and mechanisms of action. Diabetes Care 2007; 30: 1335–1343.

[15] Karl T, Hoffmann T, Pabst R, von Hörsten S. Behavioural effects of neuropeptide Y in F344 rat substrains with a reduced dipeptidyl-peptidase IV activity. Pharmacol Biochem Behav 2003; 75: 869–879.

[16] Karl T, Hoffmann T, Pabst R, von Hörsten S. Extreme reduction of dipeptidyl peptidase IV activity in F344 rat substrains is associated with various behavioural differences. Physiol Behav 2003; 80: 123–134.

[17] Holst JJ, Deacon CF. Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes. Diabetes 1998; 47: 1663–1670.

out (Burkey *et al.*, 2008).[18,19] Vildagliptin and saxagliptin are structurally similar, inhibit DPP-4 through a similar mechanism and have similar inhibitory constants for DPP-8 and DPP-9.

Findings of brain lesions in male rats are considered to be a species-specific effect of saxagliptin and not clinically relevant; this is based on the results of the submitted mechanistic studies and a lack of brain lesions in mice, female rats, dogs and monkeys (even at higher exposure levels) as well as a lack of detectable levels of cyanide in the blood of monkeys dosed at 20 mg/kg/day orally (ER_{AUC}, 74). The findings of thrombocytopenia, anaemia, lymphoid hyperplasia, pulmonary histiocytosis and GI tract toxicity are considered likely to be of limited clinical relevance as sufficiently high margins of exposure exist at the NOELs, they were not particularly severe and/or they were not consistently observed across species. The clinical significance of the skin lesions observed in dogs and monkeys is unclear, and relative exposure at the NOELs in the two species is low (1.4–3-times). The sponsor's *Clinical Overview* states that the frequency of skin-related adverse effects was generally comparable between subjects that received saxagliptin (5 mg) and placebo, however.

Toxicity studies using saxagliptin in combination with metformin or other proposed combination therapies have not been performed.

Genotoxicity

The potential genotoxicity of saxagliptin was investigated in the standard battery of tests, conducted in accordance with ICH guidelines. All assays were appropriately validated and definitive studies were conducted under GLP conditions. BMS-510849 was tested directly for mutagenicity in the Ames test and indirectly (*via* metabolic formation) in clastogenicity and unscheduled DNA synthesis assays with saxagliptin in rats (AUC values≥138 -fold the clinical exposure). Neither saxagliptin nor BMS-510849 were mutagenic in bacterial mutation assays or clastogenic *in vivo*. *In vitro* saxagliptin was clastogenic to dividing human lymphocytes, but only in the absence of metabolic activation and at a cytotoxic concentration. Based on negative responses in other genotoxicity assays the weight of evidence indicates that saxagliptin does not pose a genotoxic risk to humans.

Carcinogenicity

The carcinogenic potential of saxagliptin by the oral route was investigated in 2-year studies in mice and rats (GLP-compliant). Group sizes were appropriate and dual control groups were used, as recommended in the TGA-adopted EU guideline on carcinogenic potential.[20] The highest dose levels used in each of the studies (600 mg/kg/day in mice and 300 mg/kg/day in rats) produced excessive mortality in males, necessitating early termination of dosing in the high-dose male groups (in Week 90 for mice and Week 68 in rats). Given the late stage of termination, this is not considered to have adversely affected the adequacy of the mouse study to reveal potential carcinogenic effects. For the rat study, the next highest dose (150 mg/kg/day) is considered to be the highest one adequately tested for carcinogenic potential in males. No treatment-related increases in tumour incidence were observed in either study; exposure ratios at the highest adequate doses are ≥690 in mice, ≥45 in male rats and ≥178 in female rats.

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[18] Lankas GR, Leiting B, Roy RS *et al*. Dipeptidyl peptidase IV inhibition for the treatment of type 2 diabetes. Potential importance of selectivity over dipeptidyl peptidases 8 and 9. Diabetes 2005; 54: 2988–2994.

[19] Burkey BF, Hoffmann PK, Hassiepen U, Trappe J, Juedes M, Foley JE. Adverse effects of peptidyl peptidases 8 and 9 inhibition in rodents revisited. Diab Obesity Metabol 2008; 11: 1057–1061.

[20] EMEA, Committee for Proprietary Medicinal Products (CPMP), 25 July 2002. Note for Guidance on Carcinogenic Potential, CPMP/SWP/2877/00.

Reproductive toxicity

A standard set of GLP-compliant reproductive toxicity studies were submitted and examined both male and female fertility (in rats), embryofetal toxicity (rats and rabbits) and pre/postnatal development (rats). Adequate animal numbers and dose levels were used during appropriate gestational periods. Toxicokinetic analyses were performed in the pivotal studies with exposures significantly greater than the anticipated clinical exposure. Reduced fertility was observed in male rats treated with 400 mg/kg/day orally (NOEL 200 mg/kg/day; $ER_{AUC} = 69$). In female rats, the pregnancy rate was decreased with treatment at 750 mg/kg/day orally, a severely maternotoxic dose. Ovulation was inhibited and oestrus cycling was altered at this dose; doses≥300 mg/kg/day increased pre- and post-implantation loss (NOEL, 125 mg/kg/day; $ER_{AUC} = 47$). Given that there were no reports on impaired fertility in mice lacking DPP-4 (Marguet *et al.*, 2000), these effects on fertility are likely due to non-pharmacological actions of saxagliptin, BMS-510849 or other metabolites.[21] As the effects occurred only at very high exposures, they are unlikely to be of clinical concern.

Saxagliptin and/or its metabolites readily crossed the placenta in rats with significant exposure observed in the fetal brain, likely a result of incomplete blood-brain barrier formation. In embryofetal development studies, fetal weight was reduced in rats at 900 mg/kg/day (a maternotoxic dose), and increased incidences of fetal variations were observed in rats and rabbits. These were increased incidences of incomplete ossification of the pelvis in rats (NOEL, 64 mg/kg/day; $ER_{AUC} = 32$) and increased incidences of irregular shaped hyoid alae and increased rib ossification sites in rabbits (NOEL 40 mg/kg/day; $ER_{AUC} = 164$). As these variations were only minor, representing retardation of fetal growth (Fritz and Hess, 1970; Fritz, 1975) and large margins of exposure exist at the NOELs, the findings are unlikely to be of clinical concern.[22,23] No teratogenicity was observed in either rats ($ER_{AUC} \leq 709$) or rabbits ($ER_{AUC} \leq 1521$).

In a pre/postnatal study in rats, pups from dams that had been treated with ≥250 mg/kg/day orally saxagliptin from Gestation Day 6 and throughout lactation displayed reduced body weight gain (by about 20% pre-weaning and 10–15% post-weaning; NOEL, 100 mg/kg/day; $ER_{AUC} = 47$). Apart from growth, postnatal survival, pup reproductive function and other developmental parameters were unaffected by maternal treatment with saxagliptin (≤500 mg/kg/day orally). Saxagliptin and/or its metabolites are readily excreted in milk; it is unclear if exposure *in utero* or through the consumption of maternal milk resulted in this inhibition of body weight gain, or if it reflected reduced maternal care. Considering that birth weight was unaffected and the inhibition lessened post-weaning, postnatal exposure appears to be a more likely cause than *in utero* exposure.

Paediatric use

No specific studies in juvenile animals were submitted.

Local tolerance

In local tolerance studies, saxagliptin was not a skin irritant (*in vivo* rabbit assay) or ocular irritant (*in vitro* bovine assay), but was a potential skin sensitiser (mouse local lymph node assay).

Immunotoxicity

DPP-4 (CD26) is a co-receptor with CD3 in T-cell activation and proliferation. Various studies to assess the effects of saxagliptin on the immune system were performed, either in isolation or incorporated as end-points in repeat-dose toxicity studies. *In vitro*, there was no significant

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[21] Marguet D, Baggio L, Kobayashi T, et al. Enhanced insulin secretion and improved glucose tolerance in mice lacking CD26. Proc Natl Acad Sci USA 2000; 97: 6874–6879.

[22] Fritz H, Hess R. Ossification of the rat and mouse skeleton in the perinatal period. Teratology 1970; 3: 331–338.

[23] Fritz H. Prenatal ossification in rabbits as indicative of fetal maturity. Teratology 1970; 11: 313–319.

inhibition of human T cell activation by saxagliptin or BMS-510849 at ≤10 μM, and the IC_{50} for inhibition of T cell proliferation was about 20 μM (6.7 μg/mL; about 280-fold the clinical C_{max}). In rats, there was no effect of saxagliptin up to 200 mg/kg/day orally (ER_{AUC} = 35) on the antigen-driven T lymphocyte dependent humoral response and saxagliptin was not seen to be immunotoxic in rats. These effects are consistent with observations in a DPP-4 null mutant mouse (Vora *et al.*, 2009).[24] Thymic lymphoid depletion and/or atrophy was the only indication of possible immunotoxicity in rodents (≥600 mg/kg/day in mice and ≥300 mg/kg/day in rats; ER_{AUC} ≥286). Although DPP-8 and DPP-9 are expressed on T lymphocytes and play a role in immunosuppression (Lankas *et al.*, 2005), and saxagliptin has some inhibitory activity towards these peptidases, it was insufficient to elicit an overt immunotoxic response at exposures far-exceeding the clinical exposure.[18]

Nonclinical Summary and Conclusions

Toxicological effects of thrombocytopenia, anaemia, lymphoid hyperplasia, pulmonary histiocytosis and GI tract toxicity were not consistently observed across species, were not particularly severe and/or occurred only at sufficiently high exposures to be not of particular concern. Brain lesions, observed in male rats, are not considered clinically relevant on mechanistic grounds and based on a large margin of exposure at the NOEL (almost 200-fold).

The clinical significance of skin lesions, observed in dogs and monkeys, is unclear, and relative exposure at the NOELs in the species is low (1.4–3-times). This concern should be addressed by the clinical data.

Effects on reproductive parameters occurred at sufficiently high exposures to be not of particular concern.

The absence of pharmacokinetic drug interaction and toxicity studies with the proposed combinations was considered a deficiency of the application.

There were no objections on nonclinical grounds to the registration of Onglyza as monotherapy for the proposed indication. In the absence of nonclinical data regarding saxagliptin in combination with metformin, thiazolidinedione or a sulfonylurea, the safety of the proposed combinations will need to be addressed by clinical data.

IV. Clinical Findings

Introduction

5346 subjects were studied in the saxagliptin clinical development program. Of these, 4042 subjects were exposed to saxagliptin. About 3018.7 subject-years of exposure have accrued, almost all in Phase II-III studies of subjects with T2DM.

Clinical Pharmacology studies

The Clinical Pharmacology program included 24 studies in 673 subjects, including 620 given saxagliptin (Tables 1-4). Most of these (583/673) were in healthy volunteers.

[24] Vora KA, Porter G, Peng R, et al. Genetic ablation or pharmacological blockade of dipeptidyl peptidase IV does not impact T-cell dependent immune responses. BMC Immunol 2009; 10: 19.

Table 1: Safety/Pharmacokinetics/Pharmacodynamics/Mechanism of Action Studies

Single ascending dose (1 - 100 mg)	CV181001
Multiple ascending dose in subjects with T2DM (2.5 to 50 mg QD)	CV181002
Multiple ascending dose (40 - 400 mg QD)	CV181010
^{14}C-ADME (50 mg)	CV181004
Effects on lymphocyte count (5 and 20 mg)	CV181022
Effects on lymphocyte count and potential for cyanide formation (10 and 40 mg QD)	CV181031
Thorough QTc study (10 and 40 mg QD)	CV181032
Mechanism of action (5 mg QD)	CV181041
Exposure modelling (Clinical Pharmacology studies: 1-100 mg single dose, 25-50 mg QD; Phase III study: 2.5 - 10 mg QD)	Multiple studies

Table 2: Drug-Drug Interactions Studies

Antidiabetic Agents

Metformin (1000 mg) + Saxagliptin (100 mg)	CV181017
Glibenclamide (5 mg) + Saxagliptin (10 mg)	CV181026
Pioglitazone (45 mg QD) + Saxagliptin (10 mg)	CV181028

Other Potentially Co-Prescribed Agents

Digoxin (0.25 mg QD) + Saxagliptin (10 mg)	CV181052
Gastric acid-controllers (Aluminum + Magnesium Hydroxides + Simethicone (30 mL), Famotidine (40 mg), Omeprazole (40 mg QD)) + Saxagliptin (10 mg)	CV181035

CYP3A-Based Studies

Simvastatin (40 mg QD) + Saxagliptin (10 mg)	CV181033
Diltiazem (360 mg LA QD) + Saxagliptin (10 mg)	CV181053
Ketoconazole (200 mg q12 h) + Saxagliptin (100 mg)	CV181005

Table 3: Specific Populations

Effects of age and gender (10 mg)	CV181018
Renal impairment (10 mg)	CV181019
Hepatic impairment (10 mg)	CV181020

Table 4: Biopharmaceutics

Definitive food effect study (10 mg)	CV181034
Relative bioavailability (capsules vs tablets) (5 mg)	CV181021
Relative bioavailability/pharmacodynamics (capsules vs tablets) (5 mg)	CV181037
Relative bioavailability (10 mg vs 5 mg tablets) (10 mg)	CV181036
Relative bioavailability (capsules vs tablets) (40 mg)	CV181003

Phase II studies

There was one Phase II study, with 423 subjects (amongst whom 315 subjects with T2DM were exposed to saxagliptin). CV181008 was a dose-finding study over 6-12 weeks in treatment-naïve T2DM subjects with inadequate glycaemic control.

Phase III studies

4250 subjects were studied (36 in a mechanism-of-action study and 4214 in core studies, of whom 20 and 3087 respectively were exposed to saxagliptin).

There were 6 *Core Phase III studies* with final data from the 24 week short-term (ST) treatment period. Three doses of saxagliptin (2.5, 5 and 10 mg) were evaluated; fixed-dose regimens were emphasised. Each study was double-blind, randomised and controlled, and in each study there was a 1-4 week dietary / placebo lead-in period after screening. Studies were placebo-controlled, except for CV181039 (active control); in CV181040, the 'placebo' group received uptitrated glibenclamide.

2205 subjects received at least 166 days (close to 24 weeks) of "ST (excluding rescue)" saxagliptin therapy.

Core Phase III studies

Monotherapy studies in treatment-naïve subjects with inadequate glycaemic control with diet and exercise:

CV1810**11** (this study also included an open-label treatment group for 66 subjects with screening HbA1c >10% and ≤12%; such subjects received saxagliptin 10 mg)

CV1810**38** – this was the only Core Phase III study that did *not* evaluate saxagliptin in an exclusively fixed (non-titratable) dosing regimen

Add-on combination studies (that is, in subjects already receiving treatment):

CV1810**14 –** add-on to metformin

CV1810**13 –** add-on to thiazolidinedione

CV1810**40 –** add-on to sulfonylurea (glibenclamide)

Initial combination with metformin study in treatment-naïve subjects: CV1810**39**

Interim results from ongoing long-term (LT) extensions of the Core Phase III studies were presented.

In addition to the *Core Phase III studies* there was a Phase III study in 36 subjects with T2DM over 12 weeks that examined mechanism of action (effect on β-cell function) (CV1810**41**).

Other Studies

Studies reported as started (but without any data in the submission, except for preliminary safety data in a "120-day safety update"):

CV1810**54** – a 52-week, randomised, double-blind, active-controlled study with a 52-week extension to evaluate the safety and efficacy of saxagliptin in combination with metformin compared with SU in combination with metformin.

CV1810**56** – an 18-week, randomised, double-blind, active-controlled study to evaluate the efficacy and safety of saxagliptin in combination with metformin in comparison with sitagliptin in combination with metformin.

CV1810**62** – a 12-week, randomised, double-blind, placebo-controlled study to evaluate the effect of saxagliptin compared with placebo in adult patients with T2DM and renal impairment (moderate, severe, end-stage [dialysis]). This study includes an additional 40-week observational period.

Study CV1810**59**, a clinical pharmacology study assessing drug interactions with rifampin 600 mg QD (n=14 healthy subjects, all given saxagliptin).

Study 262-07-001, a clinical pharmacology study assessing PK in Japanese subjects (n=62, 48 of whom were given saxagliptin).

Other data

- A useful 4 month [120 day] safety update document was included.
- An assessment of environmental risk for saxagliptin was included. This has not been evaluated in this document.
- Various documents not classifiable as *Clinical Study Reports* were included in the submission. Only the more clinically relevant of these documents were assessed.

Pharmacokinetics

Absorption

Aqueous solubility is high (≥16.9 mg/mL) relative to the proposed dose of 5 mg, across pH 0.7 to 8.7. Co-administration with omeprazole did not affect saxagliptin or BMS-510849 pharmacokinetics (PK). Despite *in vitro* results predicting low intestinal permeability for saxagliptin and a possible role of P-glycoprotein transporter, oral absorption of saxagliptin in humans was high.

An absolute bioavailability study had not been conducted at the time of review by the clinical evaluator; however the study (CV181128) was subsequently conducted and completed in November 2010. The results of this study showed the mean absolute oral BA of saxagliptin was 50% (48%-52% in individual subjects).

Based on results of a mass balance study (CV181004) 75% total radioactivity in urine and predominance of oxidative metabolites was amongst the 22% of radioactivity recovered in faeces.

Pharmacokinetic parameters

Saxagliptin is rapidly absorbed after oral administration (median t_{max} <2 hours) and generally within 0.5-0.75 hours in the fasted state. It is reasonable to produce values from CV181037 because this study used a 5 mg dose of the *Phase III Clinical tablet* formulation. Subjects were healthy (not diabetic). Study CV181002 studied capsules in T2DM subjects and there was reasonable bridging from capsule to tablet (for example, CV181037 itself). t_{max} was up to 2.5 hours in this study, where saxagliptin was given with breakfast. C_{max} was 24.5 ng/mL in CV181037 for the clinical tablet, and 23 ng/mL in CV181002 (for the 5 mg capsule).

Absorption following oral dosing in fed versus fasted states

Study CV181001 included a preliminary food effect assessment. Administration with a high fat meal of a capsule formulation resulted in a 28% decrease in C_{max} and a 32% increase in AUC; t_{max} was delayed (that is, increased) by 1.25 hours.

In Study CV181034 (the definitive food effect study), administration of the clinical tablet formulation with a high-fat meal resulted in no appreciable change to C_{max} (unlike findings in CV181001), a 27% increase in the AUC from time zero to infinity (AUC_{∞})(consistent with CV181001) and a delay in t_{max} by 0.5 hours (a direction of change consistent with CV181001, although magnitude of change differed) compared with the fasted state.

The sponsor proposed on this basis that saxagliptin may be taken with or without food.

Half-life

Half-life after one dose of 5 mg saxagliptin in the fed state was 2.5 hours for saxagliptin and 3.1 hours for BMS-510849 (CV181037). Increasing to 400 mg once daily, half-life values were similar (CV181001, CV181002, CV181010), indicating linearity in distribution and clearance.

Distribution

AUC

AUC reflects exposure to drug. $AUC_{0-\tau}$ indicates exposure to the last measured time point; AUC_{∞} reflects exposure extrapolated to infinity. AUC_{∞} for a single 5 mg clinical tablet dose in CV181037 (healthy subjects) was 77.6 ng.hour/mL. $AUC_{0-\tau}$ for a 5 mg capsule in CV181002 (T2DM) was 77 ng.hour/mL at Day 1 and 81 ng.hour/mL at Day 14.

Exposure to major metabolite

Following single or once daily repeated oral doses of 5 to 400 mg saxagliptin in fed or fasted states, mean BMS-510849 AUC values were between 2- and 7-fold higher than the parent saxagliptin exposure on a molar basis (CV181001; CV181002; CV181010).

The parent to metabolite ratio was generally constant for individuals upon multiple dosing or when determined on different occasions (CV181001, CV181002, CV181010). Between-subject variability in exposure of BMS-510849 relative to parent was described as typical for a CYP3A4/5 substrate (typically 30% coefficient of variation [CV] for AUC, independent of dose). Also, distribution of exposure values for saxagliptin and BMS-510849 was continuous, with no evidence of bi- or polymodal distribution of PK values that could indicate metabolic polymorphism (for example, in CYP3A5).

Volume of distribution

Volume of distribution was not calculated at the time of review by the clinical evaluator. According to the subsequent absolute bioavailability study, the mean volume of distribution was 123L in healthy normal subjects.

Erythrocyte distribution and serum protein binding

Based on systemic exposure in blood and plasma of total radioactivity from a single oral dose of ^{14}C-saxagliptin, the concentration of saxagliptin-related compounds into erythrocytes was less than that in plasma (plasma: blood ratio of 0.62) (CV181004). Saxagliptin and BMS-510849 are not bound to plasma proteins, as determined by equilibrium dialysis. The free fraction of saxagliptin and BMS-510849 was about 100%.

Metabolism

Metabolites and metabolising systems

Saxagliptin is metabolised primarily by hydroxylation, primarily by CYP3A4 and 3A5, to an active major monohydroxylated metabolite named BMS-510849. *In vitro* enzyme kinetic binding studies indicate that BMS-510849 is 2-fold less potent than parent saxagliptin at DPP4 inhibition at 37°C. The relatively small difference between saxagliptin t_{max} and BMS-510849 t_{max} indicates that biotransformation to BMS-510849 takes place quite quickly after dosing. *In vitro* metabolism of saxagliptin by glucuronidation was extremely slow.

Potential for saxagliptin to alter CYP or transporter activity

Saxagliptin and BMS-510849 did not inhibit CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1 or 3A4 *in vitro*. Saxagliptin and BMS-510849 did not induce CYP1A2, 2B6, 2C9 or 3A4 *in vitro*. The potential for saxagliptin doses to affect other CYP3A4 substrates was studied in a simvastatin interaction study (CV181033) and in a pioglitazone (CYP3A4 and CYP2C8 substrate) interaction study (CV181028). No meaningful interactions were observed. Also, saxagliptin dosing did not meaningfully alter disposition of glibenclamide (CYP2C9 substrate; CV181026); digoxin (P-gp substrate; CV181052); or metformin (hOCT-1 and hOCT-2 substrate; CV181017). Saxagliptin is a weak P-glycoprotein substrate and it is not a substrate for a number of other major transporters tested.

Potential for changes in CYP3A activity to alter saxagliptin PK

Based on *in vitro* metabolic profiling, co-administered drugs that inhibit or induce CYP3A activity may, respectively, increase or decrease saxagliptin exposure.

Co-administration with CYP3A4/5 inducers (carbamazepine, dexamethasone, phenobarbitol, phenytoin, rifampicin) is likely to lower saxagliptin plasma concentrations – and presumably increase BMS-510849 plasma concentrations. No studies were provided to demonstrate this, but a rifampin interaction study is underway (CV181059).

Interaction studies with diltiazem (CV181053), a moderate CYP3A4 inhibitor, and ketoconazole (CV181005), a potent CYP3A4 inhibitor, were conducted. Saxagliptin C_{max} increased <2-fold with CYP3A4 inhibition. In hepatic impairment (CV181020), saxagliptin C_{max} was unaffected. These results suggest that first-pass metabolism is not the main metabolic route of saxagliptin clearance.

Saxagliptin AUC was elevated 2.5-fold with ketoconazole co-administration, vs 2.1-fold with diltiazem co-administration. BMS-510849 AUC (and C_{max}) fell in these situations, and with hepatic impairment, reflecting a reduced formation of BMS-510849.

Cyanide formation

Saxagliptin and BMS-510849 contain a cyanide moiety, but according to the sponsor humans do not generate free cyanide from saxagliptin. Male rats express high levels of CYP2C11 which can release cyanide from saxagliptin. Humans are not known to express CYP2C11, and other CYP2C isoforms show less potential to cleave cyanide from saxagliptin or BMS-510849. Study CV181031 verified that humans do not cleave cyanide from saxagliptin.

Excretion

Mass balance study

CV181004 was a mass balance study, pivotal for showing routes of excretion for saxagliptin. Recovery of administered radioactivity following oral dosing with ^{14}C-saxagliptin was 97%, and most of this was recovered within 24 hours (sum of mean 0-24 hour urinary [71.4%] and faecal [13.9%] recovery was 85.3%).

Renal clearance

Saxagliptin is eliminated via both metabolic and renal pathways, while BMS-510849 is primarily eliminated via renal excretion. In the mass balance study CV181004, an average of 75% of the dose was excreted in urine (24% of dose as saxagliptin, 36% as BMS-510849 or related compounds, 15% as other minor metabolites or degradants).

Renal clearance of saxagliptin (~230 mL/min) was ~twice estimated creatine clearance (CL_{CR}) (120 mL/min); renal clearance of BMS-510849 (~100 mL/min) was similar to estimated CL_{CR} (CV181001; CV181002; CV181010; CV181004). This suggests saxagliptin is actively secreted by

kidney (glomerular filtration + net tubular excretion) while BMS-510849 is excreted by glomerular filtration (CV181001; CV181002; CV181010; CV181004).

The identity of the renal transporter for saxagliptin is unknown, although key transporters (organic anion transporter-1 and -3; organic anion transporting polypeptide-A, -C and -8, organic cation transporter-1 and -2, sodium taurocholate co-transporting peptide, and peptide transporters PepT1 and PepT2) were excluded by *in vitro* evaluation, so the potential for renal transporter-based drug-drug interactions is unknown. BMS-510849 was not a substrate for these transporters. While saxagliptin is a poor substrate for P-glycoprotein, the contribution of P-gp to active tubular secretion is unclear.

In patients with mild renal insufficiency (creatinine clearance 50-80 mL/min), AUC of saxagliptin and BMS-510849 were 16% and 67% higher, respectively, compared to healthy subjects with normal renal function following administration of a single 10 mg dose of saxagliptin (CV181019).

In subjects with moderate (30-50 mL/min) renal impairment, AUC values for saxagliptin and BMS-510849 were 41% and 192% (2.9-fold) higher than in healthy subjects. In subjects with severe (<30 mL/min) renal impairment, AUC values for saxagliptin and BMS-510849 were 108% (2.1-fold) and 347% (4.5-fold) higher than in healthy subjects (CV181019).

It was proposed to give saxagliptin 5 mg daily in subjects with normal or mildly impaired renal function, and 2.5 mg in subjects with moderate renal impairment, severe renal impairment and end-stage renal disease requiring haemodialysis. There was no dedicated study where subjects with moderate or severe renal impairment were given 2.5 mg saxagliptin doses.

Hepatic clearance

In subjects with mild, moderate and severe hepatic impairment, mean C_{max} and AUC of saxagliptin were up to 8% and 77% higher, respectively, compared to healthy matched controls following a single 10 mg dose of saxagliptin (CV181020). The C_{max} and AUC of BMS-510849 were up to 59% and 33% lower, respectively. No dosage adjustment is proposed in subjects with hepatic impairment.

Repeat dose studies and dosing regimens

Accumulation

No appreciable accumulation was observed upon repeated once-daily dosing for up to 2 weeks using up to 400 mg (CV181002; CV181010).

Dose proportionality

C_{max} and AUC for saxagliptin and BMS-510849 increase linearly with saxagliptin dose beyond the therapeutic range. No dose- and time-dependency were observed in any relevant PK parameter for saxagliptin or BMS-510849 over 14 days of once-daily dosing with doses ranging from 2.5 to 400 mg (CV181002; CV181010).

These data suggest saxagliptin does not inhibit or induce its own metabolism or active transport.

Pharmacokinetics in different age groups, physiological states or genetic makeup

Elderly

Subjects 65-80 years of age had 23% higher C_{max} and 59% higher AUC_{∞} than subjects 18-40 years of age (CV181018), differences also reflected in BMS-510849 kinetics. The sponsor attributed these findings to declining renal and metabolic function with age. Age was not identified as a significant covariate on apparent clearance of saxagliptin and BMS-510849 in an exposure modelling analysis.

The sponsor did not propose dose adjustment for age, because of (a) <2-fold magnitude of difference in PK values between younger and older subjects, and (b) the "favourable safety and tolerability profile" in Phase III studies enrolling subjects up to 77 years of age. Most subjects in Phase III studies were <65 years of age.

Paediatric subjects

Saxagliptin has been studied only in subjects ≥18 y ears of age.

Gender

No major differences in PK were observed between males and females (CV181018).

Race

No clinical studies aimed to characterise saxagliptin PK in specific racial groups. An exposure modelling analysis compared PK of saxagliptin and BMS-510849 in 309 White subjects versus 105 non-White subjects (consisting of 6 racial groups). No differences were seen.

T2DM

No formal analysis of differences in kinetics in T2DM patients vs healthy subjects was conducted. Exposure modelling of 126 healthy subjects (CV181001, CV181018, CV181037) and 288 T2DM subjects (CV181002, CV181011) found no significant difference in kinetics in the two populations.

Pregnant or lactating women

Saxagliptin has not been studied in these populations. In a lacteal excretion study in nursing rats using ^{14}C-saxagliptin, radioactivity was distributed in milk with an AUC ratio (milk: plasma) of 0.8, suggesting that saxagliptin-derived components were secreted into milk.

Other

Effects of smoking, diet, herbal products and alcohol on saxagliptin kinetics have not been addressed.

Drug Interactions

Saxagliptin did not meaningfully alter the PK of: metformin (CV181017); glibenclamide (CV181026); pioglitazone (CV181028); digoxin (CV181052); simvastatin (CV181033); diltiazem (CV181053); and ketoconazole (CV181005).

Conversely, the PK of saxagliptin, BMS-510849 or exposure to total active components (parent + metabolite corrected for relative difference in potency of DPP4 inhibition) were not meaningfully altered by: metformin (CV181017); glibenclamide (CV181026); pioglitazone (CV181028); digoxin (CV181052); omeprazole (CV181035); aluminium hydroxide + magnesium hydroxide + simethicone (CV181035); famotidine (CV181035); simvastatin (CV181033); diltiazem (CV181053); and ketoconazole (CV181005). For the latter two drugs (CYP3A4 inhibitors), saxagliptin AUC rose substantially but BMS-510849 exposure fell, broadly balancing the impact of PK changes.

The effects of CYP3A4/5 inducers on PK of saxagliptin have not been studied. The sponsor states that "co-administration of saxagliptin and CYP3A4/5 inducers may result in decreased plasma concentrations of saxagliptin".

Pharmacodynamics

Mechanism of action

Endpoints for assessment of pharmacodynamics (PD) used in the saxagliptin programme included:

- DPP4 inhibition (represented as percent inhibition from pre-dose)
- Plasma concentrations of the substrate of primary interest (active, that is intact, GLP-1)

These endpoints were analysed in studies CV181001, CV181002 and CV181010 (as well as in CV181037, a capsule vs tablet relative bioavailability study). Other PD endpoints included markers of glucose regulation (plasma and interstitial glucose in CV181002; serum glucose in CV181010; serum insulin and C-peptide in CV181002 and CV181010). Studies CV181008 and CV181011 also assessed PD endpoints.

BMS-510849 is the major metabolite of saxagliptin, and is pharmacologically active. BMS-510849 is approximately 2-fold less potent than saxagliptin with respect to DPP4 inhibition. The sponsor characterised BMS-510849 pharmacokinetics appropriately in the study program.

Plasma DPP4 activity

In CV181001, the enzyme activity of DPP4 in human plasma was measured using glycl-prolyl-p-nitro-aniline as the substrate and incubation for 90 min at pH 7.4 and 25°C (presumably an increase in specific absorbance was then measured). In CV181001, dose dependent inhibition of DPP4 was seen after a single dose.

Similar inhibition was seen at Day 14 in CV181002 (T2DM), and slightly more pronounced inhibition at Day 14 in CV181010 (healthy subjects given higher doses). Maximum inhibition broadly coincided with t_{max} for saxagliptin and BMS-510849. DPP4 inhibition data were not presented for a 'negative' control, for example PD data were not gathered in CV181039 and -40.

Inhibition of DPP4 persisted for a longer time than saxagliptin and BMS-510849 were quantifiable in plasma. This was attributed to the slow off rate of saxagliptin and BMS-510849 from DPP4. Also, despite in CV181001 the 1 mg group having no quantifiable plasma concentrations of saxagliptin or BMS-510849, DPP4 inhibition was still 69%. Thus, relatively small concentrations of the two compounds inhibit plasma DPP4 activity.

It has been reported that DPP4 activity is reduced in smokers (relative to healthy non-smokers and allergic asthmatics) and patients with malignancy and auto-immune / inflammatory disorders, and increased in diabetics (van der Velden et al, 1999; Grouzmann and Buclin, 2007).[25,26] Generally, baseline characteristics regarding smoking were not presented for analysis. It is possible that with a reduced DPP4 activity, there is a reduced capacity for DPP4 inhibitors to work.

Plasma GLP-1 concentrations

In CV181001 (a single arm, ascending dose study), after meals mean changes in plasma active GLP-1 concentrations from baseline values in healthy subjects receiving saxagliptin were generally higher than corresponding placebo values, but no dose dependent saxagliptin effect was observed. Between-subject variability in active plasma GLP-1 concentrations was large.

In CV181002 (multiple doses in T2DM), clear difference in active GLP-1 levels between saxagliptin 5 mg and placebo emerged only at Day 14 beyond 1 hour after dosing.

In general, it was more difficult to demonstrate a clear effect of saxagliptin on plasma GLP-1 levels than on *ex vivo* inhibition of DPP4 activity. Also, GIP levels were not assessed in many studies.

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[25] van der Velden VHJ, Naber BAE, van Hal PThW et al. Peptidase activities in serum and bronchoalveolar lavage fluid from allergic asthmatics – comparison with healthy non-smokers and smokers and effects of inhaled glucocorticoids. Clin Experimental Allergy 1999; 29: 813-823.

[26] Grouzmann E, Buclin T. Is dipeptidylpeptidase IV the missing link in angiotensin-converting enzyme inhibitor induced angioedema? Hypertension 2008; 51: 45-47.

There was reasonable evidence that DPP4 inhibition using saxagliptin did, relative to placebo, increase levels of intact (active) plasma GLP-1.

An increase in post-prandial active GLP-1 would be predicted to increase glucose-stimulated insulin secretion by the β cell. In the post-prandial state, enteral stimulation increases incretin secretion. In diabetes, in this phase, there is a paradoxical rise in glucagon levels. Study CV181041 was designed to examine the effect of saxagliptin on β cell function in T2DM, in the fasting and post-prandial state.

Study CV181041 - Mechanism of Action and Efficacy of Saxagliptin (BMS-477118) in the Treatment of Type 2 Diabetic Patients

This was a randomised, double blind, placebo-controlled Phase III study designed to assess saxagliptin's mechanism of action. It used 'hyperglycaemic clamp' testing, where the hyperglycaemic stimulus to insulin secretion is held constant, a technique which is described by the sponsor as the gold standard for assessing β cell function. Treatment-naïve subjects with T2DM and Glycosylated haemoglobin HbA1c (HbA1c) 6.0-8.0% were recruited; other inclusion and exclusion criteria resembled those listed later in this section. The study was started in September 2006 and was conducted at 3 US sites.

Twenty subjects were treated with saxagliptin (SAX) 5 mg daily for 12 weeks in the short term (ST) phase of the study, and 16 subjects with placebo (PLAC). In the ST phase, mean duration of exposure to saxagliptin was 76.2 days and to placebo was 85.2 days. 16 SAX subjects and 15 PLAC subjects were included in the primary dataset; other had insufficient data.

Mean age was 55.6 (range 43-69) years and mean body mass index (BMI) was 33 kg/m^2; median body weight was 10 kg higher in the saxagliptin group than the placebo group. Mean duration of T2DM was 3 years. Mean baseline HbA1c was 6.8%, indicating a relatively mild diabetes phenotype. Mean homeostasis model assessment for β cell function (HOMA-2B) values were 102% (SAX) and 122% (PLAC), suggesting more β cell dysfunction at baseline (more advanced disease) in the SAX group, but overall no extreme loss of β cell function as might be encountered in long-standing / advanced T2DM. More importantly, there was an imbalance in insulin secretion between treatment groups at baseline (higher in the PLAC group), which somewhat undermines study results.

The primary efficacy endpoint was adjusted mean insulin secretion rate area under the curve (AUC) (that is, total amount of insulin secreted) during an IV-oral hyperglycaemic clamp study (at 180-480 minutes) after 12 weeks of treatment. A secondary objective was to examine change from baseline after 12 weeks in insulin secretion rate AUC during an IV hyperglycaemic clamp study (at 120-180 minutes). There were multiple other endpoints, not discussed here.

A standard oral glucose tolerance testing (OGTT) was performed at Day -3 of lead in and at Week 12 of the ST period (when study medication was given 60 minutes prior to ingestion of 75 g glucose at time 0).

A sequential IV-oral hyperglycaemic clamp and arginine stimulation test was performed at Day -1 of a 2-week diet and exercise lead-in ('baseline') and Week 12 of ST treatment. At Week 12, study medication was given 30 minutes prior to the start of the glucose infusion.

The first step in the 'hyperglycaemic clamp' test was to start a primed continuous glucose infusion. The rate of infusion was adjusted to achieve square wave hyperglycaemia with plasma glucose 15.5 mmol/L. Results at 120-180 minutes were designed to examine saxagliptin's effect on β cell function in the 'fasting' state.

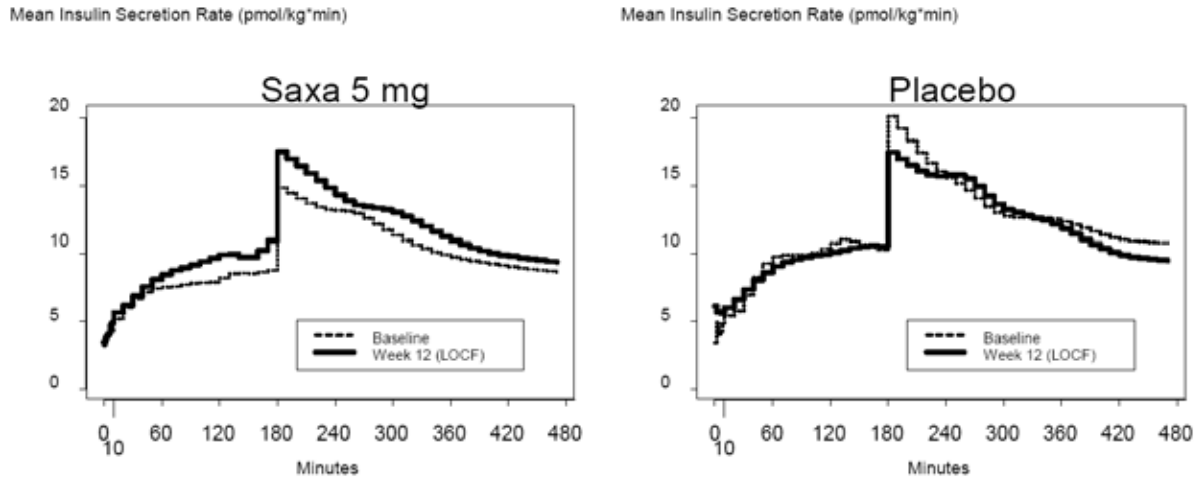
After 180 minutes, 75 g glucose was given orally ('enteral glucose load' to create a 'post-prandial state') and plasma glucose was maintained at 15.5 mmol/L via a glucose infusion. After 300 minutes, infusion was increased to maintain glucose at 25 mmol/L. At 10 minutes after stabilisation

of plasma glucose at 25 mmol/L, 5 g arginine (a powerful stimulus to β cell degranulation) was given over 30 seconds. Results at 180-480 minutes were designed to examine saxagliptin's effect on β cell function in the 'post-prandial' state. Results in the 10 minutes after arginine stimulation were designed to assess maximal insulin secretion.

Insulin secretion rate was calculated using "C-peptide deconvolution by ISEC". A population model derived C-peptide kinetics based on gender / diabetes status / age / weight / height. Based on a fit of time curve for C-peptide concentration, insulin secretion rates were estimated.

There was an 18.5% improvement in adjusted mean insulin secretion rate AUC in the IV-oral ('post-prandial') hyperglycaemic clamp study's saxagliptin group relative to the placebo group (SAX, 15.9% increase in amount of insulin secreted at 12 weeks; PLAC, 2.2% decrease) (Figure 1).

Figure 1: Mean insulin secretion rate



Thus, after 12 weeks, increased glucose-stimulated insulin secretion (and by implication, improved β cell function) were shown in the SAX arm relative to placebo.

There was a 27.9% improvement in adjusted mean insulin secretion rate AUC in the IV ('fasting') hyperglycaemic clamp study's SAX group relative to PLAC. This was perhaps surprising given the sponsor's emphasis of the point that saxagliptin's inhibition of DPP4 will augment postprandial insulin secretion, and that DPP4 inhibitors "stimulate insulin secretion in a glucose-dependent manner". It has been reported that incretins are secreted at low levels basally.

Saxagliptin was associated with increases in C-peptide and insulin AUC during the IV-oral and IV hyperglycaemic clamp (in fasting and postprandial states), a decrease in glucagon AUC in the postprandial state, and a small increase in basal β cell function as measured by HOMA-2B. There was no statistically significant difference between arms in maximal insulin secretion, reflective of total β cell mass (arginine stimulation test results).

There was no particular difference in change over 12 weeks in HbA1c between groups. Results for incretin concentrations were not presented.

There were no deaths, serious adverse effects (SAEs) or discontinuations due to adverse effects (AEs). One SAX subject had swelling of the left foot. There were 2 hypoglycaemic events in the SAX group, and 1 in the PLAC group. There were 2 subjects in the SAX group with lymphopenia (nadirs 0.68 and 0.74 x 10^3 cells / μL); both subjects tolerated rechallenge. A subject in the SAX group (and taking a statin) had symptomless elevated CK to 1545 U/L; a PLAC subject also had elevated CK.

The study was ongoing to 116 weeks (SAX subjects continued to receive saxagliptin; PLAC subjects received metformin), but only safety data were collected in this period. An interim study report was provided (cut-off, 1 Feb 2008). There were no safety findings of note.

Time course of effect

The sponsor noted that the incretin-enhancing mode of action for saxagliptin is most prominent following meals. Inhibition of DPP4 occurred within an hour of dosing, and lasted for >24 hours, regardless of meals. In CV181001 and -02, peak changes in incretin levels occurred at around 6 hours after dosing (but there was considerable variability). In CV181001, there was a suggestion that peak changes were more prominent in the fed state.

Dose / response relationship

Over the range of 1 to 400 mg, saxagliptin inhibits DPP4 enzyme activity for at least a 24 hour period and the inhibition is dose-dependent with higher doses providing longer periods of maximum DPP4 inhibition (CV181001; CV181002; CV181010; CV181037).

Maximal mean plasma DPP4 inhibition ranged from 86% of pre-dose values after 2.5 mg to 97% after 400 mg of saxagliptin (CV181002; CV181010).

Maximal plasma DPP4 inhibition did not appear to change substantially upon repeated once daily dosing with any dose, and the extent of inhibition was similar in healthy subjects and subjects with T2DM (CV181002; CV181010).

At steady state in subjects with T2DM, saxagliptin 5 mg and 15 mg maintained 65% and 76% inhibition of plasma DPP4 activity at 24 hours, respectively (CV181002).

Half-life of plasma DPP4 inhibition following a 5 mg dose of saxagliptin to healthy subjects was 26.9 hours (CV181037).

Specificity

Cardiac effects

Saxagliptin was not associated with clinically significant prolongation of the QTc interval at daily doses up to 40 mg (CV181032; CV181002; CV181010). There was no apparent effect of 10 mg or 40 mg saxagliptin on heart rate.

Immune system effects

At 100 mg in an interrupted dosing paradigm, dosing was associated with a flu-like syndrome with decreased lymphocyte counts (CV181017; CV181005).

Efficacy

General issues/methodology

The Phase III program studied both treatment-naïve and previously treated T2DM subjects. Subjects in efficacy studies were 18-77 years of age at randomisation (mean ages were 53-55 years across studies). Most subjects were White. Mean BMI ranged from 28 to 32 kg/m^2, consistent with a diabetic population. Important disparities between treatment groups, which were uncommon, are identified in evaluation of individual studies.

Subjects in monotherapy studies had a shorter duration of T2DM than subjects in add-on combination studies or the initial combination study. Baseline HbA1c values were slightly lower in monotherapy subjects. Ethnicity data were only collected in the USA; the sponsor claims this accounts for inequalities in the distribution of this parameter.

Inclusion/Exclusion criteria

These criteria were broadly the same across Phase III studies; the selected criteria below are from Study CV181011. Important variation (for example, in the range of HbA1c used to define 'inadequate glycaemic control'; in prior use of oral hypoglycaemic agents) is identified in evaluation of individual studies.

1) Subjects with type 2 diabetes who had inadequate glycaemic control defined as HbA1c ≥7.0% and ≤10.0% obtained at the screening visit. In Study CV181011 only, subjects with a screening HbA1c >10.0% and ≤12.0% who met all other inclusion/exclusion criteria were eligible for direct enrolment into an open-label treatment period.

2) Fasting C-peptide ≥1 ng/mL [C-peptide is formed during conversion of proinsulin to insulin; levels <0.6 ng/mL suggest T1DM]

3) Subjects were to be drug naïve **(**that is, never received medical treatment for diabetes, whether insulin or oral hypoglycaemic agents), although actual requirements were less strict. Exceptions were women treated for gestational diabetes during pregnancy and who were no longer receiving therapy or subjects who during a hospitalization received a short course of insulin treatment.

4) BMI ≤40 kg/m^2.

5) Men and women, ≥18 and ≤77 years of age. Women had to be non-nursing and non-pregnant. Women of childbearing potential (WOCBP) were required to use an adequate method of contraception to avoid pregnancy throughout the study and for up to 4 weeks after the study. WOCBP were required to have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 72 hours prior to the start of study medication. Despite these rigorous criteria, 12 women (9 on saxagliptin) became pregnant during the Phase II/III program, which does not indicate completely successful implementation of the protocol described above.

In Study CV181011, exclusion criteria were as follows:

1) WOCBP who were unwilling or unable to use an acceptable method of contraception to avoid pregnancy for the entire study period and for up to 4 weeks after the study

2) WOCBP using a prohibited contraceptive method

3) Women who were pregnant or breastfeeding

4) Women who had a positive pregnancy test on enrolment or prior to study drug administration

5) Symptoms of poorly controlled diabetes that would preclude participation in this placebo-controlled trial including but not limited to marked polyuria and polydipsia with greater than 10% weight loss during the last 3 months prior to screening or other signs and symptoms

6) History of diabetic ketoacidosis or hyperosmolar nonketotic coma

7) Insulin therapy within 1 year of screening (with the exception of insulin therapy during a hospitalization or use in gestational diabetes)

8) Significant cardiovascular history defined as:

a. History of myocardial infarction (MI), coronary angioplasty or bypass graft(s), valvular disease or repair, unstable angina pectoris, transient ischemic attack, or cerebrovascular accidents within six months prior to entry into the study

b. Congestive heart failure defined as New York Heart Association (NYHA) Stage 3 and Stage IV and/or known left ventricular ejection fraction of ≤ 40%

9) Chronic or repeated intermittent corticosteroid treatment (subjects receiving stable doses of replacement corticosteroid therapy could be enrolled)

10) History of unstable or rapidly progressing renal disease

11) History of alcohol or drug abuse within the previous 1 year

12) Unstable major psychiatric disorders

13) Immunocompromised individuals such as subjects who had undergone organ transplantation or subjects diagnosed with human immunodeficiency virus

14) History of hemoglobinopathies (sickle cell anaemia, thalassaemias, sideroblastic anaemia)

15) Donation of blood or plasma to a blood bank within three months of screening

16) Administration of any other investigational drug or participation in a clinical research trial within 30 days of planned enrolment to this study

17) Any condition which in the investigator's opinion could render the subject unable to complete the study or which posed significant risk to the subject

18) Active liver disease and/or significant abnormal liver function defined as aspartate aminotransferase (AST) >2 x the upper limit of normal (ULN) and/or alanine aminotransferase (ALT) >2 x ULN and /or serum total bilirubin >2.0 mg/dL

19) History or positive serologic evidence of current infectious liver disease including anti-HAV (IgM), HbsAg, or anti-HCV. Subjects with isolated positive anti-HBs may be included

20) Serum creatinine (Scr) ≥1.5 mg/dL (132.6 µmol/L) for males and ≥1.4 mg/dL (123.8 µmol/L) for females

21) Creatine kinase (CK) ≥3 x ULN

22) Anaemia, of any aetiology defined as haemoglobin ≤12.0 g/dL (120 g/L) for men and haemoglobin ≤11.0 g/dL (110 g/L) for women

23) Absolute lymphocyte count (ALC) less than 1000 cells/mm^3

24) Subjects with abnormal thyroid stimulating hormone (TSH) values at screening were to be further evaluated by free thyroxine (T4). Subjects with an abnormal free T4 were to be excluded

25) Subjects who had contraindications to therapy as outlined in the saxagliptin Investigator Brochure or metformin package insert

26) History of administration of any antihyperglycaemic therapy for more than 3 consecutive days or a total of 7 non-consecutive days during the 8 weeks prior to screening. The exceptions were women who had received treatment for gestational diabetes during their pregnancy and who were no longer receiving therapy or subjects who during a hospitalization received a short course of insulin treatment.

27) Use of any other antihyperglycaemic medication (other than open-label rescue metformin) after enrolment (except insulin therapy during a hospitalization for other causes)

28) Treatment with potent systemic cytochrome P450 3A4 (CYP 3A4) inhibitors or inducers. Also, subjects should not have consumed grapefruit or grapefruit juice one hour before or one hour after taking the study medication during this study.

29) Prior treatment with saxagliptin or any DPP-IV inhibitor

30) Platelet count less than 145,000 cells/µL

Subjects who met the following criteria were eligible for randomization into the short-term treatment period (target population HbA1c ≥7.0 % and ≤10.0 % at screening):

1) No clinically significant abnormalities in any pre-randomization laboratory analyses or electrocardiogram (ECG), which in the investigator's opinion would preclude randomization

2) Good compliance with study medication (≥80% and ≤120%) during the lead-in period. (This criterion did not apply to subjects enrolled directly into open-label treatment cohort.)

In Study CV181011, an algorithm for determining discontinuation due to lymphopenia and thrombocytopenia was used.

Efficacy endpoints

The primary efficacy endpoint in all Core Phase III studies was change from baseline in HbA1c at the 24 week primary assessment point (or the last pre-rescue post-baseline measurement prior to Week 24, if no Week 24 assessment was available).

Secondary endpoints shared across all Core Phase III studies were:

- Change from baseline in fasting plasma glucose (FPG). This was stated to correlate with glycaemic control and with chronic complications of diabetes.
- Therapeutic glycaemic response (the proportion of subjects achieving HbA1c <7.0%).
- Change from baseline in AUC from 0-180 minutes for postprandial serum glucose (PPG) response to an OGTT (including frequently sampled OGTT in CV181011).

The OGTT was generally performed at enrolment, randomisation (Day 1), after dosing and at study Week 24 for the ST period.

Across all Core Phase III studies, additional endpoints regarding hormonal parameters (insulin, glucagon, C-peptide concentrations), metabolic parameters (β-cell function [estimated using HOMA-2B]; insulin resistance [estimated using the homeostasis model assessment for insulin resistance (HOMA2-IR)]; lipid subsets; BMI; waist circumference and related measures) and inflammatory biomarkers (C-reactive protein [CRP], plasminogen activator inhibitor [PAI]-1, fibrinogen, interleukin [IL]-6) were examined.

HOMA-2B is an estimate of β cell function, however the gold standard (hyperglycaemic clamp test) was used in CV181041.

The proportion of subjects requiring rescue for failing to achieve pre-specified glycaemic targets or discontinuing for lack of efficacy within the ST period was also emphasised. Another endpoint was described in the sponsor's *Summary of Clinical Efficacy*, namely, mean duration of exposure to study medicine before rescue.

Shared statistical methods

Except where stated, all analyses on efficacy parameters used last observation carried forward (LOCF**)** methodology. Thus, where no Week X measurement was available (because the subject was rescued or discontinued, for example), the last available pre-rescue post-baseline measurement was used. Data collected after rescue for unacceptable glycaemic control and initiation of supplemental oral anti-diabetic therapy was not utilised in any of the efficacy analyses.

Additionally, observed values analyses were presented, and repeated measures analyses were conducted for some endpoints. This latter approach attempts to find a compromise between LOCF and 'observed values' approaches.

All studies were designed as superiority studies, in keeping with the general approach of comparison with placebo.

Primary analyses were based upon subjects in the Randomised Subjects Dataset (all randomised subjects who took ≥1 dose of double-blind treatment) – or the open-label cohort from CV181011 –

who had a baseline and at least one subsequent HbA1c assessment. Subjects were analysed according to randomisation group rather than treatment received. Sensitivity analyses were conducted using other datasets, for example completer analyses (subjects with baseline and Week 24 HbA1c results, omitting LOCF methodology). In general, these sensitivity analyses supported the primary analyses.

In each study, the primary efficacy analysis was an analysis of co-variance (ANCOVA) model of the primary endpoint, with treatment group as a fixed effect and baseline value as a covariate in the model. Treatment-by-baseline interaction was tested at the 0.1 level of significance. Generally, secondary endpoints were also analysed using an ANCOVA model. A two-sided Fisher's Exact test was used in analysis of proportions (proportion of subjects achieving HbA1c ≤7% at Week 24, for example).

Results of mean changes (or mean percent changes) from baseline were generally reported as adjusted means (least square means) using ANCOVA methodology.

Statistical testing of primary and secondary endpoints generally proceeded in a sequential manner, to control type I error rate within each treatment group at the 0.05 level.

The long-term (LT) efficacy analysis included the initial 24 weeks of study. Consequently, subjects who did not enter the LT treatment period were included in the analyses. Time to study discontinuation for lack of glycaemic control or rescue for failing to achieve glycaemic targets during the short-term plus long-term (ST+LT) period was summarised using Kaplan-Meier estimates of cumulative proportion.

Overall, the statistical methodology used by the sponsor was good, and did not detract from the validity of study results.

Study CV181008 – supportive, Phase II, dose-finding

This was a multicentre, placebo-controlled, double-blind, randomised study in drug-naïve T2DM subjects with inadequate glycaemic control (HbA1c 6.8-9.7%). Subjects <35 years of age were to be anti-GAD antibody negative. The study was conducted from May 2003 to May 2004 across 152 sites in the USA.

423 subjects were randomised (338 in a '0-40 mg' cohort, with 47-67 subjects per arm, and 85 in a '0,100 mg' cohort, with 41 and 44 subjects per arm).

There was a 2 week dietary and placebo lead-in period. In the 0-40 mg cohort, subjects were randomised to one of 6 treatment arms: placebo (n=67) or 2.5 mg (n=55)**,** 5 mg (n=47)**,** 10 mg (n=63)**,** 20 mg (n=54) or 40 mg (n=52) of saxagliptin (capsule formulation) for 12 weeks. In the 0,100 mg cohort (organised after a protocol amendment), subjects were randomised to placebo or 100 mg for 6 weeks. Medication was taken once daily 30-60 minutes before breakfast. After treatment there was a 4 week follow-up period.

Dose titration was not permitted; subjects with inadequate glycaemic control (at Weeks 4, 6, 8 and 10) were discontinued from study medication and entered a 4 week follow-up period on metformin.

In the 0-40 mg cohort, mean age was 54 years; 86% of subjects were <65 years of age. A total of 58% of subjects were male; 87% were White; mean BMI was 30.6 kg/m^2. Median duration of T2DM was 1.1 years (range, 0-23). Mean baseline HbA1c was 7.9% (range, 6.2-12.2%, with 3 subjects outside the HbA1c inclusion criteria). The 0,100 mg cohort had broadly similar characteristics (mean HbA1c, 7.7%), although median T2DM duration was 0.3 years.

The primary efficacy endpoint was "change in Glycosylated haemoglobin HbA1c (Hb_{A1c}) from baseline to Week 12" (LOCF); the primary analysis aimed to show a trend in lowering of HbA1c with dose. Other efficacy variables broadly overlapped with those described earlier, although

fructosamine levels were also assayed. An additional efficacy endpoint in this study was change from baseline after 6 and 12 weeks in postprandial response to a liquid meal tolerance test (MTT).

In the 0-40 mg cohort, similar reductions in HbA1c were achieved with all doses; the test for log-linear trend across treatment groups did not show a statistically significant dose response relationship after 12 weeks. There was a statistically significant reduction from baseline to Week 12 in all active treatment groups compared with placebo ($p<0.012$).

The sponsor stated that "the largest effect on glycaemic control was generally seen at a dose of 5 mg or 10 mg, with no apparent increase in efficacy at doses higher than 10 mg in the CV181008 0-40 mg cohort". The 100 mg arm had an adjusted mean change in HbA1c of -1.09%, the highest of all arms. Other efficacy results generally paralleled these findings.

While there was no HbA1c dose response, there was a dose response for mean change from baseline in DPP4 activity, before and after MTT.

Active GLP-1 was measured during the MTT (but not at baseline). Most notably at 60 minutes, active GLP-1 was higher in active treatment arms (8.4-13.3 pmol/L) than in placebo arms (5.5-7.5 pmol/L). There was no clear-cut dose effect.

Pivotal study in monotherapy - Study CV181011 – 24 weeks

This was a multicentre, randomized, double-blind, placebo-controlled, Phase III trial to evaluate the efficacy and safety of saxagliptin as monotherapy in subjects with type 2 diabetes who have inadequate glycaemic control with diet and exercise.

This was the first of two Phase III saxagliptin monotherapy studies in drug-naïve subjects. It was conducted from July 2005 to August 2006. There were 142 investigators at 137 sites (84 in the US, 6 in Puerto Rico, 29 in Canada, 8 in Mexico, 7 in Australia, and 3 in Taiwan). An additional objective was to explore relationships between drug exposure and efficacy; this study was used in the sponsor's exposure modelling analysis.

The study was described as double-blind in the ST period. Blinding methodology was adequate, with (a) dose forms of saxagliptin matching one another and matching placebo tablets; and (b) HbA1c and other relevant laboratory data masked on laboratory reports to investigators during the ST period (but not the LT period).

Study population

A total of 401 subjects were randomised and treated with double-blind therapy (102 in the 2.5 mg group; 106 in the 5 mg; 98 in the 10 mg; and 95 in the placebo arm). A total of 265 subjects completed 24 weeks of treatment. Discontinuations (including rescues) were seen in 28.4% (2.5 mg), 35.8% (5 mg), 29.6% (10 mg) and 42.1% (placebo). Commonly, discontinuation was due to lack of efficacy (14.7%, 19.8%, 14.3% and 26.3% respectively). No subjects in the placebo arm failed to complete ST treatment because of AEs vs 2.9-4.1% in the saxagliptin arms.

Rescued subjects and ~85% of subjects who completed the ST period continued in the study's LT period. 336 subjects entered the LT period.

Average age was close to 53 years in all groups; range was 18-77 years, 46-57% of subjects in each group were male, 81-88% of subjects in each group were White and 76-79% of subjects came from North America, and almost all the others came from Latin America with 5-6% from Asia-Pacific. Despite randomisation, mean weight at baseline did vary across groups: 92.1 kg in the saxagliptin 2.5 mg group, 90.9 kg in the 5 mg group, 89.3 kg in the 10 mg group and 86.6 kg in the placebo group. The difference was more pronounced when medians were considered: 91.8 kg, 89.6 kg, 89.0 kg and 83.9 kg respectively. This was reflected in mean BMI at baseline: 31.9, 32.2, 31.7 and 30.9 kg/m^2 respectively.

Mean T2DM duration was 2.6 years across all randomised subjects; this value was inflated by some subjects with a long duration of T2DM (durations >10 years were recorded in 3.1-5.9% of subjects across arms); median duration was 1.3 years. Mean baseline HbA1c values were 7.9% (2.5 mg group), 8.0% (5 mg), 7.8% (10 mg) and 7.9% (placebo). Ranges were similar across groups (6.1-11.2%). Fasting plasma glucose was marginally lower in the placebo group (8.8 mmol/L) than saxagliptin groups (8.9-9.3 mmol/L), reflecting a high proportion of placebo arm subjects with FPG <6.9 mmol/L (13.7% vs 8.2-8.8%). Baseline insulin AUC was also higher in the placebo arm (mean, 8345 μU.min/mL) than in the saxagliptin arms (7235-7361 μU.min/mL).

Subjects commonly reported a history of: obesity (49.6%); overweight (62.6%); hypertension (47.6%); hypercholesterolaemia (43.4%); dyslipidaemia (24.7%); hypertriglyceridaemia (23.9%); GI surgery (10.7%); and diabetic neuropathy (10.2%). Previous MI was reported in 3.2%; there was a history of stable angina in 2.5%.

Only 2.5% of subjects had received any previous anti-hyperglycaemic therapy (9/401 had received oral medication and 1/401 had received insulin). Presumably, after diagnosis, subjects had been controlled with diet and exercise interventions. No information was provided about these issues.

Open label cohort**.** A total of 66 subjects with HbA1c 10-12% received ≥1 dose of open label saxagliptin. In 41 (62.1%), ST therapy was not completed, commonly because of lack of efficacy (in 30 subjects; 45.5%). 32 subjects were rescued for lack of glycaemic control during the ST period. 54 entered the LT period. Mean age in the 66 subjects was 49 (range, 29-67) years; 48.5% were male; 92% were White; 80% were from North America; mean weight was 91.4 kg; mean BMI was 31.7 kg/m^2. Mean duration of T2DM was 3.1 (median, 2.3; range, 0-18.3) years. Mean baseline HbA1c was 10.7% (range, 9.2-12.9%). The pattern of medical conditions at baseline was broadly similar to that in the randomised cohort.

Interventions

Subjects entered a 2-week dietary, exercise and placebo pill lead-in period, in accordance with local dietary and exercise guidelines. Home glucose meters were provided.

There were two cohorts:

(a) main treatment cohort, including subjects with screening HbA1c 7.0-10.0%; these subjects were randomised (1:1:1:1; permuted blocks, stratified by site) to saxagliptin 2.5 mg, 5 mg, 10 mg or placebo; and

(b) open-label cohort, including subjects with screening HbA1c 10.0-12.0%; subjects received saxagliptin 10 mg. In the open-label cohort, there was no lead-in. The results refer to the main cohort unless otherwise specified.

Saxagliptin was supplied as 2.5 and 5 mg doses. Doses were taken every day prior to breakfast.

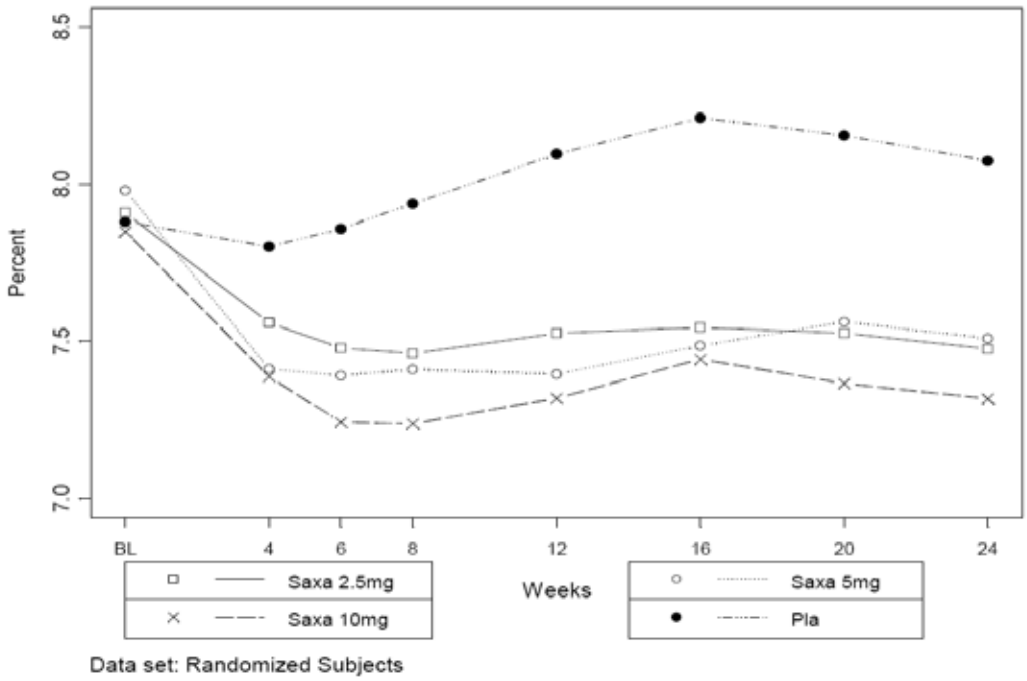
Subjects with lack of adequate glucose control during ST treatment were eligible for addition of open-label metformin as a rescue therapy. Such subjects were counted as early discontinuations for lack of efficacy.

Mean ST exposure to study drug was 134 days for placebo arm subjects and 143-147 days for saxagliptin patients. Compliance (80-120% of prescribed intake) was very good. In the open label cohort, mean exposure was 109 days.

Efficacy results

Using the LOCF methodology, there was a mean absolute reduction in HbA1c from baseline to Week 24 of 0.43% (2.5 mg), 0.46% (5 mg) and 0.54% (10 mg), and a mean increase in HbA1c in the placebo group of 0.19%. (Figure 2).

Figure 2: Study CV181011 – HbA1c (LOCF)



Whereas 23.9% of placebo arm subjects achieved HbA1c <7% by 24 weeks, 35% (2.5 mg), 37.9% (5 mg) and 41.1% (10 mg) of saxagliptin subjects reached this threshold.

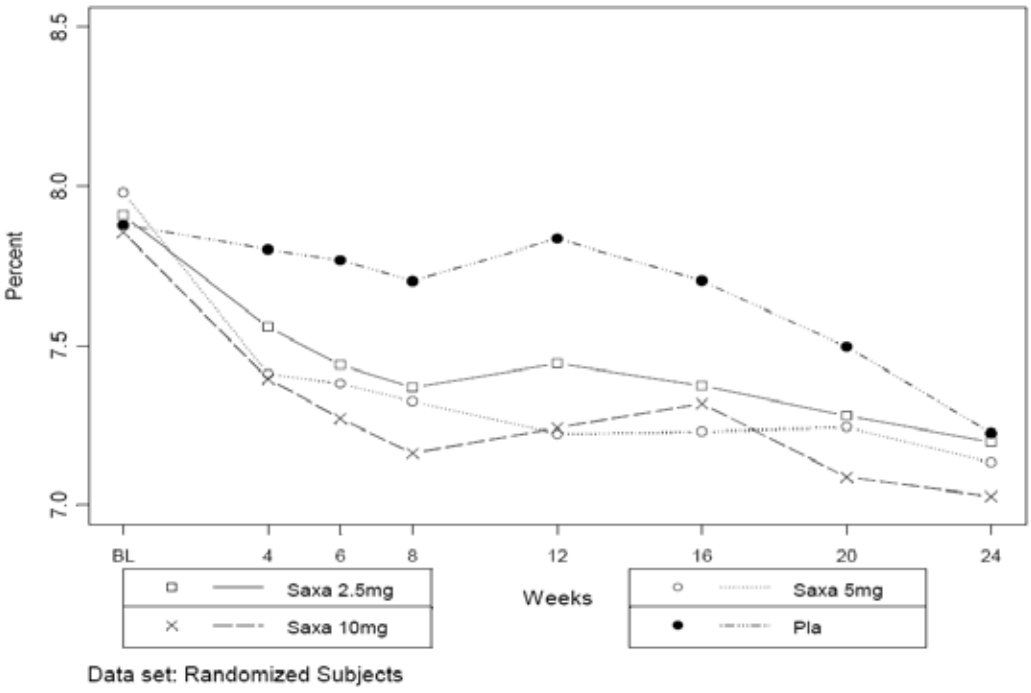
In an analysis of observed HbA1c values, adjusted mean change from baseline was -0.56% (2.5 mg), -0.57% (5 mg), -0.67% (10 mg) and -0.38% (placebo). (In this analysis, only saxagliptin 10 mg showed a statistically significant difference from placebo at Week 24; p=0.038.) For placebo, there was a considerable difference between LOCF analysis (+0.19%) and observed value analysis (-0.38%). The sponsor stated:

This difference most likely reflects the progressive selection of placebo-treated subjects with a decrease in HbA1c over time (that is, selection of placebo-treated subjects who were not discontinued or rescued for lack of glycaemic control).

Using observed values, the time-course of HbA1c change is shown in Figure 3. The contrast with LOCF methodology is most pronounced for the placebo arm, after Week 4, and most notably after Week 12. Subjects requiring rescue (that is, in whom study drug was inefficacious) would not be included in the 'observed values' analysis, as they were removed from ST study; remaining subjects would be more likely to demonstrate efficacy. Since the proportion of subjects requiring rescue was not random across arms, this introduces bias into the observed values analysis. In the observed values analysis, at Week 24, the 2.5 mg saxagliptin arm had 72 subjects (from an initial 102; 71%), the 5 mg arm had 71 (from 106; 67%), the 10 mg arm had 67 (from 98; 68%), but the placebo arm had 55 (from 95; 58%). The sponsor further notes:

This difference between LOCF and observed data is driven by missing values, with bias generated through a higher proportion of subjects in the placebo group than in the saxagliptin groups discontinued for lack of glycaemic control. An alternative method to account for missing data, repeated measure analysis using mixed model, was employed in a post-hoc manner, and also showed significant HbA1c lowering at 24 weeks for each of the saxagliptin treatment groups compared with placebo.

Figure 3: Study CV181011 – HbA1c (observed values)



Selected other endpoints are detailed below.

Postprandial insulin AUC changes from baseline at Week 24 (LOCF) were reported. The placebo arm had a higher baseline PPI AUC; nevertheless, adjusted changes from baseline were higher in the saxagliptin arms (1722-2430 µU.min/mL) than in the placebo arm (281 µU.min/mL). This supports the drug's mechanism of action, as inhibition of DPP4 allows an increase in active incretins that encourage insulin synthesis and release from β cells.

Point estimates of adjusted postprandial glucagon AUC changes from baseline at Week 24 (LOCF) favoured saxagliptin over placebo, but differences were less impressive (saxagliptin arms, -4615 to -5472 pg.min/mL vs placebo arm, -3575 pg.min/mL).

The proportion of subjects who discontinued for lack of glycaemic control or who were rescued for meeting pre-specified glycaemic criteria during the ST period was higher in the placebo group (26.3%) than in the saxagliptin arms (15.7% for 2.5 mg; 19.8% for 5 mg; 14.3% for 10 mg).

There was no apparent weight gain or BMI increase; mean change from baseline in body weight at Week 24 (LOCF) was -1.22 kg, -0.05 kg, -0.13 kg and -1.35 kg for the saxagliptin 2.5 mg, 5 mg and 10 mg arms and the placebo arm respectively. For BMI, corresponding figures were -0.43, -0.03, -0.05 and -0.49 kg/m^2. Thus, there was a hint that higher doses of saxagliptin were associated with increase in weight relative to placebo. Corresponding figures at Week 24 for mean change in waist circumference were 7.58 cm, 2.65 cm, 2.41 cm and 0.35 cm (that is, for saxagliptin there was an increase from baseline). It is difficult to reconcile the increase in waist circumference over 24 weeks with the slight decrease in weight (for example, for saxagliptin 2.5 mg arm: a loss of 1.22 kg in weight, but a gain of 7.58 cm in waist circumference), without invoking re-distribution of body fat or fluids.

Mean low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol values changed over the 24 week period: for LDL, mean percent change from baseline (LOCF) was -5.3% to 0.4% for saxagliptin arms (that is, ranging from a modest fall to essentially no change), and 5.3% for placebo (a modest increase). For HDL, the mean percent change from baseline (LOCF) was -0.5% to 3.5% for saxagliptin arms, and 5.3% for placebo.

In subgroup analyses for the primary endpoint, interactions of treatment with (1) baseline HbA1c category, (2) race and (3) gender were observed, such that there was greater HbA1c lowering in subjects with higher baseline HbA1c, in non-White subjects and in males. For saxagliptin 5 mg, in subjects with baseline HbA1c <8% the adjusted mean fall over 24 weeks (LOCF) was -0.30%, in subjects with baseline HbA1c 8-9% the fall was -0.57% and in subjects with HbA1c >9% the fall was -0.84% (vs a rise of 0.18%, 0.25% and 0.13% in the three placebo arm sub-groups, respectively). Differences for race were mainly a function of differences between White (n=77) and non-White (n=15) in the placebo arm (adjusted mean change from baseline, 0.02 and 1.06 respectively) – however the number of subjects in the non-White subgroup was small. For saxagliptin 5 mg, in males the adjusted mean fall over 24 weeks was 0.57%, vs 0.34% for females; for the placebo group, changes were +0.48% (a rise, in males) and -0.10% (a fall, in females). The number of elderly subjects was small.

Open-label cohort (10 mg)

Mean changes to 24 weeks (LOCF) in fasting HbA1c (-1.87%), FPG (1.8 mmol/L) and PPG AUC (609 mmol.min/L) were greater than in the double-blind cohort, probably due to the higher baseline HbA1c. At Week 24, 14.1% of the cohort had reached <7% HbA1c; 35.9% had reached <8%. By Week 24, 48.5% of subjects had discontinued for lack of glycaemic control and rescue for meeting pre-specified glycaemic criteria.

Pharmacodynamic results

DPP4 inhibition was monitored. At Week 24, mean change in DPP4 (measured at trough, 30 minutes before dosing) was -44.3% (2.5 mg), -55% (5 mg) and -63.6% (10 mg), vs -4.0% for placebo. At 210 minutes after dosing at Week 24, mean percent change in activity was -72% to -78% across saxagliptin arms (vs -4% for placebo). At 210 minutes after dosing on Day 1, mean percent change in activity was -70% to -76% across saxagliptin arms (vs 0% for placebo).

In an addendum to the sponsor's *Clinical Study Report* (*CSR*), analysis of GLP-1 and GIP was presented. The sponsor pointed out that results were based on the 38 subjects participating in the 'frequently sampled OGTT' (so that sample size within each arm was≤12, meaning the ability to draw conclusions was "extremely limited"). Total GLP-1 and total GIP were reported at test baseline and at 7 points to 3 hours after an OGTT, both at study baseline and at 24 weeks. After the OGTT at study baseline, total GLP-1 tended to peak at between 20-60 minutes in all arms; at Week 24 total GLP-1 was lower for saxagliptin arms (with no dose response) but also in the placebo arm. The pattern for intact GLP-1 was more variable, but suggested a decline in intact GLP-1 levels in both saxagliptin and placebo arms at Week 24 relative to study baseline. For total glucose-dependent insulinotropic polypeptide (GIP), at study baseline, the peak was at around 30-60 minutes; at Week 24, values had declined during this peak period in all saxagliptin arms and (perhaps to a lesser degree) in the placebo arm (this was also reflected in AUC analyses). Intact GIP tended to peak at 20-30 minutes, and generally increased by Week 24 in saxagliptin arms but not in the placebo arm. It is assumed that 'intact' incretins are those unaffected by enzymatic degradation. The mechanism of action would predict an increase in intact incretins after exposure to saxagliptin, but this was demonstrated only for GIP. This implicates GIP more than GLP-1 in the mechanism of action.

Study CV181011 – long-term follow-up (interim report)

An interim report for the ongoing long term (LT) phase of Study CV181011 was provided. For this, data were collected to 16 January 2008. (Total LT follow-up is planned to be 42 months; that is ST+LT is planned to be 48 months in total). While this is an interim report, results are important since treatment with oral hypoglycaemic agents is generally long-term.

The 336 subjects in the LT study had:

- (for 262 subjects) completed ST visits without meeting rescue criteria (such subjects remained on their double-blind randomised therapy, except placebo subjects who received placebo + double-blind metformin 500 mg), or
- (for 74 subjects) met rescue criteria (these subjects remained on their blinded randomised therapy but received open-label metformin 500 mg in addition).

Discontinuation from the ST+LT period has been seen in 57.8% (2.5 mg), 50.9% (5 mg), 46.9% (10 mg) and 58.9% (placebo). Main reasons include: withdrawing consent (20.6% / 17.9% / 12.2% / 20% respectively); lack of efficacy (16.7% / 14.2% / 13.3% / 17.9%); loss to follow-up (6.9% / 5.7% / 8.2% / 11.6%); and adverse events (7.8% / 7.6% / 7.1% / 3.2%).

The mean duration of exposure to study medication regardless of rescue was 66.2 weeks (2.5 mg), 67.7 weeks (5 mg), 73.5 weeks (10 mg) and 65.7 weeks (placebo). The mean duration of exposure prior to rescue was 51.6 weeks, 51.4 weeks, 52.1 weeks and 48.6 weeks respectively. The shorter exposure in the placebo group was attributed to more frequent rescue and discontinuation in this group. A total of 194 subjects received open-label metformin as rescue therapy; duration of exposure to this treatment was 38.7 weeks, 35 weeks, 37.1 weeks and 31.9 weeks respectively. In the open-label cohort, mean exposure to saxagliptin 10 mg (including rescue) was 54 weeks; prior to rescue mean exposure was 28 weeks; and in 44 rescued subjects mean exposure to metformin was 39 weeks.

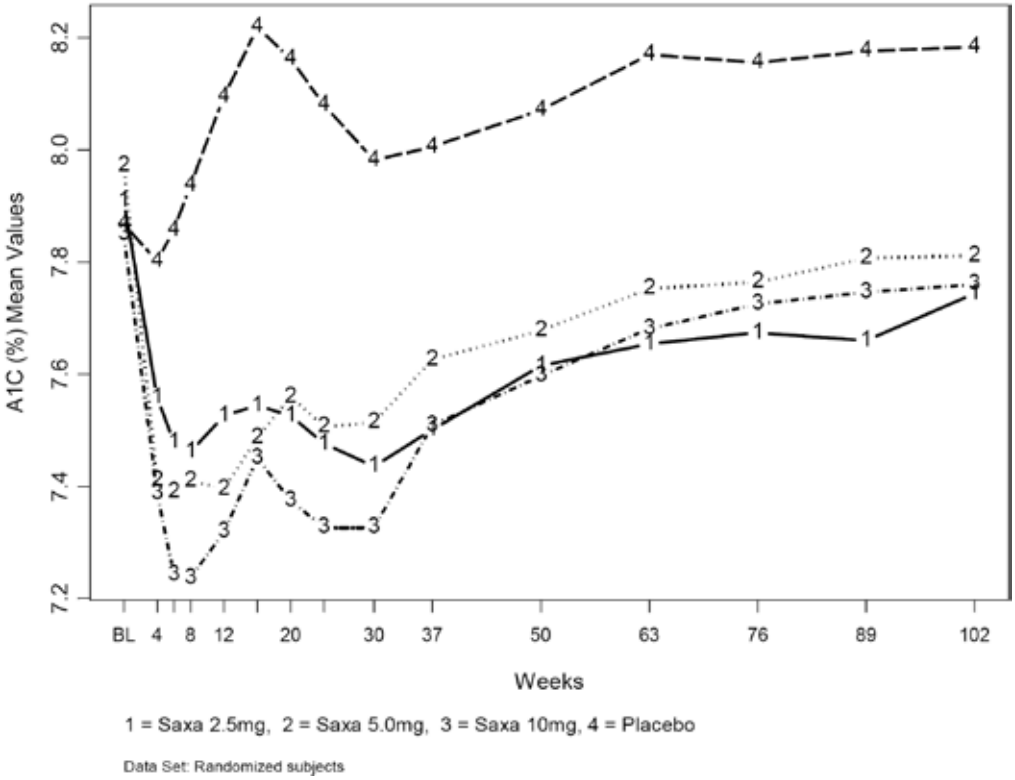
Blinded therapies could not be titrated during the LT period. Subjects (not previously rescued) with lack of glycaemic control in the LT period were eligible for addition of open-label metformin 500 mg. Many subjects (100/186) remaining in the study have received rescue medication. Open-label metformin could be titrated to 2000 mg/day to obtain glycaemic control. Lack of control after 12 weeks on maximum metformin therapy resulted in study discontinuation.

In the interim report, multiple efficacy and safety endpoints were assessed, but key endpoints were analogous to those used in the ST period. DPP4 activity was also assessed.

LOCF methodology was used to impute missing values where assessments were missing due to subject discontinuation or failure to obtain an assessment (except where lack of assessment was simply due to timing of study start, in which case subjects were excluded from analysis).

Results were reported for Week 50, Week 76 and Week 102. As can be seen in Figure 4, in the primary analysis there was a gradual return towards baseline HbA1c values in the three saxagliptin arms after Week 24; concurrently, there was a rise in HbA1c values above baseline in the control arm (which was, in the LT period, receiving metformin – although it may have taken some time for individual patients to receive a maximal dose). Adjusted mean change from baseline at Week 102 was 0.09% (2.5 mg), -0.14% (5 mg), -0.10% (10 mg) and +0.32% (placebo).

Figure 4: Study CV181011 (LT phase) – HbA1c change from baseline (LOCF)



For therapeutic glycaemic response (HbA1c <7%), there was an interesting pattern – percentages reaching this threshold in the saxagliptin arms fell consistently from Week 24 through to Week 102, while in the placebo arm the addition of metformin resulted in an increased percentage at Week 50 relative to Week 24. In the saxagliptin 5 mg arm, at Week 24 the percentage reaching the 7% HbA1c threshold was 37.9%; this fell to 35.9% at Week 50, 32% at Week 76 and 27% at Week 102 (LOCF analysis). In the placebo arm, values were 23.9%, 29.3%, 29.3% and 26.2% respectively. Thus, at Week 102 the proportion of subjects with HbA1c <7% was similar for those receiving 102 weeks of saxagliptin and those receiving no medication for 24 weeks then metformin for 76 weeks.

Multiple other endpoints were examined, with results consistent with those mentioned above. For example, in the saxagliptin 5 mg arm the percentage of subjects reaching the 6.5% HbA1c threshold was 22.3% at Week 24, 19.4% at Week 50, 16.5% at Week 76 and 15.7% at Week 102; values for the placebo arm were 14.1%, 14.1%, 15.2% and 19% respectively (LOCF).

Study discontinuation for lack of glycaemic control and rescue for meeting pre-specified glycaemic criteria was of interest. The difference between placebo and saxagliptin arms disappeared around Week 50. The criteria for rescue changed from FPG threshold in the ST period to HbA1c thresholds (changing at Weeks 30, 63 and 89) in the LT period. The sponsor interpreted this as showing that "saxagliptin appeared to delay the need for rescue".

Physical measurements were included as efficacy endpoints. Mean changes in body weight from baseline to Week 102 (LOCF) were -0.6 kg (2.5 mg group), 0.3 kg (5 mg), 0.4 kg (10 mg) and -1.1 kg (placebo). There was no clear effect of treatment on fasting lipid parameters.

DPP4 activity was assayed at trough and at 180 minutes of the OGTT at Week 50, and changes were similar to those seen at Week 24.

In the open-label cohort, decreases in HbA1c seen at Week 24 were sustained until Week 76 (the last week with sufficient numbers for analysis). Mean change from baseline (LOCF) in HbA1c to Week 76 was -1.59%. The proportions of subjects who discontinued for lack of glycaemic control

or who were rescued for meeting pre-specified criteria during the ST+LT period were 45.5% at Week 24, 65.2% at Week 50 and 68.2% at Week 76.

Study CV181038 – pivotal, monotherapy

This was a multicentre, randomised, double-blind, placebo-controlled, Phase III trial to evaluate the efficacy and safety of saxagliptin as monotherapy with titration in subjects with type 2 diabetes who have inadequate glycaemic control with diet and exercise. It was the second of two Phase III saxagliptin monotherapy studies in drug-naïve subjects. It was conducted from June 2006 to November 2007. There were 72 investigators at 72 sites (49 in the US, 9 in Russia, 8 in India and 6 in Taiwan). The study was double-blind and double-dummy in the ST period. Blinding methodology was adequate, as per CV181011.

A total of 365 subjects were randomised and treated (74 in the 2.5 mg group; 74 in the 5 mg once daily, in the morning (QAM) group; 71 in the 2.5 / 5 mg group; 72 in the 5 mg once daily, in the evening (QPM) group; and 74 in the placebo group). A total of 272 subjects completed 24 weeks of treatment. Discontinuations (including rescues) were seen in 25.7% (2.5 mg), 23% (5 mg QAM), 26.8% (2.5/5 mg), 23.6% (5 mg QPM) and 28.4% (placebo). Commonly, discontinuation was due to lack of efficacy (10.8%, 12.2%, 12.7%, 9.7% and 16.2% respectively – figures slightly lower than in Study CV181011). One subject in the placebo arm and 3 across the saxagliptin arms failed to complete ST treatment because of AEs. 56/71 subjects (78.9%) in the 2.5/5 mg saxagliptin arm were up-titrated to 5 mg in the ST period, most commonly at Week 4. A total of 311 subjects (85%) entered the LT period.

Average age was close to 55 years in all groups; range was 21-76 years. The 2.5 mg group had only 33.8% males (vs close to half for all other arms). Around 66-76% of subjects in each group were White; 19-27% were Asian. Around 45% of subjects were from North America, 34% from Europe (Russia) and 21% from Asia (India and Taiwan). Mean weight at baseline varied from 83.8% (2.5 mg) to 86.5% (5 mg QAM), with the placebo arm at 85.4 kg. BMI means ranged from 29.6 kg/m^2 (5 mg QPM) to 31.1 kg/m^2 (placebo).

The mean duration of T2DM was 1.7 years across all randomised subjects (that is, shorter than in Study CV181011), with duration ≥10 years in 0-4.2% of subjects; median duration was 0.4-0.6 years across arms. Mean baseline HbA1c values were 7.9-8.0% in the saxagliptin arms, but 7.8% in the placebo group; likewise, median HbA1c values were 7.8-7.9% (saxagliptin arms) vs 7.6% (placebo). Reflecting this slight difference, 52.1-54.1% of saxagliptin subjects but 63.5% of placebo subjects had a baseline HbA1c <8.0%. HbA1c ranges were similar across arms (5.3-10.6%). The placebo arm had fasting plasma glucose levels similar to those in saxagliptin arms.

Subjects commonly reported a history of: overweight (51.5%); hypertension (58.1%); hypercholesterolaemia (32.6%); mixed dyslipidaemia (17.5%); hypertriglyceridaemia (17%); coronary artery disease (13.4%) and stable angina (10.7%). AMI was reported in 5.2%. 5.2% of subjects had received any previous anti-hyperglycaemic therapy (mainly oral medication).

Subjects entered a 2-week dietary, exercise and placebo pill lead-in period. Then, subjects were randomised into one of five arms. The four saxagliptin arms in this study were: 2.5 mg QAM; 5 mg QAM; 5 mg QPM (dose taken prior to evening meal); and 2.5 mg with possible titration to 5 mg QAM ("2.5 / 5 mg"). The control arm received placebo. Blinded study medication was taken orally every day prior to the morning and / or evening meal.

Titration criteria in the 2.5 / 5 mg arm are shown in Figure 5.

Figure 5: Titration criteria in Study CV181038

Visit	Mean Fasting Plasma Glucose (MFPG)[a]	Mean Fasting Whole Blood Glucose (MFWBG)[a]
Week 4	≥ 150 mg/dL (8.3 mmol/L)	≥ 140 mg/dL (7.7 mmol/L)
Week 8	≥ 140 mg/dL (7.7 mmol/L) and ≤ 220 mg/dL (12.2 mmol/L)	≥ 131 mg/dL (7.2 mmol/L) and ≤ 203 mg/dL (11.3 mmol/L)
Weeks 12 and 24	≥ 126 mg/dL (7.0 mmol/L) and ≤ 200 mg/dL (11.1 mmol/L)	≥ 118 mg/dL (6.5 mmol/L) and ≤ 185 mg/dL (10.3 mmol/L)

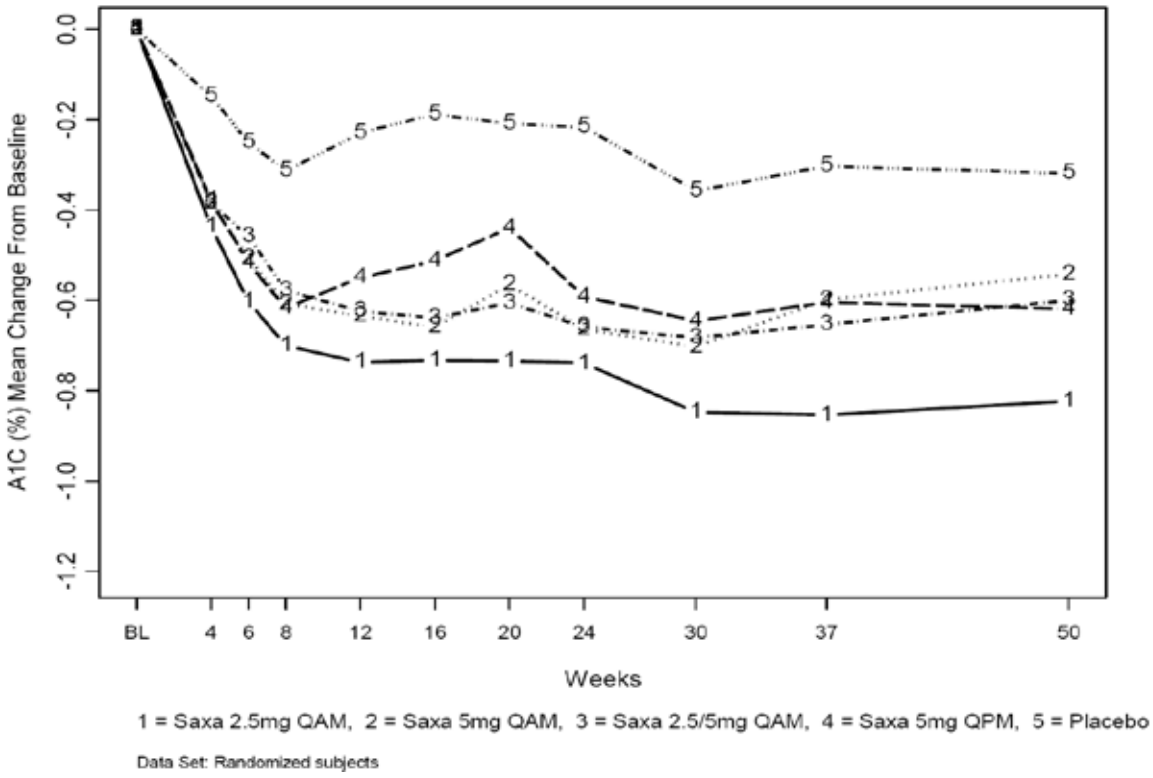
Thus, titration occurred (if at all) at different time points for different subjects, so this group must be considered heterogeneous. Subjects in this arm were also eligible for titration to 10 mg at the 24 week time point, prior to entering the study's LT period. Calculation of mean fasting glucose was based on fingerstick data from subject self-blood glucose monitoring for at least 3 of the 5 days preceding the visit.

Mean exposure to double-blind therapy was 141-148 days across saxagliptin arms and 143 days for placebo. Treatment compliance (80-120% of expected intake) was very high. 50 subjects were excluded from analyses involving OGTT as they ingested more than the protocol-specified 75 grams of glucose.

Efficacy results

Analysis of the saxagliptin 5 mg QPM arm was included with secondary endpoints. Saxagliptin arms at Week 24 (LOCF) had mean HbA1c 0.35-0.45% lower than placebo: the placebo arm's mean HbA1c value had fallen by 0.26% from baseline (from 7.79% to 7.57%), while in the saxagliptin arms the mean HbA1c value had fallen by 0.61% to 0.71%. The differences relative to placebo were statistically significant ($p \leq 0.0157$). The 5 mg arm (QAM) mean HbA1c value fell by 0.66% (0.40% relative to placebo). Figure 6 shows mean changes from baseline, including ST data.

Figure 6: Summary of Clinical Efficacy – HbA1c mean changes from baseline (LOCF) during ST+LT treatment – CV181038



The fall in HbA1c in the placebo group to Week 8 was not well explained. The adjusted change of -0.26% in the placebo group was larger than that seen in Study CV181011. The *CSR* invoked adherence to exercise and dietary intervention as reasons for this difference. There was no effort to quantify adherence to these variables. Similar results were achieved for FPG at 24 weeks (LOCF) (although the 5 mg QPM arm failed to achieve a statistically significant fall relative to placebo).

For proportion of subjects achieving therapeutic glycaemic response (HbA1c <7%), values were 35.8% (2.5 mg), 44.9% (5 mg QAM), 43.5% (2.5/5 mg), 38.6% (5 mg QPM) and 35.3% (placebo); there was no statistically significant difference between any saxagliptin arm and placebo for this variable. In explanation the sponsor noted: a slightly lower baseline median HbA1c in the placebo group; a higher percentage of placebo subjects relative to saxagliptin subjects with baseline HbA1c <7%; and the effects of lifestyle interventions.

In post hoc analysis adjusted for baseline HbA1c (slightly lower in the placebo group), there was a slight increase in the difference from placebo (for example, for 5 mg QAM, from a 9.6% difference noted above to a 13.5% difference). In subgroup analysis, no statistically significant interactions with treatment were found, although there was a trend in saxagliptin and placebo arms for a larger treatment effect in subjects with higher baseline HbA1c values.

Postprandial insulin AUC changes from baseline at Week 24 (LOCF) were reported. In the placebo group there was a decrease (from 9037 to 8006 µU.min/mL; the adjusted change was -947 µU.min/mL), while in all saxagliptin groups but the 5 mg QPM group there was an increase in postprandial insulin AUC (range: -172 to 2334 µU.min/mL). Point estimates of adjusted postprandial glucagon AUC changes from baseline at Week 24 (LOCF) revealed a decrease in the saxagliptin groups (range: -171 to -1170 pg.min/mL) but also a decrease in the placebo arm (from 11746 to 11623 pg.min/mL; the adjusted change was -291 pg.min/mL). The proportion of subjects who discontinued for lack of glycaemic control or who were rescued for meeting pre-specified glycaemic criteria during the ST period was 12.2% (2.5 mg), 13.5% (5 mg QAM), 14.1% (2.5/5 mg), 11.1% (5 mg QPM) and 16.2% (placebo).

There were reductions in mean body weight, BMI and waist circumference across all treatment groups. Mean change from baseline in BMI at Week 24 (LOCF) was -1 kg/m^2 (2.5 mg), -0.3 kg/m^2 (5 mg QAM), -0.3 kg/m^2 (2.5/5 mg), -0.1 kg/m^2 (5 mg QPM) and -0.5 kg/m^2 (placebo). Mean change from baseline in waist circumference was -0.7, -2.8, -2.1, -1.0 and -0.9 cm respectively.

Changes in lipid parameters were slight, for example, LDL percent change from baseline was -6.5% to 0.8% across saxagliptin arms and +4.7% for placebo, while HDL percent change from baseline was -2.4% to 2.1% for saxagliptin and +3.8% for placebo.

Study CV181038 – long-term follow-up

The interim study report for the ST+LT period of Study CV181038 was provided. The study is ongoing; for this report the data cut-off was 30 January 2008. Subjects who completed the ST period and subjects who met rescue criteria were eligible to enter the double-blind LT treatment period (12 months). Subjects who completed all visits and did not meet hyperglycaemia discontinuation (rescue) criteria in the ST period were allowed to titrate the dose of saxagliptin to 10 mg in the LT period. Subjects who received placebo in the ST period and were not rescued, received placebo and blinded metformin 500 mg in the LT period. Titration of this blinded metformin was not allowed. Subjects who met hyperglycaemia discontinuation (rescue) criteria during the ST period remained on the same randomized dose and treatment assigned in the ST period throughout the LT period, but received open-label metformin which could be titrated at the investigator's discretion to a maximum of 2000 mg/day, in addition to blinded study medication. Subjects with lack of adequate glycaemic control during the LT period were eligible for rescue from continued hyperglycaemia based on HbA1c.

Of 311 subjects entering the LT period, 270 were participating at the cut-off date (213 on saxagliptin; 57 placebo). Only about half of treated subjects contributed data to analysis of efficacy at Week 50 (including LOCF), as some subjects had not reached Week 50 by the cut-off date. Therefore, only key findings will be outline below. The 37 week time point had complete data; median exposure to study drug in all arms was ~37 weeks. Median exposure to the starting dose of saxagliptin was 23.8-25.4 weeks (excluding the 2.5/5 mg group).

Frequency of discontinuations from the study over the ST+LT period was 35.1% (2.5 mg), 16.2% (5 mg QAM), 32.4% (2.5/5 mg), 23.6% (5 mg QPM) and 23.0% (placebo). The first scheduled OGTT in the LT period was at Week 76, and too few subjects had reached this visit by the data cut-off date to permit analysis. During the LT period, 76.8% of 5 mg QAM subjects were titrated to 10 mg (making generalisability of results problematic). There was no additional reduction in HbA1c with such up-titration (a small effect was seen with up-titration in two other saxagliptin arms).

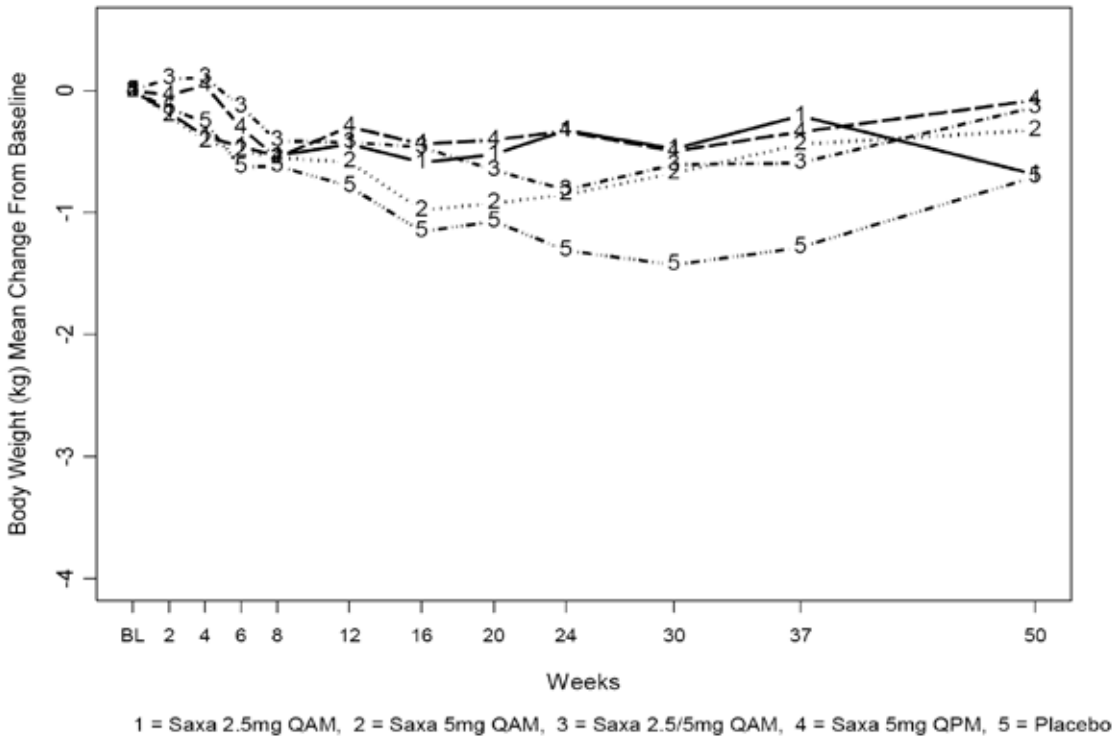
At Week 50 (LOCF), adjusted mean change from baseline in HbA1c was -0.81% (2.5 mg; n=11 observed; n=35 LOCF), -0.54% (5 mg QAM; n=12 observed; n=31 LOCF), -0.60% (2.5/5 mg; n=12 observed; n=36 LOCF), -0.60% (5 mg QPM; n=11 observed; n=32 LOCF) and -0.34% (placebo; n=12 observed; n=37 LOCF).

At Week 50 (LOCF), the proportion of subjects achieving HbA1c <7% (regardless of baseline value) ranged from 29-47.2% in the saxagliptin arms, and was 35.1% in the placebo arm (this level was attributed by the sponsor to addition of metformin and due to baseline distribution of HbA1c).

At Week 37, the proportion of subjects rescued or discontinued for lack of efficacy was 28.4% in the placebo group, vs 20.3% (2.5 mg), 17.6% (5 mg QAM), 22.5% (2.5/5 mg) and 18.1% (5 mg QPM).

Change in body weight over time (LOCF) showed an interesting trend, illustrated in Figure 7 (Week 50 results can be discounted because of incomplete data).

Figure 7: Study CV181038 (LT phase) – weight change from baseline (LOCF)



Study CV181014 – pivotal, add-on to existing metformin

This was a multicentre, randomised, double-blind, placebo-controlled, Phase III trial to evaluate the efficacy and safety of saxagliptin in combination with metformin in subjects with type 2 diabetes who have inadequate glycaemic control on metformin alone. It involved 155 investigators at 152 sites (92 USA; 23 Canada; 9 Mexico; 8 Argentina; 7 Brazil; 5 Puerto Rico; 4 Australia; 2 Taiwan; 2 Chile).

Inclusion and exclusion criteria were as previously stated except that subjects were not treatment naïve: they were on a stable dose of metformin in the range 1500-2550 mg/day for at least 8 weeks prior to screening. This difference was reflected in some exclusion criteria (for example, subjects were to have no contraindications for the rescue therapy used in this study). A total of 787 subjects entered lead-in; 743 subjects were randomised and treated; 543 completed 24 weeks of treatment. More placebo subjects discontinued (22.7-25.1% saxagliptin vs 37.4% placebo), commonly due to lack of efficacy. Of treated subjects, 50.7% were male (43.2% in the 2.5 mg group; 52.5-53.9% in other groups) and 81.6% were White. Mean age was 54.6 (range 20-77) years and 15.7% of subjects were ≥65 years. Mean body weight was 87 kg (86.0 kg in the 2.5 mg group; 87.1-87.8 kg in other groups); mean BMI was 31.4 kg/m^2 (similar across groups).

Baseline disease characteristics were similar across groups: mean duration of T2DM was 6.5 (median 5.4) years. About 24.5% of subjects had had T2DM for <3 years, 21.3% for 2-5 years and 54.2% for >5 years. Mean HbA1c was 8.0% (range 6.1-12.0%). While median metformin dose differed between saxagliptin arms (all 2000 mg) and placebo arm (1500 mg), mean dose was similar across arms suggesting no great disparity in this variable. Around 46.4-49.7% of saxagliptin subjects were on a dose <2000 mg (1500 mg most typically) vs 53.1% of placebo subjects. There was a history of overweight (64.5%), hypertension (59.1%), obesity (53.2%), hypercholesterolaemia (44.2%), dyslipidaemia (32.3%), hypertriglyceridaemia (28.8%), diabetic neuropathy (13.6%) and microalbuminuria (11.2%).

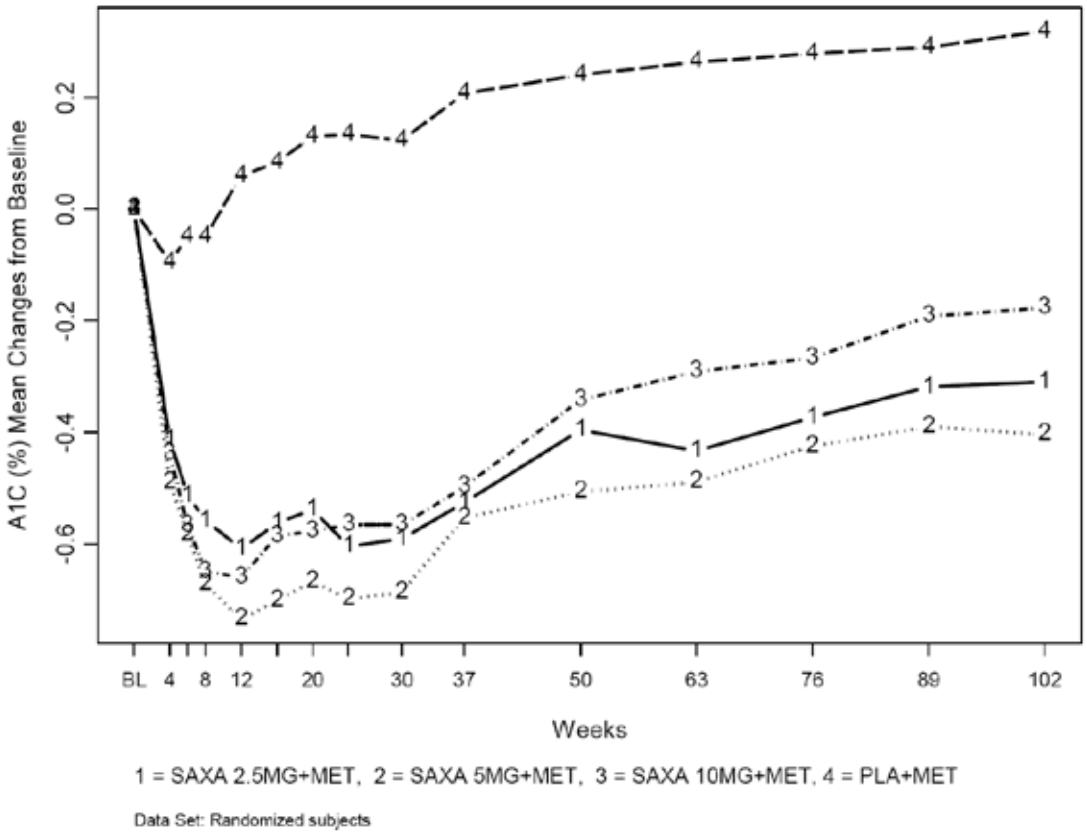
Subjects were randomised 1:1:1:1 to receive: saxagliptin 2.5 mg; saxagliptin 5 mg; saxagliptin 10 mg; or placebo (PLAC). Subjects continued to receive their current open-label dose of metformin. Neither saxagliptin (SAX) nor metformin (MET) could be titrated. Subjects with inadequate glycaemic control were eligible for addition of open-label pioglitazone 15 mg (titratable in 15 mg increments every 12 weeks to 30-45 mg/day maximum depending on country) as rescue therapy. A double-blind, double-dummy methodology was used – although metformin was open-label.

Primary comparisons (between each SAX+MET group and the PLAC+MET group) were at the 0.019 significance level (using Dunnett's adjustment) to control Type I error at 0.05.

Efficacy results

At Week 24 (LOCF), the adjusted mean change from baseline in HbA1c was -0.59% (2.5 mg), -0.69% (5 mg), -0.58% (10 mg) and +0.13% (placebo). Each comparison with placebo was statistically significant (p<0.0001). Change over time, relative to baseline, is shown in Figure 8.

Figure 8: Summary of Clinical Efficacy – HbA1c mean changes from baseline (LOCF) during ST+LT treatment – CV181014



Numerically greater HbA1c reductions were seen in the subgroup with baseline HbA1c ≥9% (for 2.5 mg and 5 mg groups though not for the 10 mg group). No statistically significant interactions with subgroups based on other parameters were observed. Adjusted mean change in FPG was -0.79 mmol/L (2.5 mg), -1.21 mmol/L (5 mg), -1.13 mmol/L (10 mg) and +0.1 mmol/L (placebo).

The proportion of subjects achieving HbA1c <7% was 37.1% (2.5 mg), 43.5% (5 mg), 44.4% (10 mg) and 16.6% (placebo). A similar difference from placebo was seen when subjects with baseline HbA1c <7% were excluded from analysis.

Discontinuation and rescue was more frequent in the placebo arm (27.4% vs 12.6-14.9% for saxagliptin), and this was reflected in extent of exposure to study medications: mean 150-152 days for saxagliptin arms, and mean 134 days for the placebo arm.

Subjects treated with saxagliptin had relatively greater decreases in fasting glucagon than placebo subjects; and there were statistically significant increases in mean postprandial insulin AUC (but not fasting insulin) in the saxagliptin arms relative to placebo.

Saxagliptin treatment did not affect mean body weight (at Week 24, -1.43 to -0.53 kg vs -0.92 kg for the placebo group), BMI or mean waist circumference. There were no clear effects of saxagliptin on mean fasting lipid levels.

Study CV181014 – long-term follow-up

The cut-off date was 17 January 2008. With LOCF methodology, all subjects contributed data at Week 76, and 97.4-98.4% of subjects contributed data at Week 102 but only around 17% of subjects had data at Week 115. Mean duration of exposure to double-blind study medication was similar across saxagliptin groups (75-81 weeks for saxagliptin, 68 weeks for placebo, when rescue medication was included; 55-60 weeks for saxagliptin and 40 weeks for placebo when time on rescue medication was excluded). Mean exposure to metformin was 89-94 weeks (saxagliptin) vs

79 weeks (placebo) (including time on rescue medication). Mean exposure to pioglitazone was 37-39 weeks (saxagliptin) vs 40 weeks (placebo).

A total of 642 subjects entered the LT period, either after completing the 24 week ST period or after glycaemic rescue. Subjects who met glycaemic rescue criteria in the ST period were eligible to enter the LT period, where they received open label pioglitazone, open label metformin and blinded study medication. Subjects who completed all visits during the ST period and did not meet glycaemic rescue criteria were eligible to enter the LT period where they received the same treatment as they received during the ST period. Subjects were eligible for rescue with 15 mg pioglitazone (titratable to 30-45 mg) in the LT period as well, based on pre-specified HbA1c thresholds at particular visits. No titration of blinded study medication or open-label metformin was to occur in the LT period.

A higher frequency of discontinuations was observed in the placebo plus metformin group (61.5%) compared with the saxagliptin plus metformin groups (38.7-44.5%). More subjects in the placebo plus metformin group discontinued treatment due to lack of efficacy (25.7%) than in the saxagliptin plus metformin groups (11.5-15.1%).

At Week 102, the proportion of subjects discontinued for lack of glycaemic control or rescued for meeting pre-specified glycaemic criteria was 71.5% for placebo but 51.8-58.3% for saxagliptin arms.

At Week 102 (LOCF), mean adjusted change from baseline in HbA1c was -0.30% (2.5 mg; n=34 observed values / n=147 LOCF values), -0.40% (5 mg; n=31 / n=152), -0.20% (10 mg; n=33 / n=144) and +0.32% (placebo; n=15 / n=157). Over 102 weeks, it is during the first 12 weeks that saxagliptin produces a difference in HbA1c. After that point, saxagliptin and placebo curves rise broadly in parallel.

At Week 102, for fasting plasma glucose, adjusted change from baseline was -0.42 mmol/L (2.5 mg), -0.62 mmol/L (5 mg), -0.43 mmol/L (10 mg) and +0.37 mmol/L (placebo). As with HbA1c, continuation of saxagliptin after 24 weeks resulted in a rise in FPG at approximately the same rate as seen in the placebo arm, to Week 102.

At Week 102 (LOCF), 24.3-32.8% of saxagliptin subjects and 11.6% of placebo subjects achieved HbA1c <7%.

Mean change in body weight at Week 102 (LOCF) was -1.0 (2.5 mg), -0.4 kg (5 mg), -0.5 mg (10 mg) and -0.8 mg (placebo). The sponsor stated that fasting lipid profiles were broadly unaffected by treatment, relative to placebo. At Week 102 there was (a) a +6.0% to + 9.6% change in LDL for saxagliptin arms vs a +3.7% change for placebo, and (b) a -1.5% to -2.8% change in HDL for saxagliptin arms vs -0.1% change for placebo.

Study CV181013 – pivotal, add-on to existing Thiazolidinedione (TZD)

This was a multicentre, randomised, double-blind, placebo-controlled, Phase III trial to evaluate the efficacy and safety of saxagliptin in combination with thiazolidinedione therapy in subjects with type 2 diabetes who have inadequate glycaemic control on thiazolidinedione therapy alone. It involved 172 investigators at 172 sites (117 USA, 15 India, 9 Canada, 9 Argentina, 6 Peru, 6 Mexico, 5 Puerto Rico, 5 Philippines).

Inclusion / exclusion criteria were as previously stated with the following exceptions. Subjects were already being treated with a thiazolidinedione. The relevant inclusion criterion was: subjects with T2DM receiving treatment with a stable monotherapy dose of a TZD (pioglitazone [PIO] 30 mg or 45 mg daily; rosiglitazone [ROSI] 4 mg once daily [QD] or 8 mg, either OD or in 2 divided doses of 4 mg) for at least 12 weeks prior to screening. There was a distinction during analysis between ‘high dose’ (PIO 45 mg; ROSI 8 mg), ‘mid dose’ (PIO 30 mg; ROSI 4 mg) and ‘undetermined dose’ TZD. The initial definition of inadequate glycaemic control at baseline allowing study

eligibility was HbA1c 7.0-10.0%, but this was amended to HbA1c 7.0-10.5%. Likewise, the initial BMI upper boundary for inclusion was 40 kg/m^2; this was amended to 45 kg/m^2. In this study, the exclusion threshold for serum creatinine was 176 µmol/L (vs 132.6 µmol/L for many other Phase III studies in the program). Subjects with contraindications for pioglitazone, rosiglitazone or metformin were excluded. History of administration of any antihyperglycaemic therapy (other than pioglitazone 30 mg or 45 mg QD, or rosiglitazone 4 mg QD, or 8 mg, either QD or in 2 divided doses of 4 mg) during the 12 weeks prior to screening was an exclusion criterion.

A total of 614 subjects entered lead in and 565 subjects were randomised and treated with double-blind therapy: 195 to SAX2.5, 186 to SAX5 and 184 to PLAC. A total of 18.5% of SAX2.5, 24.7% of SAX5 and 25% of PLAC subjects did not complete the ST period, most commonly because of lack of efficacy (9.2%, 6.5% and 10.3% respectively), withdrawal of consent (3.6%, 4.8% and 7.6%) or AEs (1%, 5.9% and 2.7%). A lower fraction (11.3%, 19.4% and 21.2%) actually discontinued the study, because many with 'lack of efficacy' were rescued into the LT period.

Mean age in the SAX2.5 arm was 54.9 years (range 25-76; 17.4% >65 years), in the SAX5 arm 53.2 years (range 21-76; 13.4% >65 years) and in the PLAC arm 54.0 years (range 30-75 years; 15.2% >65 years). Around 54.4%, 47.8% and 46.2% respectively were male. About 55% in each arm were White, with about 35% in each arm Asian. Mean weight was 82.1 kg, 80.4 kg and 80.9 kg respectively, while mean BMI was 30.0, 29.8 and 30.3 kg/m^2 respectively.

Mean duration of T2DM was 5.1-5.3 years; median duration was 4.6 years (SAX2.5), 3.5 years (SAX5) and 4.1 years (PLAC). Differences in median durations were mirrored by differences in the proportion of subjects with duration ≤3 years (37%, 47% and 45% respectively). About 5% of subjects had gestational diabetes.

Baseline HbA1c was 8.2-8.4% (mean), with a range of 6.0-13.0% (despite the study inclusion requirement for baseline HbA1c to be 7.0-10.5%). About 45% of subjects had a baseline HbA1c <8%, 30% between 8-9% and 25% >9%. FPG at baseline was 8.8-9.0 mmol/L.

A history of hypertension was present in 55%, diabetic neuropathy in 14%, hypercholesterolaemia in 52%, hypertriglyceridaemia in 32%, mixed dyslipidaemia in 30%, overweight in 51%, obesity in 38% and coronary artery disease in 4% (SAX2.5, 4.6%; SAX5, 2.2%; PLAC, 6.0%).

Of 563 randomised subjects with available data (n=2 missing), 56.5% were on pioglitazone at baseline and 43.7% were on rosiglitazone. Mean duration on thiazolidinediones was 1.3-1.5 years; >60% of subjects were on such drugs for <1 year – this raises the possibility that a stable treatment response had not been obtained in some subjects by the start of this study. Dosing at baseline is shown in Figure 9.

Figure 9: Dosing at baseline, Study CV181013

	n/N(%) of Subjects		
	SAXA 2.5MG + TZD N = 195	SAXA 5 MG + TZD N = 186	PLA + TZD N = 184
REGIMEN			
High-dose TZD (a)	65/195(33.3)	73/186(39.2)	67/184(36.4)
45 mg pioglitazone (b)	25/102(24.5)	37/108(34.3)	32/108(29.6)
8 mg rosiglitazone (c)	40/93(43.0)	36/78(46.2)	35/76(46.1)
Mid-dose TZD (a)	130/195(66.7)	113/186(60.8)	117/184(63.6)
30 mg pioglitazone (b)	77/102(75.5)	71/108(65.7)	76/108(70.4)
4 mg rosiglitazone (c)	53/93(57.0)	42/78(53.8)	41/76(53.9)

Data set: Randomized subjects.
(a) The denominator of the % is the total number of randomized subjects in the treatment group.
(b) The denominator of the % is the total number of randomized subjects in the treatment group taking pioglitazone at baseline.
(c) The denominator of the % is the total number of randomized subjects in the treatment group taking rosiglitazone at baseline.
Subjects may be represented in more than one category.

There was a 2 week dietary and exercise placebo and TZD lead-in period. Subsequently, subjects continued to receive their current open-label dose of TZD, and were randomised 1:1:1 to one of three study arms: saxagliptin 2.5 mg, saxagliptin 5 mg or placebo. Dose titration of saxagliptin was not permitted. Saxagliptin was taken before breakfast. After information was received concerning an increased cardiovascular risk with rosiglitazone, the protocol was amended to allow switching of TZDs while remaining in the study (subjects on 4 mg rosiglitazone received 30 mg daily pioglitazone; subjects on 8 mg rosiglitazone received 45 mg daily pioglitazone).

Subjects with inadequate glucose control in the ST period could receive – in addition to their current study therapy – open-label metformin as a rescue therapy, according to pre-specified parameters.

Subjects with serum creatinine≥1.5 mg/dL (male) or ≥1.4 mg/dL (fem ale) were ineligible for metformin and so were discontinued from the study. Metformin rescue therapy started at 500 mg with increments of 500 mg at 2-weekly intervals up to 2500 mg (or the maximum tolerated dose or the maximum approved dose in the country of study), according to glycaemic response (titration was recommended if FPG was >7 mmol/L).

The primary comparisons were between each of the 2 saxagliptin plus TZD treatment groups and the placebo plus TZD treatment group for the change in HbA1c from baseline to Week 24. Each comparison between saxagliptin plus TZD and placebo plus TZD was at the 0.027 level from Dunnett's adjustment so that the overall (familywise) Type I error rate was controlled at the 0.05 significance level.

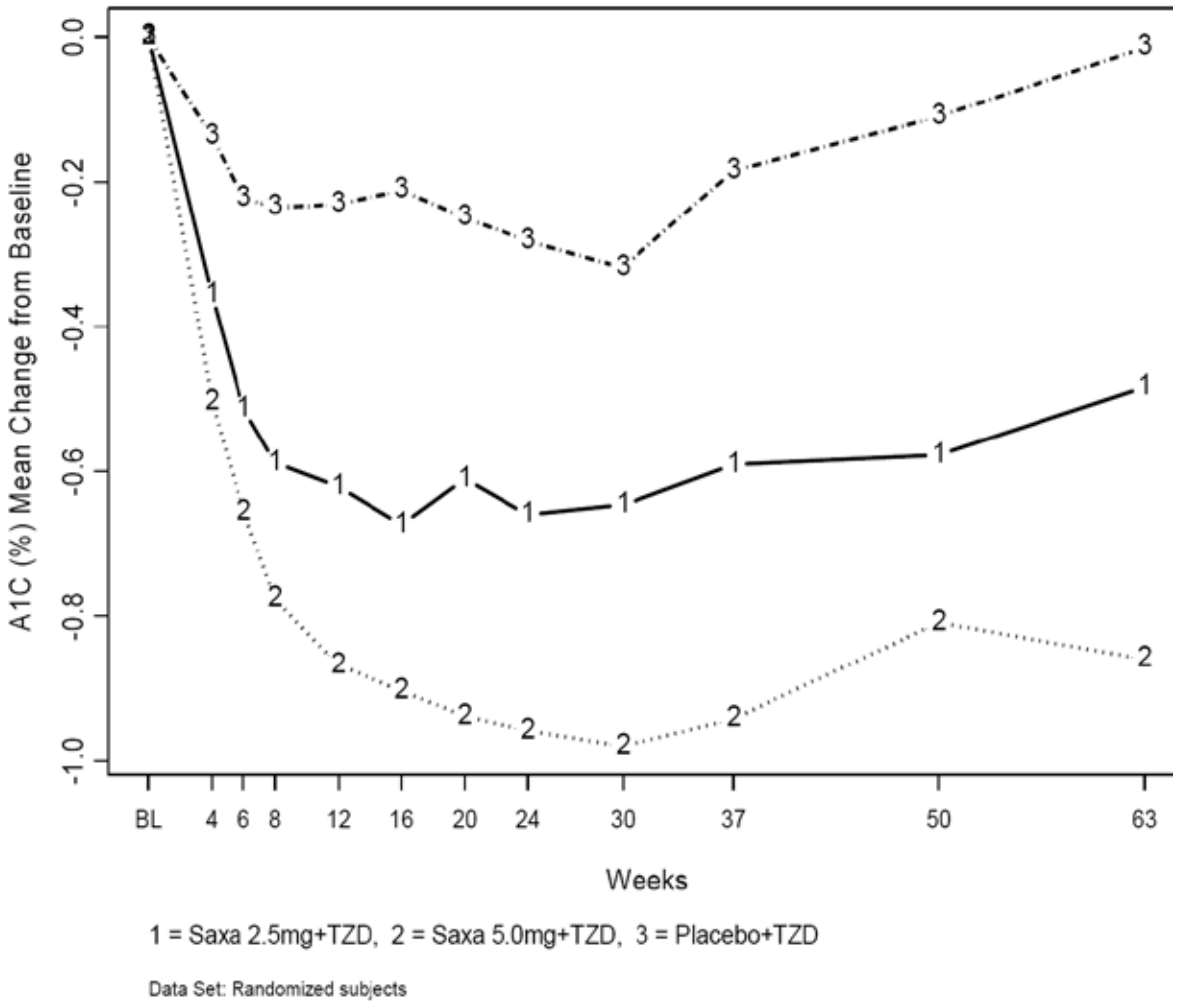
Efficacy results

Mean exposure to double-blind study medication was 147-152 days across arms. More than 60% of subjects continued on mid-dose TZD during the ST period. A total of 16 subjects switched from rosiglitazone to pioglitazone in the ST period (2.2-3.3% per arm).

Adjusted change from baseline in HbA1c was -0.66% (SAX2.5), -0.94% (SAX5) and -0.30% (PLAC), as shown in part of Figure 10. Subjects with higher baseline HbA1c (≥9%) had greater reductions in HbA1c than subjects with HbA1c 8-9% or ≤8%. This was the case for PLAC as well

as SAX subjects with higher baseline HbA1c (SAX2.5, -0.93%; SAX5, -1.54%, PLAC, -0.69%). For subjects with an intermediate baseline (8-9%), results were -0.79%, -1.01% and -0.18% respectively. For subjects with an HbA1c <8%, results were -0.43%, -0.56% and -0.16%. There was a negative correlation between baseline HbA1c and baseline β-cell function as measured by HOMA-2β, so similar observations were made for sub-groups based on baseline HOMA-2β.

Figure 10: Summary of Clinical Efficacy – HbA1c mean changes from baseline (LOCF) during ST+LT treatment – CV181013



Adjusted change from baseline in FPG was -0.79 mmol/L (SAX2.5), -0.95 mmol/L (SAX5) and -0.14 mmol/L (PLAC). Results for PPG AUC were analogous. The percentage of subjects achieving HbA1c <7% was 42.2% (SAX2.5), 41.8% (SAX5) and 25.6% (PLAC). The proportion of subjects who discontinued the study for lack of glycaemic control or were rescued for meeting pre-specified glycaemic criteria was similar across treatment groups (6.5-10.3% at Week 24).

Weight gain occurred in all groups: 1.3 kg over 24 weeks in the SAX2.5 arm, 1.4 kg in the SAX5 arm and 0.9 kg in the placebo arm. Likewise, BMI increased over this period (by 0.5, 0.6 and 0.2 kg/m^2 respectively). Mean percent change in LDL at 24 weeks (LOCF) from baseline was 4.3% (SAX2.5), 9.4% (SAX5) and 3.4% (PLAC). For HDL, results were -1.3%, +1.3% and +0.1% respectively.

Study CV181013 – long-term follow-up

The data cut-off date for this interim report was 30 January 2008. Around 72-75% of subjects in each arm provided data (whether observed or carried forward) at the 50 week time point, and about 50% at the 63 week time point, but only 16-17% at the 76 week time point. Subjects who completed

the ST treatment period and subjects who met rescue criteria were eligible to enter the double-blind LT treatment period where they received the same treatment as they received during the ST period. Subjects were eligible for rescue with open label metformin in the LT period. Creatinine had to be within acceptable levels. Metformin was titrated to maximum tolerable dose.

A total of 468 subjects (out of 565 in the ST period) entered the LT period, including 44 subjects who entered LT after rescue. In the ST+LT period, 9.2% of subjects switched from rosiglitazone to pioglitazone (8-10% per arm). Extent of exposure to double-blind study medication prior to rescue was, on average, 40.7 weeks (SAX2.5), 38.4 weeks (SAX5) and 34.7 weeks (PLAC).

Discontinuation from the ST+LT period due to lack of efficacy was reported in 5.6% (SAX2.5), 2.2% (SAX5) and 7.6% (PLAC).

Adjusted mean change from baseline in HbA1c at Week 50 (LOCF) was -0.58% (SAX2.5), -0.78% (SAX5) and -0.13% (PLAC) (see Figure 10). Adjusted mean change from baseline to Week 50 (LOCF) in FPG was -0.63 mmol/L (SAX2.5), -0.77 mmol/L (SAX5) and +0.09 mmol/L (PLAC). At Week 50 (LOCF), 41%, 40.7% and 23.8% respectively had achieved an HbA1c <7% (results broadly similar to those seen at Week 24). The proportion of subjects who discontinued due to lack of glycaemic control or who were rescued for meeting pre-specified glycaemic criteria was 26.7%, 18.8% and 35.9% respectively.

Adjusted mean change in body weight from baseline at Week 50 was 1.8 kg, 2.1 kg and 1.6 kg respectively; BMI changes were also similar, at +(0.6-0.8) kg/m^2. Convergence with placebo occurred after Week 37.

At Week 50, LDL cholesterol was increased relative to baseline by 8% (SAX2.5), 11.8% (SAX5) and 2.2% (PLAC), while HDL cholesterol decreased by 2.7%, 0.3% and 0.8% respectively (median values for the HDL decrease were 2.7%, 1.5% and 0%).

Study CV181040 – pivotal, add-on to existing glibenclamide

This was a multicentre, randomised, double-blind, placebo-controlled Phase III trial to evaluate the efficacy and safety of saxagliptin in combination with glyburide in subjects with type 2 diabetes who have inadequate glycaemic control on glyburide alone. It involved 136 investigators at 132 sites (60 USA; 10 Brazil; 10 Mexico; 9 Israel; 9 South Africa; 8 Korea; 6 Argentina; 5 Taiwan; 4 Peru; 4 Philippines; 4 Puerto Rico; 2 Hong Kong; 1 Singapore) participated in the study. Glyburide is glibenclamide (GLIB).

As inclusion criteria, subjects required a diagnosis of T2DM with treatment for≥2 months prior to study entry with a "submaximal dose of a sulfonylurea". At screening, HbA1c was to be 7.5-10.0%, and at randomisation, HbA1c ≥7.0% and MFPG ≥7.8 mmol/L. The exclusion threshold for serum creatinine was 176 µmol/L; for platelets, 140 000 c/µL. Subjects could not have contraindications to glibenclamide or metformin. The exclusion criterion of 'history of administration of any antihyperglycaemic therapy for more than 3 consecutive days or a total of 7 non-consecutive days' was during the 12 weeks prior to screening.

A total of 959 subjects entered lead-in; 768 subjects were randomised and treated with double-blind therapy. A total of 191 subjects were not randomised – including 143 because they did not meet study criteria. Of the 768 randomised subjects, 248 were randomised to SAX2.5, 253 to SAX5 and 267 to GLIB.

Mean age was 54.9-55.4 years across arms (16.6-19.3% of subjects per arm were ≥65 years; age range was 18-76 years). Around 43.5-46.1% of subjects were male. About 56.9-59.7% of subjects were White; most others were classified as 'Asian' and 'other'. Latin America contributed 63.7% of subjects, Asia / Pacific 16.7%, North America 15.4% and Europe 4.3%. Mean weight was 75.2-76.2 kg across arms; mean BMI was 28.8-29.1 kg/m^2 per arms.

Mean duration of T2DM was 6.8-7.1 years across arms (range, 0.0-34.6 years), with close to 29% with a duration of ≤3 years, 16% 3-5 years and 55% >5 years in each arm. The percentage of subjects with T2DM duration >10 years was 27.8% (SAX2.5), 24.1% (SAX5) and 22.8% (GLIB).

Baseline HbA1c was similar across arms (mean, 8.4-8.5%), with 23.8%, 30% and 28.1% having an HbA1c ≥9.0% at baseline. FPG at baseline was similar across arms, at 9.5 mmol/L.

A history of hypertension (53%) and of being overweight (49.1%) were the most common diabetes-related conditions at baseline; also common were hypercholesterolaemia (36.2%), obesity (35.9%), mixed dyslipidaemia (25.3%), hypertriglyceridaemia (23.8%) and diabetic neuropathy (15.5%). Coronary artery disease was reported in 2.4% (SAX2.5), 2.8% (SAX5) and 3.4% (GLIB) – yet previous MI was reported in 3.6%, 2.8% and 3.0% respectively.

There was a 4 week single-blind 'diet and exercise' lead-in period, during which time all subjects discontinued current sulfonylurea therapy and began treatment with open-label GLIB 7.5 mg (a 'sub-maximal' dose).

At the start of the 24 week ST period, subjects were randomised 1:1:1 to: saxagliptin 2.5 mg (SAX2.5), saxagliptin 5 mg (SAX5) or placebo plus 2.5 mg double-blind glibenclamide (that is. initial total dose in the ST period of 10 mg) (GLIB). Across arms, the glibenclamide could (once) be lowered by 2.5 mg to 5 mg for hypoglycaemia; down-titration occurred in 4.0% (SAX2.5), 5.1% (SAX5) and 2.2% (GLIB).

In the GLIB arm, glibenclamide dose could be uptitrated in a single 5 mg step to 15 mg total daily dose (7.5 mg open-label + 7.5 mg blinded) at Week 2 or Week 4, if mean FPG was ≥5.5 mmol/L.

The majority of placebo-treated subjects (92%) had an additional 7.5 mg of glibenclamide added to the baseline 7.5 mg dose. Thus, this was not simply a placebo-controlled study – the comparator regimen included a larger dose of glibenclamide. GLIB subjects were specifically not being treated with the maximal effective dose at baseline.

Double-blind study medication was taken twice daily (prior to breakfast and prior to evening meal) to allow the glibenclamide dose to be split; all saxagliptin was taken in the morning. Subjects with inadequate glycaemic control were eligible for addition of open-label metformin (500 mg).

The primary comparisons were between each of the 2 saxagliptin treatment groups and the placebo plus uptitrated glibenclamide treatment group. Each comparison between saxagliptin and placebo plus uptitrated glibenclamide was at the 0.027 level from Dunnett's adjustment so that the overall (familywise) Type I error rate was controlled at the 0.05 significance level.[27]

Efficacy results

Discontinuations in the ST period were seen in 22.6% (SAX2.5), 22.9% (SAX5) and 34.1% (GLIB). In all groups, lack of efficacy was the commonest reason (16.5%, 15%, 24.7% respectively); most such subjects were rescued into LT treatment.

Exposure to double-blind therapy was 151 days (SAX2.5), 150 days (SAX5) and 140 days (GLIB) – the shorter duration for the GLIB arm was attributed to more frequent rescue and discontinuation from the study in this group.

Adjusted mean change from baseline in HbA1c was -0.54% (SAX2.5), -0.64% (SAX5) and +0.08% (GLIB), as seen in part of Figure 11. In this study, no interaction with baseline HbA1c was observed.

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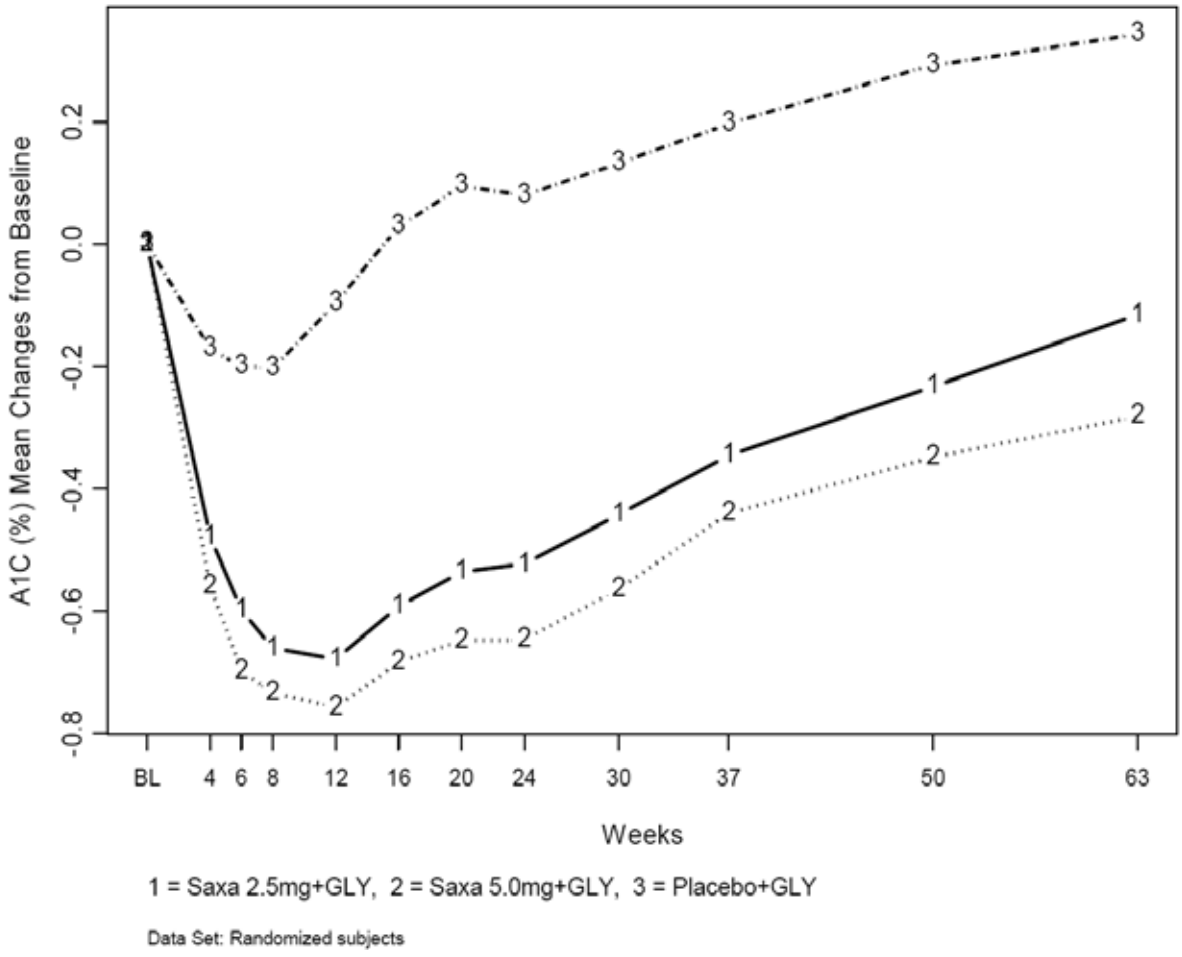
[27] Dunnett's correction: In statistics, the Bonferroni correction is the method usually used to address the problem of multiple comparisons. Dunnett described an alternative alpha error adjustment when *k* groups are compared to the same control group. This method is less conservative than the Bonferroni adjustment.

Figure 11: Summary of Clinical Efficacy – HbA1c mean changes from baseline (LOCF) during ST+LT treatment – CV181040



Adjusted mean change from baseline to Week 24 (LOCF) in FPG was -0.39 mmol/L, -0.53 mmol/L and +0.04 mmol/L respectively. Analogous changes were seen for PPG AUC.

The percentage of subjects achieving HbA1c <7% was 22.4%, 22.8% and 9.1% respectively.

The percentage of subjects discontinuing for lack of glycaemic control or being rescued after meeting pre-specified glycaemic criteria was 18.1%, 16.6% and 29.6% respectively.

Mean body weight and BMI increased for all groups, but more so for saxagliptin groups – by 0.7 kg (SAX2.5), 0.8 kg (SAX5) and 0.3 kg (GLIB), and by 0.3 kg/m^2 for both SAX groups and 0.1 kg/m^2 for the GLIB arm. From baseline to Week 24 (LOCF), mean increase in LDL was 5.5% (SAX2.5), 3.5% (SAX5) and 4.8% (GLIB). Mean decrease in HDL was -6.0% (SAX2.5), -4.5% (SAX5) and -1.8% (GLIB).

Study CV181040 – long-term follow-up

The data cut-off point for this interim report was 31 January 2008. Of 768 randomised and treated subjects, all entered the LT phase. At least 95% of subjects in each arm provided data (albeit using LOCF methodology) at Week 50, and at least 60% at Week 63.

Subjects were eligible to enter the LT period of the study via either of the following:

1) Upon completing all visits and not meeting hyperglycaemic rescue criteria in the ST period. In the LT period, subjects who received blinded placebo plus glibenclamide could have their blinded glibenclamide uptitrated to 20 mg total daily dose (if they had not already been rescued with

metformin) if HbA1c was ≥7.0% at Week 30. Subjects who received saxagliptin plus open-label glibenclamide remained on the same dose of saxagliptin as during the ST period. Glibenclamide could be down-titrated two times in increments of 2.5 mg as deemed necessary by the investigator for hypoglycaemia.

2) Upon meeting hyperglycaemic rescue criteria during the ST period, all blinded study medication remained unchanged. No up or down titration of open-label or blinded glibenclamide was permitted once rescue had occurred.

Rescue with open-label metformin was allowed in previously un-rescued subjects upon reaching pre-specified glycaemic thresholds. The metformin dose could be titrated in 500 mg increments every 2 weeks to 2500 mg (or maximum allowed per country) if mean FPG was≥7.0 mmol/L and / or HbA1c ≥7.0%. Mean duration of exposure to double-blind study medication was 50.1-50.2 weeks for SAX and 47.6 weeks for GLIB. Exposure prior to rescue was 37.6-38.4 weeks vs 30.9 weeks respectively. Exposure to rescue metformin was 22.8-23.5 weeks vs 24.4 weeks respectively.

In the ST+LT period, discontinuation was seen in 22.6% (SAX2.5), 19.8% (SAX5) and 26.2% (GLIB).

At Week 50 (LOCF), mean adjusted change in HbA1c was -0.25% (SAX2.5), -0.33% (SAX5) and +0.29% (GLIB) (see Figure 11).

At Week 50 (LOCF), mean adjusted change in FPG from baseline was 0.04 mmol/L (SAX2.5), -0.01 mmol/L (SAX5) and +0.53 mmol/L (GLIB). Also at Week 50 (LOCF), 14.4% (SAX2.5), 14% (SAX5) and 7.5% (GLIB) achieved the glycaemic response threshold of ≤7% (HbA1c). At Week 50, the proportion of subjects who discontinued for lack of glycaemic control or who were rescued for meeting pre-specified criteria was 48.8% (SAX2.5), 49.8% (SAX5) and 67% (GLIB).

Mean body weight increased to Week 50 (LOCF) by 0.6 kg (SAX2.5), 0.9 kg (SAX5) and 0.3 kg (GLIB). Mean BMI increased to Week 50 (LOCF) by 0.2, 0.3 and 0.1 kg/m^2 respectively.

To Week 50, LDL cholesterol increased by 5.0-7.4% across all groups, while HDL decreased by 3.7-3.9% (SAX) and 1.7% (GLIB).

Study CV181039 – pivotal, with metformin as initial therapy

This was a multicenter, randomized, double-blind, active-controlled, Phase III trial to evaluate the efficacy and safety of saxagliptin in combination with metformin as initial therapy compared to saxagliptin monotherapy and to metformin (MET) monotherapy in subjects with type 2 diabetes who have inadequate glycaemic control. It involved 196 investigators at 196 sites (46 Russian Federation [contributing 26% of subjects]; 44 United States [12%]; 19 Argentina [6%]; 13 India [10%]; 13 Mexico [15%]; 12 Germany [1%]; 10 Ukraine [8%]; 8 Brazil [7%]; 8 Poland [1%]; 8 Philippines [6%]; 6 Puerto Rico [5%]; 5 Hungary [3%]; 4 Italy [<1%]).

This study was conducted in drug-naïve type 2 diabetics. An important difference between this study and Studies CV181011, -038 and -014 is that "inadequate glycaemic control" was defined as HbA1c ≥8% but ≤12% (rather than 8-10%). Another difference was that subjects in this study must have received medical treatment for diabetes for less than a total of 1 month since original diagnosis (vs a total of 6 months). The exclusion criteria regarding lymphopenia and thrombocytopenia were deleted at specific sites, for some unexplained reason. Subjects with contraindications to pioglitazone were also excluded.

A total of 1394 subjects entered the lead-in period; 1306 subjects were randomised and treated: 320 in the SAX5+MET group; 323 in the SAX10+MET group; 335 in the SAX10+PLAC group; and 328 in the MET+PLAC group. A similar proportion of subjects in each arm had 'significant' protocol deviations (2.5-4.2%), mainly due to non-compliance related to titration of metformin

although two saxagliptin 10 mg subjects received insulin for ≥14 days. 'Other' protocol dev iations were more common in subjects receiving saxagliptin: 4.4% (saxagliptin 5 mg + metformin); 4.0% (saxagliptin 10 mg + metformin); 5.7% (saxagliptin 10 mg); and 2.7% (metformin).

Of 1306 randomised and treated subjects, mean age was close to 52 years in all treatment groups (range, 19-77 years), and close to 76% of subjects were White. The SAX10+MET group had a slightly higher proportion of subjects >65 years than other groups (16.7% vs 10.3-12.8%) and a higher proportion of females (54.8% vs 48.4-50.3%). Average weight was 82.1-83.1 kg across arms, with average BMI 29.9-30.3 kg/m^2 across arms.

Around 82% of subjects were recently diagnosed (≤3 years) with T2DM. Mean duration of diabetes was 1.7 years (median, 0.4 years) (2.0 years in SAX5+MET, 1.4 years in SAX10+MET, and 1.7 years in each monotherapy arm). In the SAX10+MET arm, 76.5% of subjects had a duration of T2DM of ≤1.5 years, vs 66.9-68.3% in other arms. Mean baseline HbA1c was 9.4-9.6% across arms – distinctly higher than in Studies CV181011, -038 and -014, in keeping with the different HbA1c inclusion criterion. Indeed, 34.4-38.5% of subjects had a baseline HbA1c of ≥10%. Mean FPG was 11.0 mmol/L. A history of gestational diabetes was present in 4.5% (SAX5+MET), 5.6% (SAX10+MET), 1.2% (SAX10+PLAC) and 0.6% (MET+PLAC).

Diabetic neuropathy was seen in 6% of subjects, microalbuminuria in 2.1% of subjects and diabetic retinopathy in 2.1%. Hypercholesterolaemia was present in 24.5%; overweight in 50.4% and obesity in 43.7%. There was a history of congestive heart failure in 4%, coronary artery disease in 7.6% (highest in the MET+PLAC arm, at 9.8%), hypertension in 50.5% and previous MI in 3% (1.5-3% in saxagliptin-receiving arms vs 4.9% in the metformin arm).

There was a one week placebo run in period, during which time subjects received dietary and exercise advice from a member of the study team.

Drug naïve subjects were randomised 1:1:1:1 to receive one of the following 4 treatments:

- saxagliptin 10 mg (fixed dose) plus metformin immediate release (IR) (500 mg with titration) [SAX5+MET]
- saxagliptin 5 mg (fixed dose) plus metformin IR (500 mg with titration) [SAX10+MET]
- saxagliptin 10 mg (fixed dose) plus placebo [SAX10+PLAC]
- metformin IR (500 mg with titration) plus placebo [MET+PLAC]

Thus, despite subjects being drug-naïve, there was no purely placebo control. In the sponsor's *Summary of Clinical Efficacy* it was noted that:

At the time of the design of this study, it was unclear whether saxagliptin 5 mg or 10 mg would give maximal reduction in HbA1c with longer duration of dosing beyond 12 weeks. To ensure the combination arms were compared to the maximally efficacious monotherapy dose (especially important in this population with poor glycaemic control), saxagliptin 10 mg was chosen as the dose for the monotherapy group.

Saxagliptin was either 5 mg or 10 mg tablets, and was taken daily prior to breakfast. Metformin IR was taken with the morning and evening meals.

Titration of metformin was as follows:

- at Week 1, titration was from metformin 500 mg daily to metformin 1000 mg daily in divided doses
- at Weeks 2, 3, 4 and 5, subjects were to be titrated in increments of 500 mg up to 2000 mg daily in divided doses, if mean FPG > 6.1 mmol/L or mean fasting whole blood glucose (MFWBG) >5.8 mmol/L

Subjects requiring rescue had open-label pioglitazone (15 mg) added to blinded study medications. This was titrated to 45 mg, if allowed per country, based on glycaemic control.

Prior to rescue, mean duration of exposure to double-blind saxagliptin was 151 days (SAX5+MET), 151 days (SAX10+MET) and 137 days (SAX10+PLAC). Mean duration of exposure to double-blind metformin was 152 days (SAX5+MET), 151 days (SAX10+MET) and 144 days (MET+PLAC).

In groups that received metformin, titration from the initial 500 mg daily dose was performed in most subjects (93-96%); in 8-10% the final dose was 1000 mg, in 7-15% the final dose was 1500 mg, in 67-76% the final dose was 2000 mg and in 3-4% the final dose was 2500 mg.

Each combination treatment was compared with the monotherapy treatments, so each comparison was performed at the 0.027 alpha level to contain overall Type I error at 0.05 significance level. This testing strategy excluded the comparison of monotherapies (that is, SAX10+PLAC was not formally compared with MET+PLAC).

Efficacy results

In this study, 311 subjects ("evenly distributed across treatment groups") ingested more than the appropriate amount (75 mg) of glucose specified in the protocol – these subjects were excluded from OGTT analysis.

A total of 81.9% of SAX5+MET subjects completed the 24 week ST period, 80.8% of SAX10+MET, 67.2% of SAX10 and 74.1% of MET. Discontinuations from the ST period were seen in 18.1%, 19.2%, 32.8% and 25.9% respectively. Commonly discontinuation was due to lack of efficacy – this was particularly the case in the saxagliptin monotherapy group (6.3%, 5.9%, 19.1% and 9.1% respectively). Adverse events contributed to discontinuation in 2.2-3.4% across arms. The largely overlapping endpoint of discontinuation or rescue for lack of glycaemic control was reached in 7.5%, 5.9%, 21.2% and 10.1% respectively.

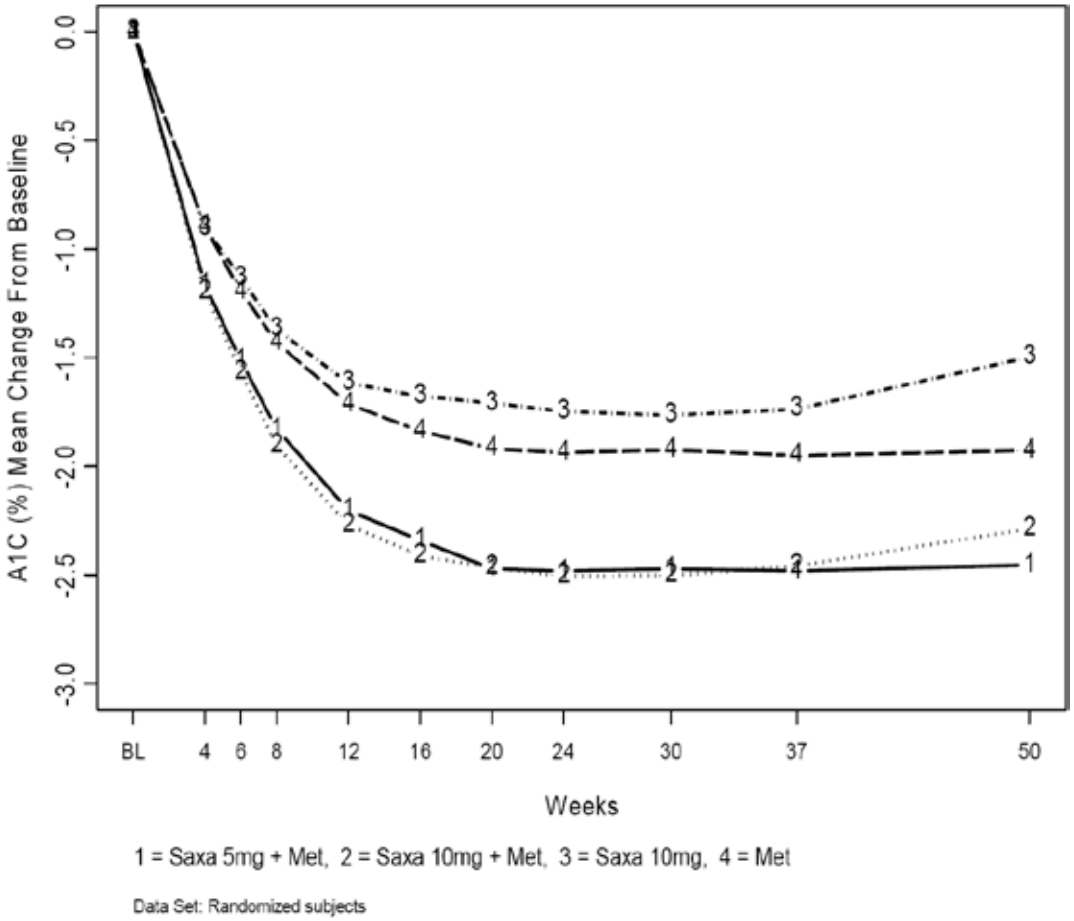
> The evaluator noted that these and similar results prompt the question, 'Why would a clinician commence a treatment-naïve subject on saxagliptin monotherapy?'

At Week 24 (LOCF), adjusted mean change from baseline in HbA1c was -2.53% (SAX5+MET), -2.49% (SAX10+MET), -1.69 (SAX10+PLAC) and -1.99 (MET+PLAC) (Figure 12). Using observed values, adjusted mean change from baseline at Week 24 was -2.66%, -2.75%, -2.09% and -2.27% respectively.

The number of subjects achieving HbA1c <7% was 60.3%, 59.7%, 32.2% and 41.1% respectively. The number of subjects achieving HbA1c ≤6.5% was 45.3%, 40.6%, 20.3% and 29% respectively. Changes from baseline in PPG AUC were consistent with changes in these other endpoints (despite exclusion of 315 European subjects due to a systematic error in glucose administration).

There was a small, similar reduction from baseline to Week 24 in weight, waist circumference and BMI in all treatment groups. Mean changes in body weight to Week 24 (LOCF) were -1.8 kg (SAX5+MET), -1.4 kg (SAX10+MET), -1.1 (SAX10+PLAC) and -1.6 (MET+PLAC); a similar pattern was seen for BMI and waist circumference. The mean decrease in LDL cholesterol was slightly lower in the SAX10+PLAC arm (-0.5%, vs -3.8% to -4.6% for metformin-containing arms). Likewise, the mean increase in HDL was lowest in the SAXA10+PLAC group (3.9% vs 6.2-8.9% for metformin-containing arms). The decrease in mean triglyceride levels was lowest in the MET+PLAC arm (-1.5%, vs -3.0% to -5.8%).

Figure 12: Summary of Clinical Efficacy – HbA1c mean changes from baseline (LOCF) during ST+LT treatment – CV181039



Likewise, adjusted mean change from baseline in FPG was 3.3 mmol/L, 3.4 mmol/L, 1.7 mmol/L and 2.6 mmol/L.

Subgroup analysis of efficacy was notable for greater HbA1c reductions with increasing baseline HbA1c strata. Also, in the MET+PLAC group, subjects at Asian sites had a smaller reduction in HbA1c (-1.1%, vs -1.99% overall). In Black / African American subjects, decrease in HbA1c was -1.99% to -2.70% for metformin-containing arms, vs -0.71% for the saxagliptin monotherapy arm.

Study CV181039 – long-term follow-up

The cut-off date for this report was 6 February 2008. A total of 1103 subjects entered the LT period (either completing the ST period or entering LT treatment after rescue due to lack of glycaemic control). Subjects were eligible for rescue with pioglitazone in the LT period as well. Unless contraindicated, subjects meeting rescue criteria received additional open-label pioglitazone at a recommended initial dose of 15 mg QD. This dose could be titrated to a maximal dose of 45 mg QD, according to local country or regional policy. Subjects whose fasting plasma glucose (FPG) did not decline by at least 1.65 mmol/L within 8 weeks after initiating rescue therapy were discontinued from the study and referred for additional anti-hyperglycaemic therapy.

Only a third of treated subjects (95-106 per arm) contributed to analysis of efficacy at Week 50 (and even fewer, at around 30-50 per arm, had observed values) – thus, interim study results do not provide a good comparison over the long term of SAX+MET vs SAX vs MET. For this reason only key outcomes will be evaluated below.

Mean duration of exposure to saxagliptin (including after rescue) in the ST+LT period was 32-34 weeks. Mean duration of exposure to metformin (including rescue) was 31-34 weeks. Mean

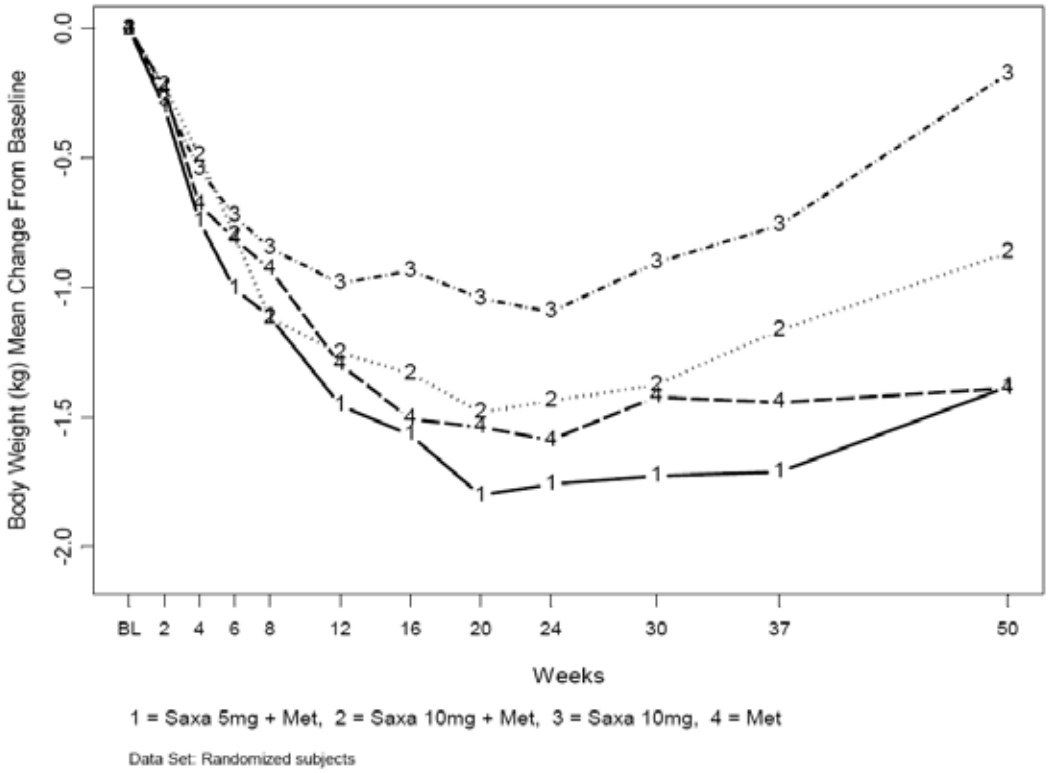
duration of exposure to pioglitazone (the rescue therapy) in the LT period was 14.8 weeks (SAX5+MET), 12.3 weeks (SAX10+MET), 14.5 weeks (SAX10+PLAC) and 9.4 weeks (MET+PLAC). Frequency of discontinuation from the study was 20%, 18.9%, 24.8% and 21.6% respectively. Common reasons were withdrawal of consent, loss to follow-up and AEs. Frequency of discontinuation from the LT period was 7.2%, 4.7%, 11.9% and 3.4% respectively. The commonest reason was lack of efficacy (3.3%, 1.1%, 4.9% and 1.5% respectively).

At Week 50 (LOCF), adjusted mean change in HbA1c from baseline was -2.48% (SAX5+MET), -2.31% (SAX10+MET), -1.38% (SAX10+PLAC) and -1.99% (MET+PLAC), illustrated in Figure 12. The apparent 'upswing' for the saxagliptin monotherapy arm at Week 50 should be interpreted in the light of relatively low subject numbers in this interim report.

Also at Week 50 (LOCF), adjusted mean change in FPG from baseline was 3.3 mmol/L, 3.1 mmol/L, 0.8 mmol/L and 2.7 mmol/L respectively. At Week 50 (LOCF), the percentage of subjects with HbA1c <7% was 60%, 55.4%, 24.5% and 40.7%.

Weight change over 50 weeks is demonstrated in Figure 13.

Figure 13: Study CV181039 (LT phase) – weight change from baseline (LOCF)



Cross-study comparisons and pooled datasets

There were two data pools: (a) the two monotherapy studies; and (b) the five placebo-controlled studies. While pooling may increase precision, it relies for validity on acceptable homogeneity of patient populations. Various tables facilitate cross-study comparisons including prior treatment status, rescue criteria in the ST phase, rescue criteria in the LT phase, demographic characteristics, cross-study comparison of discontinuation and rescue rates and efficacy results.

Monotherapy studies

In the pooled monotherapy dataset, the primary efficacy endpoint was analysed using an ANCOVA model including treatment group and study as fixed effects and baseline value as co-variate. Secondary endpoints for FPG and PPG were analysed using ANCOVA. The Mantel-Haenszel test was used to assess the association between treatment group and therapeutic glycaemic response

adjusted for study. The Breslow-Day test was used to examine homogeneity of effect across studies.

Table 5 presents the primary efficacy endpoint for both monotherapy studies and for the pooled monotherapy dataset. The sponsor notes in the *Summary of Clinical Efficacy* that the adjusted change from baseline in HbA1c for the placebo group in CV181038 was larger than in CV181011, and that:

The reduction in HbA1c as well as the moderate reduction in weight observed in the placebo group (1.3 kg) supports the notion that the dietary and exercise intervention (as per local guidelines) were followed by subjects in this group. Adherence to diet and exercise intervention in the context of a low HbA1c and FPG at baseline may have also lessened the placebo-subtracted HbA1c reduction observed, particularly given the glucose-dependent mechanism of action of DPP4 inhibitors.

> The evaluator noted that this 'notion' was of concern in that it implies dietary and exercise changes may have been suboptimal elsewhere. There was no attempt to quantify dietary and exercise changes in the Core Phase III studies.

Also presented were tables which presented the secondary efficacy endpoint of fasting plasma glucose for both monotherapy studies and for the pooled monotherapy dataset, the secondary efficacy endpoint of 'percentage of subjects achieving therapeutic glycaemic response (HbA1c <7%)' for both monotherapy studies and for the pooled monotherapy dataset, and the secondary efficacy endpoint of change in post-prandial glucose AUC from baseline. Analogous results were also presented for 120 minute PPG.

The proportion of subjects who discontinued for lack of glycaemic control or who were rescued for meeting pre-specified glycaemic criteria was higher in the placebo group than in the saxagliptin groups in both monotherapy studies.

Physical measurement outcomes were analysed in the pooled monotherapy dataset. For body weight and BMI in both monotherapy studies, point estimate mean reduction was greater in the placebo group than in the saxagliptin arms. The sponsor's interesting comment is that "this would be the expected pattern assuming that investigators intensify diet and exercise instruction for subjects treated with placebo with minimal response in their fingerstick and laboratory measurement of FPG". An alternative, equally untested explanation is a drug effect. Again, the implication is that dietary and exercise interventions are not necessarily optimal in the general course of the Phase III studies.

Table 5: Summary of Clinical Efficacy – HbA1c changes from baseline at Week 24 (LOCF) – Phase III 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)	--

Source: CV181013ST CSR Table 7.2.1A; CV181040 STCSR Table 7.2.1A; CV181040ST CSR Table 7.2.1A
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

Add-on combination therapy studies

Table 5 presents the primary efficacy endpoint of HbA1c change from baseline to Week 24 (LOCF) across the add-on combination therapy studies. Various secondary efficacy endpoints were also assessed including FPG across add-on combination therapy studies, the 'therapeutic glycaemic index (HbA1c<7%)' endpoint and the post-prandial glucose AUC endpoint. Analogous results were presented for 120 minute PPG changes from baseline at Week 24.

The proportion of subjects who discontinued for lack of glycaemic control or who were rescued for meeting pre-specified glycaemic criteria was higher in the placebo / uptitrated glibenclamide groups than in the saxagliptin groups.

Physical measurement outcomes were analysed. In CV181014, differences in 'change in body weight over 24 weeks' between saxagliptin and placebo were not marked, and weight was lost

across all groups. In the other two add-on studies, weight was gained over the 24 weeks, and slightly more weight was gained in the saxagliptin groups than in control groups. Outlier analysis of weight was not shown. Mean changes of over 1 kg in 24 weeks are significant only because this indicates some subjects will have a far greater weight gain in this interval (and, potentially, beyond this interval).

Discussion of efficacy

Core Phase III studies were appropriately randomised and double-blinded. Complex medication administration arrangements were required to maintain double-blinding; yet no problems with non-compliance were recorded.

Dose selection was aided by the dose-ranging study CV1810008 and by use of once daily 2.5, 5 and 10 mg doses across the Core Phase III studies. The 5 mg dose is proposed (except in subjects with significant renal impairment), but results in arms given 2.5 mg and 10 mg are useful to assess efficacy in those with outlying low exposure to a 5 mg dose (for example, due to PK variability), and safety in those with outlying high exposure.

The sponsor noted that saxagliptin 5 mg groups consistently had better glycaemic control than 2.5 mg groups; differences were generally modest. The sponsor speculated that the 'suboptimal' results for the 2.5 mg arm were related to a lower area under the effect curve (for DPP4 inhibition) seen with 2.5 mg compared to higher doses.

Study CV181038 (second monotherapy study) was atypical in that the 2.5 mg arm performed marginally better than the 5 mg arms. The sponsor noted that in this study subjects had a relatively short duration of diabetes, that subjects had a relatively large reduction in HbA1c, and that there were relatively few subjects per arm. At least for HbA1c, actual differences between studies were only moderate (for example, for 5 mg, relative to baseline: 0.46% vs 0.66% falls). Despite this, it is reasonable to accept 5 mg as the proposed dose.

HbA1c is a stable minor haemoglobin variant formed by post-translational, non-enzymatic, irreversible modification of the main form of haemoglobin by glucose. The sponsor states that "HbA1c is widely accepted as a surrogate marker for long-term glycaemic control (American Diabetes Association 2008)" and that the major studies DCCT and UKPDS have demonstrated that HbA1c correlates with risk for developing diabetes complications. Given the importance of HbA1c in this submission, it is worth noting information in a paper by Kilpatrick (2008):[28]

"Glycation of haemoglobin occurs over the entire 120-day lifespan of the red cell, but within this 120 days recent glycaemia has the largest influence on the HbA1c value. Indeed, theoretical models and clinical studies suggest that a patient in stable control will have 50% of their HbA1c formed in the month prior to sampling, 25% in the month before that, and the remaining 25% in months 2–4. This explains why, traditionally, HbA1c has been thought to represent average glycaemia over roughly the last 6–8 weeks."

Saxagliptin was generally shown to decrease HbA1c maximally by 8-12 weeks. Substantial falls in HbA1c were already apparent within 4 weeks of commencing treatment – yet HbA1c reflects glycaemic values over 120 days (the lifespan of a red blood cell). The apparently 'sudden' change in HbA1c could be because recent glycaemic status has the largest influence on HbA1c. The sponsor did not explore this issue.

Red blood cell turnover influences HbA1c: subjects with recent accelerated red blood cell regeneration may have a large proportion of red cells with low HbA1c. Any drug effect on erythropoiesis may impact on HbA1c. There were pre-clinical indications of a drug effect on red

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[28] Kilpatrick ES. Haemoglobin HbA1c in the diagnosis and monitoring of diabetes mellitus. J Clin Pathol 2008; 61: 977-982.

cells (anaemia at ~33-fold the clinical AUC). These indications were not borne out in clinical trials. Also, HbA1c changes paralleled changes in other glycaemic indicators.

HbA1c is a good surrogate of glycaemic control. Elevated HbA1c itself is unlikely to cause diabetic complications, and is considered only a surrogate for clinically important endpoints (complications such as microvascular and macrovascular disease). Furthermore, the correlation between HbA1c and complications of diabetes mellitus is complex. Firstly, while the correlation between HbA1c and glycaemia is good, it is not perfect. Secondly, diabetic complications are not the product of hyperglycaemia alone (metabolic changes in T2DM are extensive). Thirdly, risks associated with hypoglycaemia must be considered in setting target HbA1c. It would be preferable to demonstrate prevention of diabetic complications via outcome studies rather than to demonstrate improvement in HbA1c. This would involve studies stretching over many years, and oral hypoglycaemic drugs have traditionally been registered on the basis of HbA1c and related results.

In this evaluation HbA1c is accepted as a reasonable primary endpoint variable (given the basis for approval of most oral hypoglycaemic agents, the lack of specific claims regarding prevention of diabetic complications in the proposed PI and the absence of a strong suspicion of a detrimental effect of saxagliptin). Nevertheless, evidence of net benefit would be strengthened by long term outcome studies using clinically important endpoints.

Use of LOCF methodology, 'observed value' methodology and repeated measures analysis has been discussed and in evaluation of CV181011 the LOCF analysis was compared with the observed value analysis. Impact on efficacy outcomes was generally small, with the different approaches tending to provide consistent conclusions.

The general outcome of saxagliptin treatment was a 're-setting' of HbA1c to a lower value within 8-12 weeks after treatment, with no subsequent improvement relative to control treatment. After re-setting to a lower HbA1c, there was typically a steady rise in HbA1c over time, but at broadly the same rate as was seen in control arms. Extent of DPP4 inhibition with saxagliptin does not seem to change over time. Changes in regulators of glycaemia unaffected by saxagliptin may cause deterioration in HbA1c over time – from the low-point after re-setting of levels – despite ongoing inhibition of DPP4. There was no saxagliptin 'de-challenge' study in the submission, so it is not known whether, without ongoing DPP4 inhibition, HbA1c would rise to control levels.

The magnitude of mean treatment effect with saxagliptin (relative to control arms) was generally moderate, and varied across studies. It is relevant to quote from the TGA-adopted EMEA diabetes guideline (2002):[29]

"…even an apparently small reduction in HbA1c is considered clinically relevant in terms of risk reduction of diabetic complications. It is therefore necessary to balance the degree of potential inferiority against some other clinical advantage such as safety, tolerability, compliance and improvement in cardiovascular risk profile."

The small treatment effect in many saxagliptin studies should be viewed in the context of the 1.0-1.5% decrease in HbA1c often obtainable through lifestyle interventions in T2DM patients (Therapeutic Guidelines, 2009).[2]

The sponsor presented studies of saxagliptin in treatment of 'treatment-naïve' T2DM subjects in two contexts: (a) saxagliptin monotherapy (CV181011, -38), and (b) saxagliptin in combination with metformin (CV181039). The latter study (CV181039) compared 'saxagliptin and metformin' vs 'saxagliptin alone'. A difference between study populations or methodologies is evident in examination of the primary endpoint: in CV181039, saxagliptin (10 mg) alone decreased HbA1c by

[29] EMEA, Committee for Proprietary Medicinal Products (CPMP), 30 May 2002. Note for Guidance on Clinical Investigation of Medicinal Products in the Treatment of Diabetes Mellitus, CPMP/EWP/1080/00.

1.69% at 24 weeks, whereas in the monotherapy study with a 10 mg arm, the decrease was 0.54%. One explanation for this stark difference is that in CV181039, subjects generally had a higher baseline HbA1c; treatment effect size is related to baseline HbA1c. Whether this can account for the size of the difference (1.69% vs 0.54%) is unclear.

Setting this difference aside, in CV181039 combination therapy delivered an improvement in the primary outcome relative to saxagliptin monotherapy alone. There were also suggestions that metformin monotherapy was more efficacious than saxagliptin monotherapy.

The sponsor did not explore indications for initiating combination vs monotherapy in treatment-naïve subjects. The proposed indication for initial combination therapy suggests its use "when dual saxagliptin and metformin therapy is appropriate". This may be why the proposed European indications do not include a monotherapy indication. Another possible consideration is the moderate heterogeneity in efficacy results between the two monotherapy studies, with less than overwhelming efficacy outcomes in CV181038 (for example, the need to invoke differential patterns of diet and exercise across study arms, without quantification; the lack of any difference between placebo and saxagliptin arms in the proportion of subjects achieving HbA1c <7%; etc), alongside the moderate signal from CV181039 that metformin monotherapy is more efficacious than saxagliptin.

An important consideration is the impact of 'rescue' on efficacy results. While data collected after rescue were not included in efficacy analyses, rescue criteria changed at different time points during each study. The sponsor included as an efficacy endpoint the proportion of subjects discontinuing for lack of efficacy or requiring rescue. This generally favoured saxagliptin over control. What constitutes a clinically relevant difference in this proportion is debatable.

While HbA1c was the primary endpoint in these studies, monitoring of the effect of saxagliptin on lipids, blood pressure and weight is crucial in the estimation – in lieu of long-term studies directly assessing microvascular and macrovascular complications – of net benefit. At the least, new oral hypoglycaemic agents should not have a negative effect on central adiposity, blood pressure, lipid levels and other cardiovascular risk factors. Changes in lipids and blood pressure were generally presented as changes in mean values, which has limitations in that the proportion of subjects with clinically significant changes cannot be uncovered. In contrast, the sponsor carefully analysed absolute lymphocyte count (ALC) by means of (a) changes in mean values, (b) proportions of subjects exceeding pre-set fractions of change from baseline [for example, 10%, 20%, 30%...] and (c) proportions of subjects with marked abnormalities. Similarly, for HbA1c, the sponsor analysed the proportion of subjects achieving HbA1c <7%, <6.5%, a >0.7% change, etc. It would have been appropriate to apply the same rigorous analyses to variables such as lipids, weight and blood pressure.

Within the constraints of examining changes in means, there were some hints that saxagliptin is not associated with beneficial changes in lipid profiles or weight loss (for example, LT phase of CV181013). In some studies, there was the subtle suggestion of a negative effect.

A concern raised above was that HbA1c may be a good marker of glycaemic control, but that glycaemia may not be an ideal surrogate for assessing prevention of complications arising from T2DM. While the 10 year follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) supports glycaemic control as a good surrogate for improved health in T2DM, other studies are less persuasive. In ACCORD, the intensive therapy group had an increased rate of all-cause death. Differences in mortality appeared within 1-2 years and persisted during follow-up. This is reassuring in the sense that saxagliptin interim reports of LT follow-up, some with reasonable numbers of subjects followed for 2 years, do not reveal an increased rate of death in the test arm. These studies are ongoing (and are not primarily designed to compare mortality rates).

Sub-group analyses were conducted in Pooled Monotherapy and Pooled Monotherapy / Add-on datasets, "to provide greater sensitivity to detect variations in treatment effect". Nominal p-values for subgroup by treatment interactions were not adjusted for multiplicity of testing. The sponsor examined whether the effect of saxagliptin on HbA1c was modulated by subgroup to a degree that might influence clinical decisions by taking the following steps:

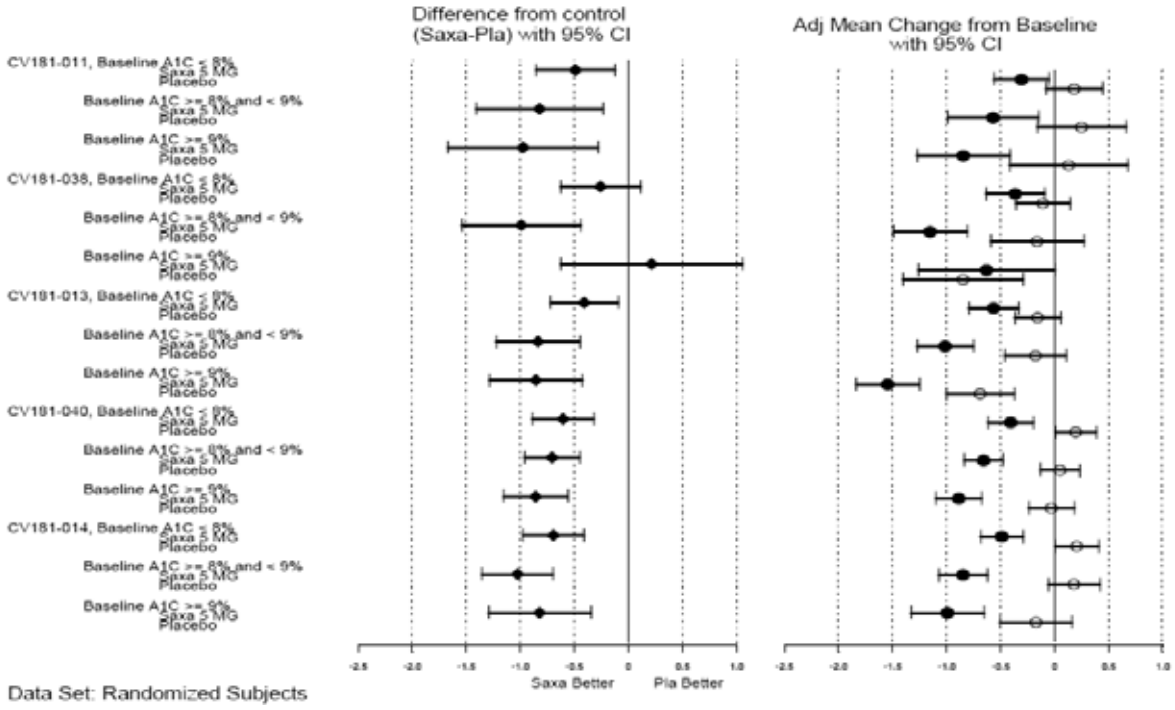
- treatment-by-subgroup interaction testing to detect, rank and evaluate subgroup categories where effect of saxagliptin might vary
- closer examination of subgroup categories with an interaction p-value <0.1 in more than one study (namely: baseline HbA1c; race; baseline HOMA-2B; and baseline creatinine clearance), by construction of lattice plots of change from baseline in HbA1c for the saxagliptin 5 mg and placebo groups

In T2DM subjects having a long duration of diabetes (for example, 10-15 years, some of which time may have been prior to diagnosis), there may be low or no β cell function. Given the mechanism of action of saxagliptin relies on the capacity of islet β cells to produce insulin, effectiveness of saxagliptin in such patients requires careful assessment. No interaction of efficacy and length of T2DM was detected in the sponsor's analysis.

The sponsor used the threshold of 65 years to assess age-related differences. Assessment of efficacy by 10- or 15-year age bracket would have been informative. Age as analysed was not shown to interact with change in HbA1c.

Saxagliptin produced greater reductions from baseline for those with higher baseline HbA1cs. Figure 14 shows adjusted mean change from baseline in HbA1c, by baseline HbA1c for Core Phase III studies excluding Study CV181039. The right-hand column provides more detail, showing values for saxagliptin and placebo, whereas the left-hand column shows only net 'saxagliptin minus placebo' values. Saxagliptin was generally better than placebo even in T2DM subjects with a lower baseline HbA1c.

Figure 14: Summary of Clinical Efficacy – Plot of adjusted mean change from baseline in HbA1c and 95% CIs at Week 24 for saxagliptin 5 mg groups in each protocol, by baseline HbA1c subgroups



Interaction p-values <0.01 for race were seen only in studies with treatment-naïve subjects. The sponsor states: "The HbA1c response observed in the comparator groups in these studies may be plausibly related to initiation of diet / exercise and other lifestyle changes inconsistently applied across a study or with differential response by race." Figure 15 shows adjusted mean change from baseline in HbA1c, by race, for Core Phase III studies excluding Study CV181039.

Figure 16 plots adjusted mean change from baseline in HbA1c at Week 24 for saxagliptin 5 mg groups in Core Phase III studies (except Study CV181039), by baseline HOMA-2B subgroups. Values were relatively consistent for saxagliptin, but varied more for comparator. An impression was left that mean change from baseline in HbA1c was slightly greater in subjects with HOMA-2B > median, although this was not the case in the saxagliptin arm of CV181011.

Figure 15: Summary of Clinical Efficacy – Plot of adjusted mean change from baseline in HbA1c and 95% CIs at Week 24 for saxagliptin 5 mg groups in each protocol, by race subgroups

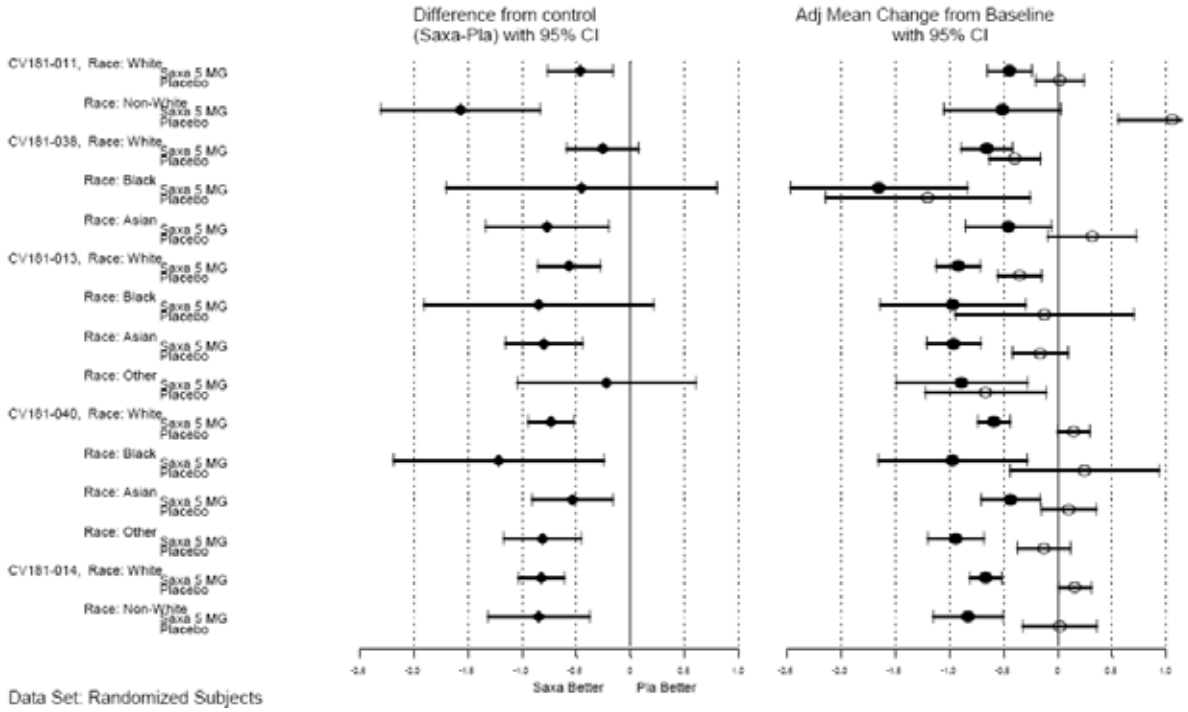


Figure 16: Summary of Clinical Efficacy – Plot of adjusted mean change from baseline in HbA1c and 95% CIs at Week 24 for saxagliptin 5 mg groups in each protocol, by baseline HOMA-2B subgroups

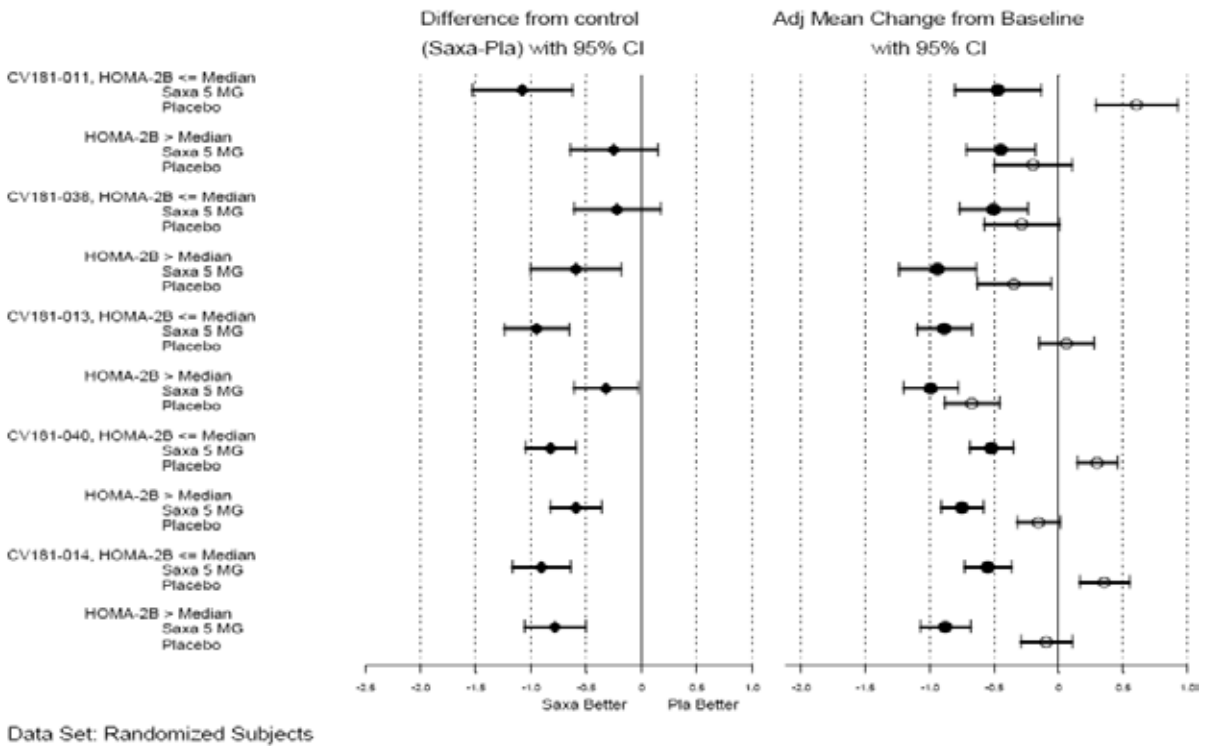
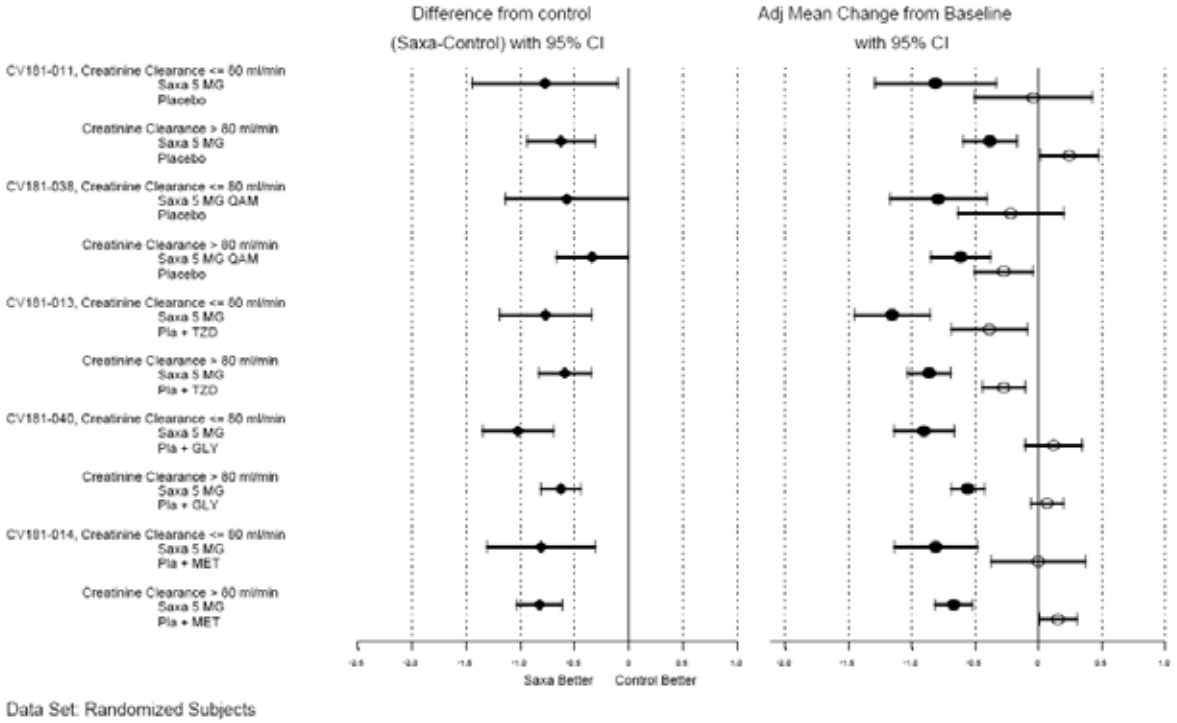


Figure 17 plots adjusted mean change from baseline in HbA1c at Week 24 for saxagliptin 5 mg groups in Core Phase III studies (except Study CV181039), by baseline creatinine clearance. There was a clear trend in the saxagliptin arms for greater change from baseline in HbA1c in subjects with $CL_{CR} \leq 80$ mL/min than in subjects with $CL_{CR} > 80$ mL/min. This trend was weaker for comparator arms. The sponsor interpreted this picture as:

"…a greater dose response separation in subjects in the subgroup with baseline creatinine clearance ≤80 mL/min in the add-on combination studies… The basis for this observation is not fully understood at this time. The pharmacokinetics of saxagliptin are unlikely to explain this pattern. Because saxagliptin increases post-prandial insulin secretion, reduced renal clearance of insulin might contribute to these findings."

Figure 17: Summary of Clinical Efficacy – HbA1c changes from baseline in subgroups based on creatinine clearance in mono and add-on therapy studies



There was evidence in some studies (CV181014, -40 and -13) that a 2.5 mg dose in subjects with CrCl <80 mL/min was sub-optimal for efficacy relative to a 5 mg dose.

Subgroup analysis by smoking would have been relevant, given the suggestion that DPP4 levels vary with smoking status (van der Velden et al, 1999).[25] One paper has noted that atorvastatin is a competitive inhibitor of porcine DPP4 *in vitro* (Taldone et al, 2008).[30] Thus, subgroup analysis by statin use would have been relevant.

The populations studied were typical of Phase III trials in having been selected from the overall T2DM population by use of extensive exclusion criteria. These criteria exclude sicker subjects, or subjects with unstable disease (for example, cardiovascular disease manifest within 6 months of screening). Thus, there is a lack of generalisability to this important sub-group of T2DM subjects (that is, sicker subjects, who may be less likely to benefit from treatment for various reasons, for example, altered PK, increased risk of drug interactions, increased vulnerability to AEs, etc).

Setting this important issue aside, the populations studied were representative of T2DM populations in Australia, except that few subjects in Core Phase III studies were >75 years of age (1.4%), no or virtually no studied subjects were indigenous Australians, and no detailed information regarding diet and exercise patterns was provided.

Evidently, a reasonable number of subjects >75 years of age must be studied to ensure efficacy and safety in this more vulnerable population.

It is also possible that T2DM is becoming more prevalent in younger people, for example, adolescents. No studies were conducted in subjects <18 years of age. It was not clear how many subjects were <30 years of age, <40 years of age, etc, as the sponsor focused on the 65 and 75 year thresholds in demographic analysis. About 25% of subjects were <48 years of age ('Q1, Q3 = 48.00, 62.00'), however it is likely most of these subjects were in their 40s.

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[30] Taldone T, Zito SW, Talele TT. Inhibition of dipeptidyl peptidase IV (DPP-IV) by atorvastatin. Bioorg Medicinal Chem Lett 2008; 18: 479-84.

Indigenous Australians have a disproportionately high rate of T2DM. In population exposure modelling, there was a minor signal that PK varied with racial group. It would have been ideal to present data in this regard concerning indigenous Australians.

Information regarding diet and exercise is important to assess the response to an oral hypoglycaemic agent. It may be that T2DM subjects in Australia follow different patterns of diet and exercise interventions, which might alter the comparison between saxagliptin and 'placebo' arms.

Across the Core Phase III studies saxagliptin was compared with placebo, metformin, thiazolidinediones and glibenclamide (a second generation sulfonylurea). During CV181013, cardiovascular safety of rosiglitazone was raised as an issue, and there was a shift within the study's control arm towards use of pioglitazone.

Comparison with glibenclamide was meant to allow generalisability to other sulfonylureas. Sulfonylureas may differ, one from another, in significant aspects (for example half-life).

One criticism with the dose choice for add-on therapies is that doses of pre-existing therapies were not uniformly maximal. This was explicit in CV181013 ("submaximal dose of a sulfonylurea") but in CV181014 (metformin add-on) and in CV181013 (TZD add-on) many subjects were not on maximal current therapy. In practice, subjects are likely to be titrated up to maximal safe and approved therapy before a second agent is added.

There was no study of saxagliptin with insulin.

The general approach in both monotherapy and add-on studies was to compare saxagliptin to placebo. In CV181039, a saxagliptin monotherapy arm and a metformin monotherapy arm were present (along with combined therapy arms). The saxagliptin monotherapy dose was 10 mg rather than the proposed 5 mg. Given that in terms of efficacy, a 10 mg dose is not expected to produce worse results than a 5 mg arm, the study design is still useful in terms of the direct comparison with an active control. The study's statistical plan avoided formal comparison between saxagliptin and metformin monotherapies. It is relevant that the TGA-adopted EMEA diabetes guideline states:

"Monotherapy studies comparing the test drug to normal standards of practice are always needed to obtain a marketing authorisation for monotherapy…"

Similarly, there was no comparison of saxagliptin add-on to 'alternative treatment' add-on, that is, in add-on studies, the only comparison was with placebo – yet in practice, an active treatment will be used (ongoing studies may address this point).

It would have been interesting to compare treatment in drug-naïve subjects to a carefully constructed intensive (as opposed to standard) dietary / exercise arm. Studies generally stated that "subjects must have made every attempt to adhere to… dietary and physical activity changes and goals as discussed with the registered dietician, registered nurse, physician, certified diabetes educator, or nutritionist" – but as stated earlier, compliance with these goals was not quantified. While a double-blind and randomised study design 'should' eliminate disparity in 'changes in diet and exercise' across arms, the magnitude of saxagliptin's impact on glycaemic targets could well change depending on extent of changes in diet and exercise across the patient population.

The TGA-adopted guidance document suggests that use of placebo should be reserved for patients at an early stage of disease, and that patients with HbA1c 8.5-10% should be studied for less than 3 months. There were sufficient rescue criteria built into Phase III studies to address this ethical issue.

Subjects treated with oral hypoglycaemic agents will remain on these agents in the long term, unless discontinuation is required due to occurrence of AEs. This means subjects may receive treatment for decades. Efficacy data for saxagliptin are available only for several years – and for less time in

some Phase III studies. All long-term results (that is, results beyond 24 weeks) were presented in interim reports, and the LT section of these studies is ongoing. Cut-offs for data inclusion were mid-January to early February 2008 (for safety, summary data were available for a further 120 days). The major impact was that in each study, not all patients were included in analyses at later time points; and for some studies, few patients were analysed beyond 37 weeks. The key question is, to what extent can 'LT' data as presented in the submission be generalised to the true 'long term' (that is, many years of daily treatment). The risk is that patients will remain on saxagliptin for the long term, with consequent risks of AEs (not to mention financial imposition), despite a tailing off of efficacy. To about 2 years saxagliptin appeared to maintain relative improvement over control treatments, despite all arms tending to show a parallel decline in HbA1cs over time.

Safety

Safety data were presented for subjects receiving ≥1 dose of study medication. Subjects who required rescue with an open-label hypoglycaemic agent were immediately entered into the LT period of the study. The sponsor states that "a higher proportion of subjects in the placebo groups required rescue agents relative to the saxagliptin groups" and that "this led to a modest exposure imbalance in some studies, which could have resulted in numerical imbalances of AEs since the frequencies of [AEs] were not adjusted for exposure".

Adverse events (AEs) were classified by intensity as: mild (Grade 1: awareness of event, but easily tolerated); moderate (Grade 2: discomfort enough to cause some interference with usual activity); severe (Grade 3: inability to carry out usual activity); and very severe (Grade 4: debilitating; significantly incapacitating despite symptomatic therapy).

AEs were classified by causal relationship with treatment as assessed by the study investigator, as certain / probable / possible / not likely / unrelated. The first three classes were grouped as 'related'.

Safety endpoints were based on: AEs, serious AEs (SAEs), discontinuations due to AEs, and results from ECGs, vital sign monitoring and clinical laboratory testing (haematology / serum chemistry including liver function tests / urinalysis). Some clinical laboratory parameters identified by the sponsor as of interest were analysed by change in mean values, outlier analysis, shift table analysis and analysis of 'marked abnormalities'. Other parameters were not necessarily analysed with outlier analysis or shift table analysis. Also, not all laboratory abnormalities were necessarily defined as 'AEs'.

120 day safety update

The sponsor provided an update to the safety information contained in the application. The update document was dated 18 October 2008. It included:

- additional LT data from ongoing Phase III studies (cut-offs discussed above were Jan-Feb 2008; cut-offs in the 120-day update were June-July 2008)
- preliminary safety data from 3 still blinded, ongoing Phase IIIb studies (CV181054; CV181056 and CV181062, all of which are still recruiting subjects), and from 2 newly completed pharmacology studies (CV181059 and Study 262-07-001)

This amounted to 823.84 extra subject-years in Phase III studies (the submission had data for 3010 subject-years), including 329 extra subject-years receiving 5 mg saxagliptin, although these exposure data do not include exposure in studies remaining blinded.

In the updated pooled safety analysis, common treatment emergent adverse effects (TEAEs) including updated information were generally no more common in the 5 mg saxagliptin arm than in the placebo arm, but some AEs were more common in the 10 mg arm:

- nasopharyngitis [8.3% for 2.5 mg; 9.5% for 5 mg; 14.3% for 10 mg; 9.9% in the placebo arm]

- influenza [7.4%, 6.8%, 12.5% and 7.6%]
- sinusitis [4.4%, 3.6%, 8.6% and 3.0%]
- tooth infection [1.1%, 1.0%, 2.2% and 1.0%]
- myalgia [3.1%, 2.0%, 3.6% and 2.5%]
- headache [8.6%, 8.5%, 14% and 8.9%]
- falls [0.6%, 1.0%, 2.9% and 0.9%]
- rash [2.0%, 2.8%, 5.4% and 1.4%]
- contact dermatitis [1.7%, 1.0%, 2.5% and 0.6%]
- blood pressure increased [0.7%, 0.7%, 2.2% and 0.3%]
- haematuria [0.5%, 0.8%, 2.5% and 1.0%]
- depression [1.5%, 2.7%, 4.3% and 1.4%]
- anxiety [1.5%, 2.2%, 2.9% and 1.1%]

There were increases across all saxagliptin doses relative to placebo for chest pain of unspecified origin [2.7%, 2.0%, 1.8% and 1.5%] and blood CK increased [2.0%, 2.7%, 2.2% and 1.6%].

In the new reporting period, 7 new deaths were reported in Core Phase III studies: 3 subjects in the saxagliptin combination therapy groups (all cardiovascular events), 3 subjects in the placebo group (1 infection and 2 cardiovascular) and 1 subject in the metformin group (cardiovascular).

There was no meaningful increase in SAEs during the additional reporting period. There were no major imbalances in SAE frequencies for saxagliptin vs placebo. In the additional reporting period, one SAE of note was elevated ALT (2375 U/L), resulting in study drug discontinuation.

For hypoglycaemia, the most notable difference relative to placebo was in the sulfonylurea add-on study (18.2% for 5 mg saxagliptin vs 12% for placebo).

AEs of special interest

Unless stated otherwise, AEs are from the ST phase of studies (that is, to 24 weeks).

Death

In Phase II-III studies, 16 subjects died during the ST+LT period: 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%) in the placebo group, and 4 subjects (1.2%) in the metformin monotherapy group. In Phase 1 studies, there were 3 deaths – all in the hepatic impairment study (CV181020). Two subjects died prior to dosing. One subject (Child-Pugh Class C) died of multi-organ failure 40 days after one 10 mg dose of saxagliptin.

Overall, there was no indication that saxagliptin was associated with increased mortality. Although follow-up beyond 26 weeks was incomplete across Phase III studies, most studies had data from a reasonable number of subjects at 1 year. Thus, although final LT study reports are required to confirm this (for example CV181011 is planned to run for 4 years), the lack of a safety signal regarding mortality appears reassuring.

Hypoglycaemia

The sponsor claims that saxagliptin's glucose-dependent mechanism of action should mitigate the risk of hypoglycaemia. Most studies compared saxagliptin to placebo, so incidence of hypoglycaemia cannot be compared across oral hypoglycaemics.

Across studies, confirmed hypoglycaemia was defined as symptoms consistent with hypoglycaemia (sweating, shakiness, increased heart rate, hunger, confusion, dizziness / light-headedness) with confirmatory finger stick blood glucose reading of≤2.8 mmol/L. Reports distinguished between confirmed and unconfirmed hypoglycaemia.

Table 6 shows incidence of all hypoglycaemia AEs in Core Phase III studies. Incidence in monotherapy studies was pooled, but for these studies further detail was provided. In one study (CV181011), incidence appeared dose-related but was no higher in the 5 mg arm than in the placebo arm (which experienced what seemed to be a fairly high incidence of events ascribed to hypoglycaemia). In the other study (CV181038), incidence was broadly dose-related, and higher than in the placebo arm.

There was an increased incidence of hypoglycaemia in Phase II Study CV181008 in the saxagliptin arm relative to placebo.

No hypoglycaemic event was considered serious by the investigator. One AE lead to discontinuation; this was in a subject in the saxagliptin 5 mg + glibenclamide arm. No hypoglycaemic AE required medical assistance.

The sponsor analysed falls, accident and trauma-related AEs on the grounds that hypoglycaemia could cause such events. Given the abundance of other causes for these events, and the absence of a large disparity in (other) hypoglycaemic AEs between saxagliptin and comparator groups, it seems unlikely studies of this scale would detect differences of this nature. Indeed, falls / accidents / trauma-related AEs occurred in 1.0% of saxagliptin patients and 0.9% of comparator patients. No reported hypoglycaemia AEs had a temporal relationship with falls / accidents / trauma-related AEs. Serious AEs of road traffic accidents were more commonly reported in subjects given saxagliptin (on at least 7 occasions, one of which was fatal, vs 0 for control subjects). In the 120 day update of safety, in the 10 mg arm, falls occurred in 2.9% (vs 0.6% for 2.5 mg, 1.0% for 5 mg and 0.9% for controls).

Table 6: Summary of Clinical Safety – All reported hypoglycaemic AEs – Core Phase III studies

Monotherapy and combination studies:

	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Placebo
ST Period, Excluding Rescue					
Pooled Monotherapy (CV181011, CV181038)	4.0% (10/247)	5.6% (14/252)	8.2% (8/98)	5.4% (32/597)	4.1% (7/169)
Add-on Combination					
+ Met (CV181014)	7.8% (15/192)	5.2% (10/191)	3.9% (7/181)	5.7% (32/564)	5.0% (9/179)
+ SU (CV181040)	13.3% (33/248)	14.6% (37/253)	N/A	14.0% (70/501)	10.1% (27/267)
+ TZD (CV181013)	4.1% (8/195)	2.7% (5/186)	N/A	3.4% (13/381)	3.8% (7/184)
Up to Week 24, Regardless of Rescue Status					
Placebo-controlled Pooled Safety	7.6% (67/882)	7.8% (69/882)	5.4% (15/279)	7.4% (151/2043)	6.8% (54/799)

Note: The frequencies for the individual populations added together do not equal the frequencies for Pooled Safety since that analysis included AEs after the initiation of rescue therapy.

Abbreviations: AE = adverse event; Met = metformin; N/A = not applicable; Saxa = saxagliptin; ST = short term; SU = sulfonylurea; TZD = thiazolidinedione.

Initial combination study with metformin:

Saxa 5 mg + Met	Saxa 10 mg + Met	Saxa 10 mg	All Saxa	Met
3.4% (11/320)	5.0% (16/323)	1.5% (5/335)	3.3% (32/978)	4.0% (13/328)

Skin disorders

Administration of DPP4 inhibitors to monkeys was associated with dose and duration-dependent necrotizing cutaneous lesions at multiple distal sites (digits, ears, nose, feet, scrotum and tail). Patients were monitored for similar findings (ulcers, erosions and necrosis). A confounding factor is the possibility of diabetic ulceration.

Few skin AEs were SAEs or lead to drug discontinuation. Incidence of 'skin and subcutaneous tissue disorders' in the ST period was marginally higher in the combined saxagliptin arms than in the comparator arms, across Core Phase III studies. In Study SV181008, incidence of skin and subcutaneous tissue disorders was 7.9-14.5% across treatment groups (including 100 mg group), and 0-6% across placebo groups.

In pooled monotherapy studies, 'rash' was more prominent in the combined saxagliptin arm relative to placebo (2.5% vs 0.6%), as was contact dermatitis (1.2% vs 0%). Four saxagliptin patients discontinued treatment due to skin-related AEs, vs none in the placebo arm. These findings were supported in the 120 day update of safety: rash was reported in 2.0% (2.5 mg), 2.8% (5 mg), 5.4% (10 mg) and 1.4% (placebo); contact dermatitis was reported in 1.7%, 1.0%, 2.5% and 0.6% respectively. No clear-cut picture of a distinctive type of rash (except contact dermatitis) emerged.

Pre-clinical study of DPP4 inhibitors (not saxagliptin) in rats suggested that DPP4 inhibitors may influence collagen metabolism (Jost et al, 2009).[6] Another pre-clinical study suggests DPP4 inhibition influences collagen secretion via an effect on TGF-β (Thielitz et al, 2008).[31]

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[31] Thielitz A, Vetter RW, Schultze B et al. Inhibitors of dipeptidyl peptidase IV-like activity mediate antifibrotic effects in normal and keloid-derived skin fibroblasts. J Invest Dermatol 2008; 128: 855-66.

Infections

This AE was identified as of special interest due to theoretical considerations – namely, interaction of saxagliptin with DPP4 (that is, CD26) on the cell surface of T cells. While infections were generally not associated with lymphopenia, this does not rule out a qualitative effect of saxagliptin on lymphocyte function – especially since many substrates of DPP4 are chemokines – contributing to susceptibility to infection.

There was no consistent indication that saxagliptin predisposed to infection with particular types of microorganism. There was no increase in the frequency of infections traditionally associated with T cell dysfunction. There was a signal that overall, infection was more frequent with saxagliptin treatment. Many of the types of infections encountered would be seen with a defect in mucosal immunity. There was no evidence of an increase in infections in normally sterile settings (for example meningitis, endocarditis, etc).

Higher frequencies of infections were observed for treatment-naïve subjects in the combined saxagliptin arms than in placebo arms (Pooled Monotherapy dataset) – 31.5% vs 23.7%.

In Study CV181011, ST period, incidence of AEs in the Infections and Infestations category was 29.5% (placebo), 33.3% (2.5 mg), 36.8% (5 mg) and 38.8% (10 mg).

In Study CV181038, ST period, incidence of AEs in this category was 27% (2.5 mg), 25.7% (5 mg QAM), 31% (2.5/5 mg) and 23.6% (5 mg QPM), vs 16.2% (placebo).

Preferred term AEs with higher incidence in the combined saxagliptin arm (pooled monotherapy) were: urinary tract infection (UTI) (4.7% vs 3.6%); sinusitis (4.2% vs 1.8%); gastroenteritis (1.3% vs 0%); influenza (2.3% vs 0.6%); and bronchitis (1.7% vs 0%). Upper respiratory tract infections were more common in the combined placebo arm (8.9% vs 10.1%). Most AEs were mild or moderate and did not require treatment interruption. Two saxagliptin patients discontinued due to infection (hepatitis C and tinea pedis). Also, 4 saxagliptin patients (one of whom discontinued and was counted above) had 5 SAEs of infection (cellulitis; gastroenteritis; hepatitis C; pyelonephritis; and pneumococcal sepsis). No placebo subjects had SAEs of infection or discontinued due to infection.

In add-on (combination) studies, incidences were comparable (though generally higher than in treatment-naïve subjects). Eight saxagliptin patients and four placebo arm patients had infection either classified as SAEs or resulting in study drug discontinuation. In Study CV181039 (initial combination with metformin), incidences were also comparable between arms. 4 SAX patients and no placebo arm patients had infections classified as SAEs.

Upper respiratory tract infections were commoner in saxagliptin-treated subjects in some placebo-controlled studies, but not others:

URI (%)	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Placebo
Pooled monotherapy	8.5%	8.3%	11.2%	8.9%	10.1%
Add-on to metformin	6.8%	4.7%	8.3%	6.6%	5.0%
Add-on to SU	4.4%	6.3%	N/A	5.4%	6.7%
Add-on to TZD	7.7%	9.1%	N/A	8.4%	7.1%

Abbreviations: N/A = not applicable; Saxa = saxagliptin; SU = sulfonylurea; TZD = thiazolidinedione; URI = upper respiratory tract infection.

There was a more consistent increase in incidence of sinusitis with saxagliptin:

Sinusitis (%)	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Placebo
Pooled monotherapy	4.5%	3.2%	6.1%	4.2%	1.8%
Add-on to metformin	1.6%	2.1%	4.4%	2.7%	2.8%
Add-on to SU	1.6%	1.6%	N/A	1.6%	1.1%
Add-on to TZD	3.6%	2.7%	N/A	3.1%	0.5%

Abbreviations: N/A = not applicable; Saxa = saxagliptin; SU = sulfonylurea; TZD = thiazolidinedione.

Higher incidence of gastroenteritis in saxagliptin subjects was relatively consistent across studies:

Gastroenteritis (%)	Saxa 2.5 mg	Saxa 5 mg	Saxa 10 mg	All Saxa	Placebo
Pooled monotherapy	0.8%	2.0%	1.0%	1.3%	0.0%
Add-on to metformin	2.1%	1.0%	2.2%	1.8%	1.1%
Add-on to SU	2.8%	2.8%	N/A	2.8%	0.7%
Add-on to TZD	1.0%	2.7%	N/A	1.8%	1.6%

Abbreviations: N/A = not applicable; Saxa = saxagliptin; SU = sulfonylurea; TZD = thiazolidinedione.

The assumption in such analyses is that sinusitis, gastroenteritis, etc, had an infectious origin, but there was no microbiological proof of this.

In Phase III studies (ST phase), abscesses at any site were encountered rarely (n=24/3021, 0.79%) with saxagliptin, and similarly rarely (n=8/1127, 0.71%) in control arms.

In the 120-day update of safety, nasopharyngitis, influenza, sinusitis and tooth infection were all AEs with a clear-cut higher incidence in the 10 mg arm than in other arms; there was generally little difference in incidence between the 5 mg arm and placebo.

Lymphopenia

There was a modest, dose-dependent reduction in the absolute lymphocyte count (ALC) among subjects receiving saxagliptin.

The sponsor notes that in T helper cells and subsets of macrophages and other haematopoietic cells, CD26 has DPP4 enzymatic activity, but states that "the weight of the evidence suggests that the catalytic site of DPP4 is not involved in CD26-dependent cellular functions" and that "the role (if any) of the catalytic activity of DPP4 in T cell biology is not yet clear".

The sponsor presented data concerning (a) the reported AE of lymphopenia; and (b) changes in lymphocyte count. Concerning the latter, the sponsor defined two thresholds: lower limit of normal (LLN; $\leq 1.0 \times 10^3$ c/μL) and marked abnormality (MA;$\leq 0.75 \times 10^3$ c/μL).

AEs of lymphopenia and / or decreased lymphocyte count resulted in discontinuation of study drug in 8 saxagliptin-treated subjects. Events were characterised as mild or moderate by investigators. All subjects had baseline ALCs that were low or low-normal. There was a 'lymphopenia algorithm' in Core Phase III studies that may have lead to "protocol-mandated discontinuation of study medication".

In one subject (CV181014-97-261), lymphopenia (0.62×10^3 cells / μL) at Day 31 was associated with prostatitis / UTI. Lymphopenia recurred three days after rechallenge with saxagliptin, before final discontinuation of study drug. In another (CV181039-11-339), lymphopenia (0.36×10^3 cells / μL) at Day 56 was associated with URI and asthma, with a left shift (that is, increased appearance of immature neutrophils, consistent with infection).

In addition to reporting AEs related to lymphopenia, the sponsor provided information concerning trends in ALCs. The sponsor reported that:

- Saxagliptin 10 mg was consistently associated with a reduction in ALC, and in studies with longest follow-up this decline was 10% relative to placebo at 12 months, apparently not increasing in magnitude at later time points. Table 7 quantifies this information for the pooled monotherapy dataset; broadly similar results were obtained in Study CV181014, which also followed a reasonable number of subjects to 2 years. Subjects in the top third for baseline ALC experienced the largest absolute decline in lymphocyte count (for example, in the placebo-controlled pooled safety dataset, for combined saxagliptin subjects the median decline was 0.32 x 10^9 c/L, vs a 0.20 x 10^9 c/L decline for placebo). The clinical significance of such findings is only in their reflection of larger declines in outlier subjects (in particular, declines below the lower limit of normal, and declines to the point where infection risk is increased).

Table 7: Summary of Clinical Safety – Absolute lymphocyte count (x 10^3 c/µL) in the pooled monotherapy population (ST+LT) – percent change from baseline

	Treatment Group	N =	Percent Change From Baseline			
			Mean	SE	Median	95% CI
6 months (Week 24)	Saxa 2.5 mg	194	3.17	2.353	0.22	-1.47, 7.81
	Saxa 5 mg	195	-2.17	1.762	-3.78	-5.64, 1.31
	Saxa 10 mg	78	-3.99	2.447	-5.49	-8.86, 0.88
	All Saxa	467	-0.25	1.295	-2.33	-2.8, 2.29
	Placebo	133	4.48	2.730	-1.66	-0.92, 9.88
12 months (Week 50)	Saxa 2.5 mg	96	1.29	3.941	-3.50	-6.54, 9.11
	Saxa 5 mg	99	-1.77	2.305	-2.74	-6.35, 2.8
	Saxa 10 mg	71	-9.34	2.270	-11.29	-13.87, -4.82
	All Saxa	266	-2.69	1.781	-5.53	-6.19, 0.82
	Placebo	80	1.04	2.346	0.00	-3.63, 5.71
18 months (Week 76)	Saxa 2.5 mg	51	2.39	5.946	-4.21	-9.55, 14.33
	Saxa 5 mg	60	-0.67	3.284	-3.90	-7.25, 5.9
	Saxa 10 mg	63	-6.34	2.749	-7.57	-11.84, -0.85
	All Saxa	174	-1.83	2.306	-5.53	-6.38, 2.72
	Placebo	49	-7.54	2.676	-6.79	-12.92, -2.16
24 months (Week 102)	Saxa 2.5 mg	22	-4.34	4.868	-5.89	-14.46, 5.79
	Saxa 5 mg	35	2.01	5.669	-4.03	-9.52, 13.53
	Saxa 10 mg	40	-8.21	2.847	-10.68	-13.97, -2.45
	All Saxa	97	-3.64	2.618	-8.28	-8.84, 1.55
	Placebo	26	-5.38	3.686	-1.43	-12.97, 2.21

Abbreviations: CI = confidence interval; LT = long-term; Saxa = saxagliptin; SE = standard error; ST = short term.

- In the placebo-controlled pooled safety dataset, in the 5 mg group the decline in mean ALC at 6 months was 0.1 x 10^9 c/L relative to placebo (from a baseline of 2.2 x 10^9 c/L)
- In the placebo-controlled pooled safety dataset, changes in ALC were comparable in the saxagliptin 2.5 mg group and the placebo group
- In outlier analysis, SAX 10 mg was associated with "a measurable reduction in ALC as assessed by the number of subjects reaching pre-defined thresholds"; this was the case to a lesser extent for saxagliptin 5 mg, and not the case for saxagliptin 2.5 mg. The sponsor noted that substantial variation in percentages was driven by small numbers of subjects.

- In an analysis of any subject with an ALC≤0.75 x 10^3 c/μL, in the dataset of 'all Core Phase III studies with a fixed dose saxagliptin dosing regimen', in the ST+LT period, 27 subjects given saxagliptin (out of 2126; 1.27%) had such a MA, vs 4 comparator subjects (out of 1051; 0.38%). 10/27 saxagliptin subjects received 10 mg doses. 22/27 MAs were recorded in the ST period. It should be noted that in Study CV181038 (with an uptitratable saxagliptin protocol), 7/282 saxagliptin subjects (2.5%) and 0/74 placebo subjects had this marked level of lymphopenia. Similarly, a pooled analysis of results from all Phase II-III studies revealed a frequency of MAs (ALC ≤0.75 x 10^3 c/μL) of 0.9% (8/924) for saxagliptin 2.5 mg, 1.5% (19/1255) for saxagliptin 5 mg, 1.4% (15/1046) for saxagliptin 10 mg, 0.5% (5/911) for placebo arm subjects, and 0% (0/328) for metformin subjects. Three additional subjects with marked lymphopenia received saxagliptin 20-40 mg.
- Of the 50 subjects in Phase II-III studies with marked lymphopenia, 20 experienced 'isolated' declines; in 10 of these subjects, study drug was interrupted, and in 1 subject the drug (placebo) was discontinued. 30 subjects (29 saxagliptin; 1 placebo) experienced non-isolated declines to ≤0.75 x 10^3 c/μL; the lowest value recorded was 0.30 x 10^3 c/μL. Of the 30 subjects, 14 had interruption to treatment (12/14 were rechallenged with saxagliptin; 3 of these 12 subjects experienced a further MA, but these 3 subjects had lowish baseline ALCs), 9 discontinued and 7 had no action taken (2 of these 7 subjects recorded a further MA).
- All subjects given saxagliptin 10 mg or less who developed a MA in ALC had a baseline count <2 x 10^3 c/μL.
- Subjects with MAs in ALC were assessed for higher rates of infection and for infections traditionally associated with T cell dysfunction (herpes virus; varicella; EBV; CMV; TB; serious fungal infection). No correlations were observed. While 16 of 30 subjects with non-isolated marked lymphopenia had temporally related infectious AEs, the sponsor noted that depending on length of follow-up the incidence of infectious AEs in some studies (for example, CV181014) was over 50%. The sponsor did not report any "unusual or opportunistic" infections in these subjects, despite the combination of lymphopenia and diabetes. However, 15/3422 (0.44%) saxagliptin subjects vs 3/1251 (0.24%) comparator subjects experienced herpes zoster. A similar proportion of subjects experienced herpes simplex AEs. One 2.5 mg saxagliptin subject (and no comparator subjects) experienced onset of pulmonary tuberculosis; the subject had no history of TB. Few of these subjects with HSV or VZV infection had an AE of lymphopenia or marked lymphopenia.

In several early clinical pharmacology studies of drug interactions (CV181005, -17), a third of subjects developed lymphopenia and flu-like symptoms. In subsequent studies designed to examine this AE (without actually replicating the design of studies CV181005 or -17), and in Phase III studies, this syndrome was not recapitulated.

Once saxagliptin is marketed, lymphopenia may not be monitored as closely as in clinical trials. Those who are susceptible to lymphopenia will have it for longer as the study drug may not be discontinued early (in Phase III studies an algorithm was used to determine drug discontinuation based on ALC). Those patients may be more vulnerable to infection. Also, subjects with immunodeficiency or lymphopenia at baseline were excluded from study.

As noted above, measuring the number of lymphocytes in blood does not capture many important aspects, such as lymphocyte function, differential changes in sub-groups of lymphocytes (for example, those that rely more on DPP4 substrates), lymphocytes in compartments other than blood, etc.

In Study CV181031, immunophenotyping was utilised to measure percentage and absolute number of T and B lymphocytes, NK cells and subsets. No particular lymphocyte population was affected following 40 mg saxagliptin rechallenge where decreases in ALC were observed. "Most CD4 and CD8 T cells express relatively high levels of CD26, while fewer B cells and NK cells expressed

relatively low level of CD26 molecule" [sic]. CD26 expression was slightly higher on CD4 and CD8 effector memory populations.

No increase in apoptosis or necrosis was observed after 40 mg saxagliptin rechallenge based on annexin V and 7AAD staining. No decrease in lymphocyte proliferation was observed. The sponsor states that the mechanism for the lymphocyte decrease remains unknown. An untested mechanism is sequestration – relevant because (a) pre-clinical studies identified what was termed 'lymphoid hyperplasia' in some lymphoid organs, and (b) DPP4 acts on some chemokines. The AE of lymphadenopathy was not prominent. Another theoretical possibility is decreased lymphopoiesis.

Thrombocytopenia

In the 'placebo-controlled pooled safety' dataset, 8/2043 saxagliptin subjects (0.4%) and 1/799 placebo subjects (0.1%) had AEs related to thrombocytopenia. In the monotherapy population, one subject in the saxagliptin 10 mg group had a severe AE with 'certain' relationship to study drug. This subject had a nadir of 51 x 10^9 cells / L at Day 313, with preceding bleeding-related AEs; on Day 469 a positive indirect anti-platelet test lead to a presumptive diagnosis of autoimmune thrombocytopenia. The subject continued on aspirin throughout. The thrombocytopenia resolved without treatment. The relationship does not appear 'certain' – 'possible' seems more appropriate.

Another patient in the saxagliptin 5 mg group had severe thrombocytopenia on Day 365, requiring hospitalisation; a bone marrow aspirate was interpreted as myelodysplastic syndrome. A 'probable' relationship was ascribed. Because of a response to prednisone and single cell line involvement, a haematologist diagnosed ITP rather than MDS. There was an absence of increased megakaryocytes in the bone marrow – atypical for ITP.

The sponsor analysed platelet counts, and found no meaningful change based on measures of central tendency. A slight decrease in mean counts was discernible, persisting to 24 months. At 6 months, median change in platelet count for all saxagliptin patients in the Pooled Monotherapy studies was -3.5%, and for placebo arm -2.1%. At 24 months, median change for saxagliptin subjects was 0.0% and for placebo arm subjects 4.6%. In outlier analysis, the number of subjects reaching ≥20% or ≥30% reduction in platelet counts was comparable between saxagliptin and comparator arms, although results at 18 and 24 months were difficult to interpret because of small sample size. Markedly low platelet counts were "infrequent (0-1 subject in any treatment group of any study)" but these data were not tabulated.

Localised oedema

Symptomatic oedema of the hands and feet has been observed with another DPP4 inhibitor. In the saxagliptin Core Phase III program, a difference between groups was only observed in the saxagliptin 5 mg (add-on to TZD) arm vs placebo (add-on to TZD) arm of Study CV181013 (7.0% vs 2.7%). In the saxagliptin 5 mg arm, of the 13 events, 11 were pedal oedema, 1 was eyelid oedema and 1 was periorbital swelling; all events were mild. The lower dose saxagliptin arm had a frequency of 1.0%. In studies where subjects could be rescued with TZD (and thus take the combination of saxagliptin and TZD), there was no evidence of a significant incidence of localised oedema.

In the addendum to the sponsor's *Clinical Study Report* 181011, it was noted that in the ST treatment period, in the saxagliptin arm there were 4 cases of pedal oedema or foot swelling, and one case of eyelid and palatal oedema, whereas there were no cases of localised oedema in the placebo arm.

In Study CV181038 (ST period), localised oedema was reported in 0.68% of saxagliptin subjects (pedal) and 2.7% of placebo subjects (digital and pedal).

Co-use of saxagliptin with ACE inhibitors may be predicted in the T2DM population. Some research has suggested that the combination may increase risk of ACEI-induced angioedema (Grouzmann and Buclin, 2008).[26] The basis of this claim is that DPP4 acts on substance P, and that substance P may be implicated with bradykinin in a cascade leading to angioedema. The sponsor did not analyse oedema or angioedema by ACE inhibitor use.

Cardiovascular events

Cardiovascular events are a complication of T2DM and could reflect ineffective (prior) treatment, but could also be AEs. Data concerning these AEs must be interpreted in the context of the patient population being treated. An older group, or a group with a longer history of T2DM, may have a different cardiovascular AE profile.

Cardiovascular AEs (limited to: cerebrovascular accident; unstable angina; myocardial ischaemia) to 24 weeks were no more frequent in the saxagliptin group of the 'Placebo-controlled Pooled Safety' dataset (7/2043; 0.3%) than in the placebo group (8/799; 1.0%). In Study CV181039, frequencies were 0.6% (all saxagliptin) and 0.9% (metformin only).

Using a broader definition of cardiovascular AEs, many more events were recorded. For example, 'chest pain' (otherwise unspecified) was reported in multiple subjects, without qualification as to its origin.

Some oral hypoglycaemic agents are reported to have a positive or a negative impact on cardiovascular risk factors, with implications for long-term benefit of treatment. Therefore, it is important to examine evidence that saxagliptin may influence cardiovascular risk factors other than hyperglycaemia itself.

Hypertension was prominent as an AE in multiple settings. Firstly, in the LT phase of CV181038, hypertension was reported as an AE in 2.7% of saxagliptin subjects vs 1.4% of placebo subjects. Secondly, in CV181013, hypertension was considered a treatment-related SAE in one saxagliptin subject. Thirdly, in CV181040, hypertension was reported as an AE in 5.0% (SAX) vs 2.2% (GLIB) (with a difference persisting into the LT phase). Fourthly, in CV181039, hypertension was reported as an AE in 4.5-5.3% (saxagliptin-containing arms) vs 3.4% (MET+PLAC arm). Finally, in the 120 day safety update (which would incorporate some of the above information), it was noted that the AE of increased blood pressure occurred in 0.7% (2.5 mg), 0.7% (5 mg), 2.2% (10 mg) and 0.3% (control). Blood pressure was monitored in all Core Phase III studies but only means relative to baseline were presented in CSRs. No notable changes were shown. Presumably, hypertension as an AE would have been picked up by outlier analyses. Likewise, it would have been informative to present outlier analyses for weight change and lipid (for example, HDL: LDL) changes.

Arrhythmias and QT prolongation

Study CV181032 examined the effect of saxagliptin on QT interval. The assay was sensitive enough to detect a QTc increase with moxifloxacin of 7.83 msec. Following 10 and 40 mg once daily dosing with saxagliptin, maximum increases in placebo-corrected mean change in QTc interval from baseline were 2.3 msec at 4 hours post-dose and 2.4 msec at 24 hours post-dose, respectively. The sponsor concluded that saxagliptin did not significantly prolong the QTc interval or alter heart rate at these doses.

In Core Phase III studies, ECG results were reported as 'normal' vs 'abnormal' tracings, that is, reporting was not sensitive to particular ECG changes. Specific arrhythmias were reported as AEs. There was no apparent trend towards higher incidence of arrhythmias with saxagliptin.

Myopathy

Myopathy may be reflected in reports of myalgia or creatine kinase elevation. The broad term musculoskeletal pain could also include myopathic events, but may also include bone and joint

pathology. The sponsor reported both AEs pertaining to myopathy and trends in creatine kinase levels (specifically, marked abnormalities in CK, that is, CK >5 x ULN).

An increased frequency of markedly high CK levels was seen for saxagliptin relative to comparator arms only in the add-on combination studies. In a pool of all Phase II-III studies, marked elevation of CK was seen in 1.1% of both saxagliptin and placebo subjects. In the 120-day update of safety, incidence of myalgia was 3.1% (2.5 mg), 2.0% (5 mg), 3.6% (10 mg) and 2.5% (placebo). Incidence of elevated blood CK was 2.0%, 2.7%, 2.2% and 1.6% respectively. Overall, there is a modest signal that saxagliptin use increases the risk of markedly elevated CK.

Psychiatric AEs

There were isolated signs for psychiatric AEs, but no consistent picture emerged in individual studies:

- In the ST+LT analysis of CV181011, depression was reported in 4.6% (saxagliptin) vs 2.1% (placebo). (In study CV181038 there was no such picture.)
- In CV181014, aggravation of schizophrenia and major depression were AEs leading to discontinuation of saxagliptin.

In pooled datasets, a modest signal was apparent:

- In the placebo-controlled pooled dataset to Week 24, psychiatric disorders as a category were reported in 33/882 (3.7%) in the 2.5 mg arms, 42/882 (4.8%) in the 5 mg arms, 14/279 (5.0%) in the 10 mg arms and 27/799 (3.4%) in the placebo arms.
- In the 120-day update of AEs, it was notable that depression was reported in 1.5% (2.5 mg), 2.7% (5 mg), 4.3% (10 mg) and 1.4% (placebo). Likewise, incidence of anxiety was 1.5%, 2.2%, 2.9% and 1.1% respectively.

There is a moderate signal for these important AEs. Substrates for DPP4 include neuropeptide Y, substance P, endomorphin, etc.

Hepatic function

The sponsor noted that vildagliptin was associated with effects on liver transaminases. The sponsor assessed (a) AEs concerning hepatic function, and (b) trends in liver function tests (LFTs) (change from baseline; marked abnormalities; shift tables; combinations of abnormalities). Changes in gamma-glutamyl transaminase (gGT) were not reported.

Marked abnormalities were balanced across saxagliptin and comparator arms in the ST period (in the placebo-controlled pooled safety dataset). The only subject with AST or ALT >10 x ULN was in the saxagliptin 2.5 mg group. This AE was ascribed to acute hepatitis C by a hepatologist (antibody positive despite a negative baseline result; viral RNA load by PCR, >750 000 IU/mL). The AE resulted in study drug discontinuation at Day 56.

Over the ST+LT period in Phase II-III studies, marked abnormalities for LFTs were comparable across saxagliptin and comparator arms. There was no clear excess of elevations in aminotransferases >3 x ULN in saxagliptin subjects relative to controls. However, 2/3376 saxagliptin subjects had AST elevations >10 x ULN (vs 0/923 for placebo) and 4/3376 saxagliptin subjects had ALT elevations >10 x ULN (vs 0/923 for placebo). The relatively small number of placebo subjects means that it is difficult to rule out a signal for rare but serious hepatotoxicity.

One subject in the saxagliptin 10 mg group stopped treatment on Day 273 because of AST and ALT >10 x ULN on Day 269 (Alkaline phosphatase [ALP] and bilirubin); LFTs had almost normalised by Day 281. Another subject in the saxagliptin 100 mg group had increased LFTs (AST and ALT)

from Day 29, peaking on Day 43 at >5 x ULN and resolving around Day 84. Another subject's outlying LFT increases were attributable to hepatitis A infection.

An additional concern identified was the modest increase in frequency of elevated total bilirubin in saxagliptin subjects relative to placebo arm. Injury to hepatocytes sufficient to cause jaundice or near jaundice is an important signal for the potential for drug-induced liver injury. For example, elevation >1.5 x ULN for total bilirubin was seen in 23/3375 saxagliptin subjects (0.7%) vs 3/912 placebo subjects (0.3%) – but this threshold was also reached in 3/319 metformin subjects (0.9%). Elevation to >2 x ULN was seen in 5/3375 saxagliptin subjects (0.1%), 0/923 placebo subjects and 1/319 metformin subjects (0.3%).

Bone

In Study CV181038 (ST period), reduction in alkaline phosphatase from baseline to Week 24 was noticed in the saxagliptin arms but not the placebo arm. This was also noticed in Study CV181014 (mean change from baseline: -4.1 to -7.8 in the saxagliptin arms vs -2.1 U/L in the placebo arm). In Study CV181014, LT period, the decrease in alkaline phosphatase was observed to Week 102 in the saxagliptin groups, although a decrease in this parameter in the placebo group was also noticed from Weeks 63-102. It would have been informative to include outlier analysis for this parameter. Also, with available data, it is not clear which isoenzyme is being affected (for example, liver vs bone). There is no evidence to suggest this decrease in alkaline phosphatase is due to decreased bone turnover. In lieu of analysis by the sponsor, crude analysis (by searching for the term 'fracture' excluding tooth fracture) of the Core Phase III trials found 36 'fracture' events in the ST+LT phase in 3021 saxagliptin-treated subjects (13/882 for 2.5 mg; 12/1202 for 5 mg; 11/937 for 10 mg), vs 8 event in comparator subjects (n=799). This equates to 1.19% frequency for saxagliptin and 1.00% for control subjects, but does not account for time exposed to drug. DPP4 inhibitors have been associated with alterations in collagen metabolism; collagen is a key component of bone. Taken together, these data provide a moderate safety signal. It may also be that any increase in fractures could be related to an increase in falls and other accidents.

Renal function

The frequencies of elevated creatinine, elevated urea and altered urinary protein / blood / red cells were comparable across saxagliptin, placebo and metformin arms in the Phase II-III studies (ST+LT).

In the placebo-controlled pooled safety dataset, 4/2043 saxagliptin subjects but 0/799 placebo subjects discontinued due to increased blood creatinine.

An inconsistent picture emerged of pyuria (white blood cells detected on urinalysis). Generally, only a fraction of subjects provided data for this variable. For example, in CV181038 and in CV181039, less than a third of subjects provided data. Also, there was considerable variability across studies. For example, in CV181011, pyuria was in the order of 2.3% (placebo) to 5.8% (saxagliptin) in the ST phase, while in CV181038, incidence of pyuria was 5.6% (placebo) vs 21.1-35.3% (saxagliptin). Potentially, some detection of white cells on urinalysis could be due to UTI, and in CV181011 there was an increased incidence of UTI in the saxagliptin arm (6.9% vs 4.2%). In CV181014, there was no signal for pyuria, while in CV181039, incidence was higher in the non-saxagliptin (metformin control) arm than in saxagliptin arms.

Hyponatraemia (serum sodium <0.9 x baseline and≤130 mEq/L) was more common in Phase II-III studies in the saxagliptin 10 mg arm (9/1047; 0.9%) than in other saxagliptin arms (2.5 mg arm: 0%; 5 mg arm: 0.2%), placebo arms (0.2%) and the metformin arm (0%).

Hypersensitivity

A pre-defined list of preferred terms was used to identify AEs potentially related to hypersensitivity. In the ST+LT period, in the pooled monotherapy dataset, 19/597 (3.2%) subjects had such AEs, vs 3/169 (1.8%) in the comparator arm. All hypersensitivity AEs in the saxagliptin arm were mild or moderate; none led to study drug discontinuation.

Marginally higher rates were seen in the saxagliptin arm relative to comparator for all add-on combination studies (2/1446 saxagliptin subjects discontinued due to hypersensitivity AEs); but for the initial combination study with metformin, frequencies were similar.

In the Phase IIb study CV181008, there was a suggestion of dose-dependency for frequencies of hypersensitivity AEs (frequencies of 1.8%, 2.1%, 3.2%, 0% and 3.8% in the saxagliptin 2.5, 5, 10, 20 and 40 mg groups, vs 1.5% in the placebo group). There were no cases in the 0,100 mg cohort.

Across the Phase II-3 program, in the saxagliptin arms, neither of the 2 hypersensitivity AEs of severe intensity were characterised as causally related to saxagliptin, however, 3 hypersensitivity AEs resulting in study drug discontinuation (face oedema on Day 93; urticaria on Day 219; urticaria on Day 28) were at least possibly related to saxagliptin.

Drug-induced nephritis may be signalled by eosinophilia, fever and sterile pyuria. Some studies reported an increased incidence of eosinophilia in saxagliptin subjects, and some studies reported an increased incidence of pyuria (not necessarily sterile) in some subjects on saxagliptin, but there was no clear-cut signal for drug-induced nephritis in the data provided.

Flu-like syndrome

In drug interaction study CV181005, flu-like syndrome (headache, myalgia, fever or chills) was reported in 5/15 subjects taking a second dose of saxagliptin 100 mg, 1-2 weeks after dose 1. In drug interaction study CV181017, the syndrome was reported in 4/16 subjects in the same dosing context. All subjects with the syndrome had ALCs below LLN, but counts returned to normal within 72 hours of dosing. Studies CV181022 and CV181031were conducted to examine this phenomenon further, following daily and / or interrupted 5 to 40 mg doses of saxagliptin or 20 mg saxagliptin plus ketoconazole. No clinical signs or symptoms of flu-like syndrome were detected. The flu-like syndrome with lymphopenia was not observed in Phase III studies (with 10 mg saxagliptin or lower). The syndrome was also not observed with daily saxagliptin up to 400 mg once daily for 2 weeks (CV181010), 100 mg once daily for 6 weeks (CV181008) and 40 mg once daily for 12 weeks (CV181008).

Discussion of safety

Havale et al (2009) identify two theoretical concerns with use of DPP4 inhibitors: (a) side-effects due to inhibition of other functions of DPP4 (mainly degradation of other DPP4 substrates); and (b) selectivity against closely related enzymes (DPP2 or QPP; DPP8; DPP9; and FAP).[7] Thus, there are plausible mechanisms of action to support a broad range of AEs.

The following issues are highlighted:

- There was no overall mortality signal, although studies were not powered to examine mortality (and studies examined use of saxagliptin to only about 2 years).
- Hypoglycaemia did occur with use of saxagliptin, though not at a particularly high rate; the higher rate of falls in the 10 mg arm could possibly be linked to hypoglycaemia.
- While pre-clinical signals for skin disorders were not detected in clinical studies, saxagliptin use did appear to be associated with rash and contact dermatitis.

- There was a suggestion that saxagliptin use slightly increased the risk of infection, but no specific type of infection was implicated (beyond infection at mucosal surfaces such as sinusitis and gastroenteritis). Infection at normally sterile sites was not prominent.
- There was a definite if generally modest drug effect of saxagliptin on lymphocyte count, but details of any effect on lymphocyte function were lacking. The best read-out of lymphocyte function is incidence of infection, which as stated above was slightly elevated overall.
- There was no striking increase in cardiovascular AEs. Any impact may not be revealed in the short (generally <2 year) time patients were under study. As a surrogate, cardiovascular risk factors were examined: there was no evidence of any particular benefit provided by saxagliptin for lipid profile and weight (although evidence of a negative impact was slight), while there were some minor signals regarding hypertension in patients treated with saxagliptin.
- There was the suggestion that in rare instances, patients given saxagliptin may develop elevated CK; incidence of clinical myopathy (that is, myalgia etc) was very low.
- For psychiatric AEs and for fractures, there was a modest safety signal, but these AEs were not rigorously analysed in the submission.
- While drug-induced liver injury could not be ruled out as a consequence of saxagliptin use in some subjects, no classic safety signals based on appropriate elevations in AST / ALT / bilirubin relative to placebo emerged.
- In two early pharmacology studies, a distinctive syndrome of flu-like illness and decreased lymphocyte count emerged with the interrupted use of saxagliptin and either metformin or the CYP3A4 inhibitor ketoconazole. The cause of such a syndrome could not be established, not could the syndrome be detected in further studies.

Broad analysis of AE frequency by intrinsic factors (for example, age by category; gender; BMI; duration of diabetes) revealed no important differences in AE frequency. Actual differences in AE frequency between such subgroups (for example, male vs female) may be limited to particular AEs, and thus disguised by broad analysis of all AEs.

In the placebo-controlled pooled safety dataset, in the ST period, analysis of AE frequency in subjects with renal impairment (estimated creatinine clearance ≤80 mL/min) vs subjects without renal impairment did not uncover a greater incidence of AEs in subjects with renal impairment. This was a conservative analysis in that it was not restricted to renally impaired subjects given saxagliptin 2.5 mg; instead, renally impaired subjects received 2.5 – 10 mg. Amongst commoner AEs, only gastroenteritis was more common in saxagliptin subjects relative to placebo arm subjects in the renally impaired subset. In the smaller Pooled Monotherapy dataset, in the renally impaired subset, URTI (7.8% vs 5.7%) and influenza (6.9% vs 2.9%) were more frequent in the saxagliptin arm than in the placebo arm; many other AEs were less frequent in the saxagliptin arm (for example, UTI; pharyngitis). In the small 'initial combination with metformin' dataset, both 'blood creatinine increased' and hypertension were (a) increased in the saxagliptin arm vs the metformin arm in the renally impaired subgroup, and (b) increased in the saxagliptin, renally impaired arm vs the saxagliptin, renally unimpaired arm (the outcome of this latter comparison is expected for the AE of 'blood creatinine increased'). Increases in creatinine were generally modest.

A total of 12 women (9 receiving saxagliptin) became pregnant during the Phase II-III clinical program. At least 4 subjects had insufficient data or were still pregnant. This number of subjects is insufficient to draw robust conclusions. Mention was made of one pregnancy in the saxagliptin group that resulted in abortion, with the abortus having a 'birth defect' (no further details were supplied).

Finally, the population studied was selected from the general T2DM population by use of inclusion and exclusion criteria. Saxagliptin's safety profile in the more general population may be different from that outline above. For example, subjects with serum creatinine >132.6 µmol/L were excluded from many Core Phase III studies. This means that few subjects with moderate renal impairment, and probably none with severe impairment, were included in Core Phase III studies. Nevertheless, the sponsor is seeking to register saxagliptin for use in these populations, as evidenced by the special dose reduction proposed in such patients on the basis of a Phase 1 pharmacology study.

Clinical Summary and Conclusions

Pharmacology

Saxagliptin pharmacokinetics and pharmacodynamics were generally well characterised. Sufficient data were presented to characterise the principle aspects of saxagliptin's absorption, metabolism and elimination, and likewise for saxagliptin's main metabolite (BMS-510849). Data provided in pharmacology studies generally supported saxagliptin's proposed mechanism of action. Saxagliptin, by inhibiting dipeptidyl peptidase 4, increases intact incretin concentrations. Relative importance of GIP and GLP-1 in glycaemic control remains unclear. Relative importance of C_{max} and AUC to efficacy and safety of saxagliptin is not well characterised. Effects of saxagliptin on other DPP4 substrates were not characterised.

General issues regarding efficacy and safety

Few subjects >75 years of age (n=59) were included in Phase III studies, yet T2DM is commonly encountered in this age group. Subjects in this age group are vulnerable to consequence of AEs and are more likely to have declining renal function, use of concomitant medications, etc. The evaluator recommended emphasising in the Product Information that safety and efficacy in this age group is not well characterised. A reasonable, alternative approach would be to contraindicate use in this age group until further clinical trial data are available for analysis.

T2DM is a chronic disease. The saxagliptin development program provided efficacy and safety data to about 2 years (although the long-term component of Phase III studies is incomplete). The sponsor should be asked to provide all further interim analyses of the long-term phase of Core Phase III studies, and analyses of completed long-term Phase III studies, as promptly as possible.

Treatment-naïve subjects

Phase III monotherapy studies confirmed that saxagliptin treatment was superior to placebo in treatment of treatment-naïve T2DM subjects. In practice, a treating doctor will not be reassured by superiority of saxagliptin over placebo. Either superiority over a carefully structured intensive programme of diet and exercise improvements, or superiority over currently used pharmacotherapies, would be reassuring. The former comparison was not made. The latter comparison was made in Study CV181039 (where a 10 mg saxagliptin monotherapy dose rather than a 5 mg dose was chosen for study). Metformin is widely used as an initial therapy in T2DM, alongside lifestyle intervention (Davis, 2008).[3] No formal comparisons were attempted between saxagliptin monotherapy and metformin monotherapy in this study; the study did not have a non-inferiority design. Initial use of saxagliptin and metformin appeared more efficacious than initial use of saxagliptin. Despite the lack of formal statistical comparisons, it also appeared that metformin monotherapy was marginally more efficacious than saxagliptin monotherapy in this setting (though its statistical superiority was not tested). These efficacy outcomes should be considered alongside safety outcomes. Serious AEs (including deaths), discontinuations due to AEs and hypoglycaemic AEs were all experienced slightly more frequently in the metformin monotherapy arm than in the saxagliptin monotherapy arm, in the short term (24 week) phase. For treatment-naïve patients, net benefit appears to be greatest with initial combination treatment with saxagliptin (5 mg) and metformin. Therefore, for treatment-naïve subjects, the evaluator recommended approval of the initial combination indication but not the initial saxagliptin

indication. Use of initial combination therapy is not common practice, but results of CV181039 support this approach. As with use of saxagliptin in general, studies of initial combination therapy that confirm a long-term benefit on outcomes other than surrogate outcomes should be conducted, although it may be difficult to enforce their conduct.

Add-on therapies

Phase III add-on studies confirmed that saxagliptin was superior to placebo when added to existing therapies that are failing to provide adequate glycaemic control. Given the need for alternative agents in T2DM, it is reasonable to accept the 'add-on' indications for saxagliptin.

Safety

The safety of saxagliptin was reasonably characterised. The sponsor described an overall clinical AE profile comparable to placebo, but saxagliptin produces a sustained decrease in lymphocyte counts (marked in some subjects), has a poorly characterised effect on lymphocyte function and is associated with a slightly higher overall risk of infections. There were also modest safety signals for rash (including contact dermatitis), hypertension, elevations in CK, depression, anxiety, fractures and hypersensitivity.

Recommendations based on net benefit

The evaluator recommended approval of registration of saxagliptin for:

Initial combination

Onglyza is indicated for use as initial combination therapy with metformin, in patients with type 2 diabetes mellitus, to improve glycaemic control as an adjunct to diet and exercise, where diet and exercise alone does not improve glycaemic control.

Add-on combination

Onglyza is indicated in patients with type 2 diabetes mellitus, to improve glycaemic control, in combination with metformin, a sulfonylurea, or a thiazolidinedione, as an adjunct to diet and exercise, when the single agent alone does not provide adequate glycaemic control.

V. Pharmacovigilance Findings

There was no Risk Management Plan submitted with this application as it was not a requirement at the time of submission.

VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The pharmaceutical chemistry evaluator noted that saxagliptin is presented in film coated and unscored tablets. The molecule is chiral – saxagliptin is present as a single enantiomer. Saxagliptin is present in the tablets as the base – one polymorph is known. Saxagliptin is freely soluble in water. The different strengths are not direct scales (that is, identical qualitative formulation; dose proportional only for the active ingredient).

Bioavailability

No initial absolute bioavailability study was done, even though saxagliptin is readily water soluble and an intravenous infusion could have been done. In lieu of an absolute bioavailability study, data from a radiolabelled pharmacokinetic study, CV181004, using an oral solution containing saxagliptin 50 mg, in six volunteers, was presented. From this, it was concluded that about 70% of the administered radioactivity appears in the urine and about 22% in the faeces, "mainly as oxidative metabolites". The sponsor concluded that oral absorption is high.

The early clinical trials used a capsule formulation that included saxagliptin benzoate. Later formulations used free base and saxagliptin hydrochloride.

No studies have been done that include the final formulation intended for marketing and a number of studies included strengths of clinical trial tablets that are not intended for registration (10 and 20 mg).

Several bioavailability studies were summarised by the pharmaceutical chemistry evaluator – by linking several studies (in which rate of absorption was not bioequivalent), the sponsor purports to demonstrate bioequivalence of early and late trial formulations.

Food effects were studied using two formulations, as well as various doses, unrelated to those intended for marketing: in these studies, food delayed the absorption of saxagliptin but increased the extent of its absorption.

Subsequent to the PSC recommendations an absolute bioavailability study was conducted. The results of this study showed the mean absolute oral bioavailability (BA) of saxagliptin was 50% (individual absolute BA values ranged from 48% to 52% and 90% confidence interval of 48% to 53%).

Nonclinical

The nonclinical evaluator noted that saxagliptin and is principal metabolite (BMS-510849) selectively inhibit dipeptidyl peptidase 4 (DPP-4), with significantly less inhibition of DPP-8 and DPP-9 – "Several toxicological effects observed in the submitted studies can be attributed to inhibition of these peptidases." In this respect, saxagliptin resembles vildagliptin. By contrast, the kinetics of binding to the target receptor are slower for saxagliptin than for vildagliptin and sitagliptin.

The pharmacokinetics of saxagliptin was similar in the species studied, including humans. It was well absorbed and not bound significantly to plasma proteins. The chief metabolic enzyme systems involved are CYP-3A4 and CYP-3A5, suggesting susceptibility to metabolic interactions. Saxagliptin was not shown to be an inhibitor or inducer of hepatic enzymes. The principal metabolite is eliminated more slowly than the unchanged drug. Renal excretion of the unchanged drug and its principal metabolite was important in the species studied, including humans.

In terms of nonclinical models of efficacy, the evaluator remarked that "Saxagliptin had greater effects on plasma glucose clearance in diabetic rats than healthy rats. Chronic studies in a rat model of diabetes demonstrated that after 14 days, saxagliptin reduced fasting plasma glucose levels by 17%. However, by 35 days, there were no differences between control animals and those receiving saxagliptin, suggesting the animals responded well to saxagliptin in the early stages of diabetes development but as the rats reached a severely diabetic state, their response was diminished."

Saxagliptin was not genotoxic. Studies in rats and in mice did not suggest carcinogenicity.

The oral toxicity, including reproductive toxicity, of saxagliptin was low. On chronic oral dosing, diverse toxicities (thrombocytopenia, anaemia, lymphoid hyperplasia, pulmonary histiocytosis and GI tract toxicity) were shown and skin lesions in dogs and monkeys, as well as brain lesions in male rats, are of note. The lesions, degeneration/rarefaction with variable gliosis, were located in the corpus callosum, thalamus and caudate putamen and were consistent with cyanide toxicity. A satisfactory mechanistic explanation was provided: the neurotoxicity in male rats was attributable to cyanide release from saxagliptin via the androgenically controlled CYP2C11 enzyme.

Exposure ratios in the toxicity studies were adequate.

The evaluator did not object on nonclinical grounds to the registration of Onglyza as monotherapy for the proposed indication. Owing to an absence of nonclinical data regarding saxagliptin in

combination with metformin, thiazolidinedione or a sulfonylurea, the safety of the proposed combinations would need to be addressed by clinical data.

Also, the lack of an absolute bioavailability study in humans and other species causes one to be conservative about the interpretation of exposure ratios.

Clinical

The evaluator has appraised the data set in detail. There are several ongoing studies that were not evaluable for efficacy.

Pharmacodynamics

The evaluator noted that saxagliptin and its principal metabolite are potent, selective inhibitors of DPP-4 and that this effect is significant even after oral dosing with saxagliptin 1 mg. Maximal mean plasma DPP4 inhibition ranged from 86% of pre-dose values after 2.5 mg; it did not appear to change substantially upon repeated once daily dosing with any dose. GLP-1 levels also rose, without evident dose dependency and with some intersubject variability. Data on GIP were not described. Saxagliptin was associated at Week 12 with increased postprandial secretion of insulin in type 2 diabetics (Study CV181041). As noted by the evaluator, "In CV181001 and -02, peak changes in incretin levels occurred at around 6 hours after dosing (but there was considerable variability). In CV181001, there was a suggestion that peak changes were more prominent in the fed state." However, the inhibition of DPP-4 is evident for more than 24 hours, exceeding clearance (half-life after one dose of 5 mg saxagliptin in the fed state was 2.5 hours for saxagliptin and 3.1 hours for BMS-510849 - Study CV181037) and suggestive of slow dissociation from the site of action. The active metabolite is present at higher concentrations in plasma (> 2-fold) than saxagliptin.

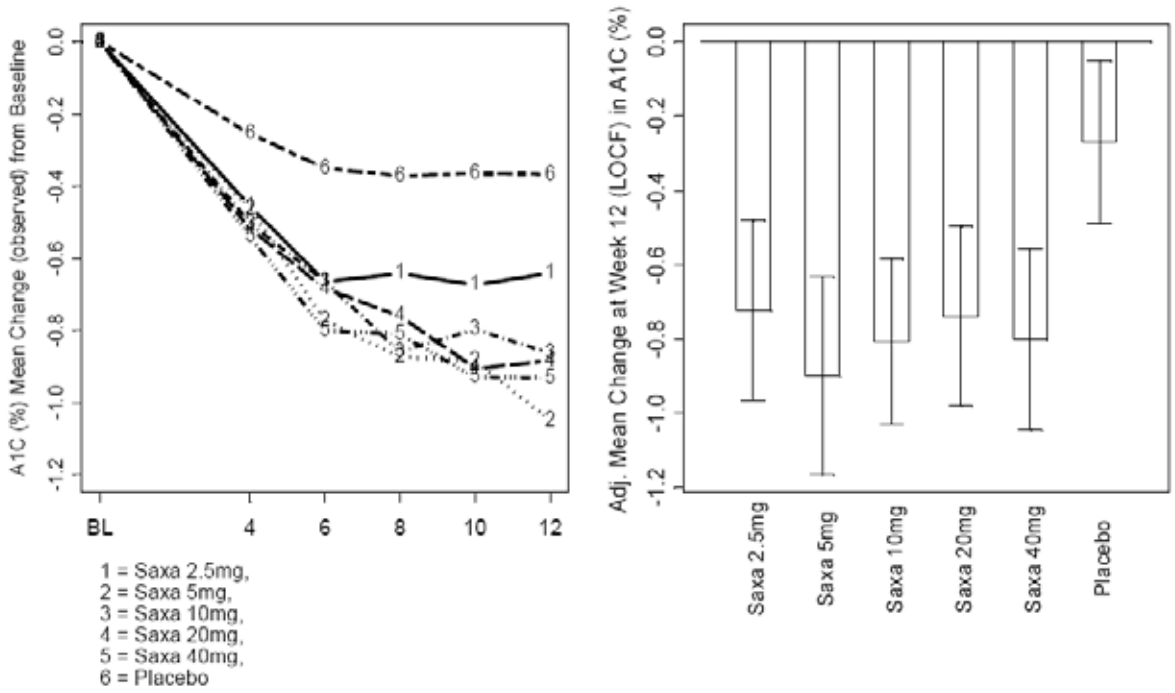
The Delegate noted that there was little evidence of any dose response in these studies or in the sponsor's pooled analysis to differentiate 2.5 mg/day from 5 mg/day.

Dose Ranging Study

Study CV181008 was a 12 week, double-blind, fixed dose (0, 2.5,5, 10, 20 or 40 mg daily), placebo controlled, parallel group (n=47-67 per group), randomised study in typical, drug-naïve Type 2 diabetes mellitus subjects with inadequate glycaemic control (HbA1c 6.8-9.7%). A second control was provided by a group (n= 85) that received a dose of 0.1mg daily. Dosing occurred 30-60 minutes before breakfast.

Little dose response was seen (Figure 18). Some dose response was seen for DPP-4 inhibition, from placebo to 5 mg saxagliptin.

Figure 18: Dose response



Pharmacokinetics

As noted by the evaluator, "Following single or once daily repeated oral doses of 5 to 400 mg saxagliptin in fed or fasted states, mean BMS-510849 AUC values were between 2- and 7-fold higher than the parent saxagliptin exposure on a molar basis (CV181001; CV181002; CV181010)." This echoes the nonclinical evaluator's suggestion that the major metabolite is clinically significant. Accumulation was not seen in the pharmacokinetic studies.

Inhibitors of CYP3A4 increase exposure to saxagliptin but reduce the formation of the active metabolite. Mild to moderate hepatic impairment had similar effects. Renal impairment predictably increases exposure to saxagliptin and its principal metabolite. Somewhat surprisingly, "There was no dedicated study where subjects with moderate or severe renal impairment were given 2.5 mg saxagliptin doses." Exposure to saxagliptin is higher in the elderly ("Subjects 65-80 years of age had 23% higher C_{max} and 59% higher AUC_{∞} than subjects 18-40 years of age (CV181018) …") but no dosage adjustment is proposed. Studies in adolescents were not done.

Efficacy

The studies were conducted in adults with Type 2 diabetes mellitus, typically overweight (mean BMI ranged from 28 to 32 kg/m^2) and White. Essentially similar inclusion and exclusion criteria were used throughout. Saxagliptin was given in the morning unless otherwise specified.

The primary efficacy endpoint in all pivotal Phase III studies was change from baseline in HbA1c at the 24 week primary assessment point (or the last pre-rescue post-baseline measurement prior to Week 24, if no Week 24 assessment was available). All studies were designed as superiority studies, in keeping with the general approach of comparison with placebo.

Secondary endpoints shared across all Core Phase III studies were:

- Change from baseline in fasting plasma glucose (FPG). This was stated to correlate with glycaemic control and with chronic complications of diabetes.
- Therapeutic glycaemic response (the proportion of subjects achieving HbA1c <7.0%).

· Change from baseline in AUC from 0-180 minutes for postprandial serum glucose (PPG) response to an OGTT (including frequently sampled OGTT in CV181011).

The OGTT was generally performed at enrolment, randomisation (Day 1) after dosing and at study Week 24 for the ST period. Study medication was administered between -30 minutes and 0 minutes; blood samples were taken at -30 minutes, 0 minute, and at +30, +60, +120 and +180 minutes after ingestion of 75 grams of glucose.

The Delegate noted that the last of these three endpoints would be expected to favour saxagliptin. The first is of interest by Week 24 because it will give a clue as to durability of effect of saxagliptin versus control.

Predictably, the patients in monotherapy studies had a shorter duration of Type 2 diabetes mellitus than those in add-on combination studies or the initial combination study. Baseline HbA1c values were slightly lower in monotherapy subjects.

As classified by the evaluator, the Core (pivotal) Phase III studies were:

Monotherapy studies in treatment-naïve subjects with inadequate glycaemic control with diet and exercise:

- CV181011 (this study also included an open-label treatment group for 66 subjects with screening HbA1c >10% and ≤12%; such subjects received saxagliptin 10 mg)
- CV181038 – this was the only Core Phase III study that did not evaluate saxagliptin in an exclusively fixed (non-titratable) dosing regimen

Add-on combination studies (that is, in subjects already receiving treatment):

- CV181014 – add-on to metformin
- CV181013 – add-on to thiazolidinedione (pioglitazone)
- CV181040 – add-on to sulfonylurea (glibenclamide)

Initial combination with metformin study in treatment-naïve subjects:

- CV181039

The Delegate noted that the Phase III studies are of acceptable design (double-blind, randomised and controlled, and in each study there was a 1-4 week dietary / placebo lead-in period after screening and of up to 24 weeks' duration) but it was noted that they are not replicated, that is, there is generally one study for each sub-indication.

Phase III Studies

Monotherapy Drug-Naïve Patients

Study CV181011 was a 24 week study. There were 142 investigators at 137 sites, 401 subjects were randomised and treated with double-blind therapy (102 in the 2.5 mg group; 106 in the 5 mg; 98 in the 10 mg; and 95 in the placebo arm). Of note, 265 subjects completed 24 weeks of treatment. The reasons, as presented by the evaluator are, "Discontinuations (including rescues) were seen in 28.4% (2.5 mg), 35.8% (5 mg), 29.6% (10 mg) and 42.1% (placebo). Commonly, discontinuation was due to lack of efficacy (14.7%, 19.8%, 14.3% and 26.3% respectively). No subjects in the placebo arm failed to complete [short term that is, 24 weeks] treatment because of AEs, vs 2.9-4.1% in the saxagliptin arms."

The study was stratified into two cohorts, according to baseline glycosylated haemoglobin levels:

"There were two cohorts: (a) main treatment cohort, including subjects with screening HbA1c 7.0-10.0%; these subjects were randomised (1:1:1:1; permuted blocks, stratified by site) to saxagliptin 2.5 mg, 5 mg, 10 mg or placebo; and (b) open-label cohort, including subjects with screening

HbA1c 10.0-12.0%; subjects received saxagliptin 10 mg. In the open-label cohort, there was no lead-in. Results refer to the main treatment cohort unless otherwise specified."

At Week 24, the blinded, main treatment cohort showed a modest but not dose-dependent treatment effect. The graphical presentation of the primary endpoint is of interest (Figure 2).

The evaluator observed that observed values are subject to discontinuation of non-responders. Secondary endpoint changes were modest. The open label cohort achieved greater absolute improvements in the primary endpoint than the blinded cohorts: mean changes to 24 weeks (LOCF) in fasting HbA1c (-1.87%). Also of note is that a substudy suggested subacute improvements in intact GIP after an oral glucose tolerance test.

There was a long term (LT) extension, "Rescued subjects and ~85% of subjects who completed the short term (ST) that is, 24 weeks period continued in the study's LT period. 336 subjects entered the LT period."

The 336 subjects in the LT study had:

- (for 262 subjects) completed ST visits without meeting rescue criteria (such subjects remained on their double-blind randomised therapy, except placebo subjects who received placebo + double-blind metformin 500 mg), or
- (for 74 subjects) met rescue criteria (these subjects remained on their blinded randomised therapy but received open-label metformin 500 mg in addition).

The Delegate noted that these patients are heterogeneous by way of responsiveness to blinded treatment and whether on monotherapy or rescue therapy (that is, metformin or both metformin and saxagliptin).

Blinded therapies could not be titrated during the LT period. Subjects (not previously rescued) with lack of glycaemic control in the LT period were eligible for addition of open-label metformin 500 mg. As reported by the evaluator, "Adjusted mean change from baseline at Week 102 was 0.09% (2.5 mg), -0.14% (5 mg), -0.10% (10 mg) and +0.32% (placebo)."

The Delegate noted that these improvements for saxagliptin at 102 weeks look trivial. This trend, as shown in Figure 2, to loss of control, for a lagging indicator like HbA1c, is consistent with a rapid onset of effect and slow loss of control. Deterioration was evident in all groups, including placebo (which was switched to metformin 500 mg after Week 24). Durability of treatment to target (HbA1c <7%) was similar in all arms. The sponsor should confirm the rescue dose of metformin.

Study CV181038 was another pivotal, monotherapy study of similarly acceptable design in drug-naïve patients. There were 72 investigators at 72 sites that contributed 365 patients into 5 parallel groups. The study used morning doses from 2.5 to 5 mg per day including a dose-titration arm and 5 mg evening dose. The efficacy results are shown in Table 8.

Table 8: Summary of Clinical Efficacy – HbA1c changes from baseline at Week 24 (LOCF) – Phase III 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)	--

Source: CV181011ST CSR Table 7.2.1; CV181038ST CSR Table 7.2.1A and Table 7.3.1A; Appendix 5.1
Data set: Randomized Subjects
n=number of subjects with assessments at baseline and at Week 24; N = number of subjects randomized
All secondary endpoints were tested (sequentially) at the 0.05 significance level and only for groups where primary endpoint showed statistical significance.
[*]p-value<0.0001 (Between group comparisons significant at a = 0.019, applying Dunnetts adjustment)
[**]p-value=0.0023;
[***]p-value=0.0059 (test performed at the 0.027 significance level, applying Dunnetts adjustment)
[****]p-value=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-value=0.0157
[#]p-value<0.0001 (calculation was 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

The short term (24 weeks) and interim long term phase results are presented graphically (see Figure 6)

The Delegate noted that these modest results are similar for the larger study CV181011. No obvious dose response is seen and evening dosing was also superior to placebo.

With regard to a potential treatment target, the evaluator commented, "For proportion of subjects achieving therapeutic glycaemic response (HbA1c <7%), values were 35.8% (2.5 mg), 44.9% (5 mg QAM), 43.5% (2.5/5 mg), 38.6% (5 mg QPM) and 35.3% (placebo); there was no statistically significant difference between any saxagliptin arm and placebo for this variable. " The sponsor pled some mismatching at baseline of the parallel groups.

As for the preceding study, an interim follow-up of the long term extension was available. Non-rescued saxagliptin patients could be titrated up to 10 mg/day; non-rescued placebo subjects were

switched to metformin 500 mg per day. Rescued saxagliptin patients were given add-on metformin that could be titrated up to 2 g per day. Thus, 311 patients entered the extension and about half had reached Week 50 by cut-off (including last observation carried forward results). The numbers by Week 52 were small. Titration to saxagliptin 10 mg per day was not reported by the evaluator – this is a marker for failure and the sponsor was invited to comment.

First Line Dual Therapy in Drug-Naïve Patients:

Study CV181039 was a Phase III study that is unusual: saxagliptin was given with metformin as initial therapy in drug-naïve type 2 diabetics. There were four parallel study arms but no placebo control.

The enrolled patients were treatment-naïve with inadequately controlled diabetes mellitus type 2 , defined as HbA1c ≥8% but ≤12%; the average BMI 29.9-30.3 kg/m2 across arms. 196 investigators participated at 196 sites and contributed 1,306 patients who were randomised and treated: 320 in the saxagliptin 5 mg + metformin 500 mg with titration group; 323 in the saxagliptin 10 mg + metformin 500 mg with titration group; 335 in the saxagliptin 10 mg + placebo group; and 328 in the metformin 500 mg with titration + placebo group. Metformin could be up-titrated weekly over the first 5 weeks to 2.5g/day. Pioglitazone 15-45 mg per day was the rescue medication.

Metformin could be titrated according to this schedule:

"Subjects meeting the randomization criteria were randomized (1:1:1:1) in a double-blind fashion to either saxagliptin 10 mg plus metformin IR 500 mg (Saxa 10 mg + Met), saxagliptin 5 mg plus metformin IR 500 mg (Saxa 5 mg+Met), saxagliptin 10 mg plus placebo (Saxa 10 mg), or metformin IR 500 mg plus placebo (Met). At Week 1, subjects receiving metformin as monotherapy or in combination with saxagliptin were to be titrated, as tolerated, from metformin 500 mg/d to 1000 mg/d in divided doses. At Weeks 2, 3, 4, and 5, subjects were to be titrated, as tolerated, in increments of 500 mg up to a maximum of 2000 mg/d in divided doses if mean fasting plasma glucose (MFPG) > 110 mg/dL (6.1 mmol/L) or mean fasting whole blood glucose (MFWBG) > 104 mg/dL (5.8 mmol/L)."

The doses of metformin were conventional:

"In the groups that received metformin, a similar proportion of subjects (93% - 96%) titrated their dose from the initial 500 mg daily dose (Table 9). A higher proportion of subjects in the metformin monotherapy group (78.0%) titrated to a dose ≥ 2000 mg compared with the combination groups: Saxa 5 mg + Met (71.3%) and Saxa 10 mg + Met (72.4%). The final mean metformin dose in the groups receiving metformin was > 1700 mg/day."

Table 9: Number of subjects treated and final titrated dose of metformin – summary during short term treatment period

Metformin Final Titrated Dose (mg)	Number (%) of Subjects			
	SAXA 5 mg + MET N = 320	SAXA 10 mg + MET N = 323	SAXA 10 mg N = 335	MET N =328
500	13(4.08)	21(6.52)	4(66.67)	19(5.88)
1000	31(9.72)	27(8.39)	0(0.00)	26(8.05)
1500	47(14.73)	40(12.42)	1(16.67)	22(6.81)
2000	216(67.71)	221(68.63)	1(16.67)	244(75.54)
2500	11(3.45)	13(4.04)	0(0.00)	11(3.41)
>=3000	1(0.31)	0(0.00)	0(0.00)	1(0.31)
SUMMARY STATISTICS:				
n	319	322	6	323
MEAN (SE)	1790.0(24.91)	1776.4(26.28)	916.7(271.31)	1817.3(25.42)
MEDIAN	2000	2000	500	2000
MIN, MAX	500,3500	500,2500	500,2000	500,3000
NUMBER OF SUBJECTS TITRATED	315(98.75)	312(96.89)	6(100.00)	313(96.90)

Data set: Treated Subjects
The denominator of each % is the number of subjects whose final dose of metformin were available in the treatment group.

The results were that 81.9% of the saxagliptin 5 mg + metformin 500 mg with titration group subjects completed the 24 week ST period, 80.8% of saxagliptin 10 mg + metformin, 67.2% of saxagliptin 10 mg and 74.1% of metformin completed 24 weeks. Discontinuation was often due to lack of efficacy – this was particularly the case in the saxagliptin monotherapy group (6.3%, 5.9%, 19.1% and 9.1% respectively). The evaluator commented that "The largely overlapping endpoint of discontinuation or rescue for lack of glycaemic control was reached in 7.5%, 5.9%, 21.2% and 10.1% respectively. These and similar results prompted the question, 'Why would a clinician commence a treatment-naïve subject on saxagliptin monotherapy?' "

At Week 24 (LOCF), adjusted mean change from baseline in HbA1c was -2.53% (saxagliptin 5 mg + metformin 500 mg with titration group), -2.49% (saxagliptin 10 mg + metformin 500 mg with titration group), -1.69 (saxagliptin 10 mg + placebo) and -1.99 (metformin + placebo). Figure 12 illustrates these changes. Using observed values, the evaluator reported adjusted mean change from baseline at Week 24 was -2.66%, -2.75%, -2.09% and -2.27% respectively. Other glycaemic measures were consistent. There was a small, similar reduction from baseline to Week 24 in weight, waist circumference and BMI in all treatment groups.

Long Term Extension: 1,103 subjects entered the LT period (either completing the ST period or entering LT treatment after rescue due to lack of glycaemic control). Subjects were eligible for rescue with pioglitazone in the LT period as well. The evaluator is not satisfied with the lack of data in this phase, "Only a third of treated subjects (95-106 per arm) contributed to analysis of efficacy at Week 50 (and even fewer, at around 30-50 per arm, had observed values)." At Week 50 last observation carried forward (LOCF), adjusted mean change in HbA1c from baseline was- 2.48% (saxagliptin 5 mg + metformin 500 mg with titration group), -2.31% (saxagliptin 10 mg + metformin 500 mg with titration group), -1.38% (saxagliptin 10 mg + placebo) and -1.99% (metformin + placebo).

Add-on Studies

Add-on to metformin

Study CV181014was a pivotal trial, large - 155 investigators at 152 sites contributed 743 subjects were randomised and treated of which 543 completed 24 weeks of treatment. Saxagliptin was used as an add-on to existing metformin (1,500-2,550 mg/day). Subjects were randomised equally to receive, prior to breakfast, one of saxagliptin 2.5 mg; saxagliptin 5 mg; saxagliptin 10 mg; or placebo plus the prior dose of metformin – all doses were fixed thereafter. Pioglitazone was the rescue therapy.

In terms of the primary outcome, there was a modest but not dose dependent treatment effect at Week 24: the (LOCF) adjusted mean change from baseline in HbA1c was -0.59% (2.5 mg), -0.69% (5 mg), -0.58% (10 mg) and +0.13% (placebo). Each comparison with placebo was statistically significant ($p<0.0001$). Adjusted mean change in FPG and the proportion of subjects achieving HbA1c <7% showed a treatment effect without dose dependency.

The long term extension had interim data, all subjects (n=642) contributed LOCF data at Week 76, and 97.4-98.4% of subjects contributed data at Week 102, but only around 17% of subjects had data at Week 115. These 24 week and extension data are presented graphically in Figure 8.

The evaluator commented that fasting plasma glucose and HbA1c rose in parallel in all study arms.

Add-on to Pioglitazone:

Study CV181013 was a study of add-on saxagliptin in patients with inadequate control on pioglitazone. The study was large: 172 investigators at 172 sites. A total of 565 subjects were randomised and received double-blind therapy: 195 to saxagliptin 2.5 mg, 186 to saxagliptin 5 mg and 184 to placebo plus pioglitazone 30 or 45 mg daily (or, initially, 4 or 8 mg rosiglitazone daily); all doses were thereafter fixed. Open-label metformin was the rescue therapy, titrated by 500 mg quanta. The study showed some slight dose dependency in the short term (24 week) phase and some dose dependency was seen in discontinuation rates in both phases:

The adjusted change, from baseline to Week 24, in HbA1c was -0.66% (saxagliptin 2.5), -0.94% (saxagliptin 5) and -0.30% (placebo). Discontinuation from the ST+LT period due to lack of efficacy was reported in 5.6% (saxagliptin 2.5), 2.2% (saxagliptin 5) and 7.6% (placebo) (Figure 10)

The Delegate noted that these absolute differences are small. Weight gain occurred in all groups in both phases, an effect that is attributable to pioglitazone and not ameliorated by saxagliptin. The study was not designed to show a pioglitazone dose-sparing effect.

A total of 468 patients (out of 565 in the ST period) entered the LT period, including 44 who entered LT after rescue.

Add-on to sulphonylureas – second agent therapy:

Study CV181040 was a parallel group study, testing add-on saxagliptin or placebo to glibenclamide, in patients who were previously treated with submaximal doses of glibenclamide. At screening, HbA1c was to be 7.5-10.0%, and at randomisation, HbA1c ≥7.0%. The study was large: 136 investigators at 132 sites: 768 subjects were equally randomised (saxagliptin 2.5 mg or 5 mg per day or placebo) and treated with double-blind therapy for 24 weeks. The initial dose of glibenclamide in the ST phase was 10 mg per day, with a single downward titration allowed. In the glibenclamide arm, glibenclamide dose could be uptitrated in a single 5 mg step to 15 mg total daily dose (7.5 mg open-label + 7.5 mg blinded) at Week 2 or Week 4, if mean FPG were ≥5.5 mmol/L.

ST Phase Results: Down-titration of glibenclamide occurred in 4.0% (saxagliptin 2.5), 5.1% (saxagliptin 5) and 2.2% (glibenclamide); in all groups, lack of efficacy was the commonest reason for discontinuation (16.5%, 15%, 24.7% respectively); adjusted mean change from baseline in HbA1c was -0.54%, -0.64% and +0.08% respectively; the percentage of subjects achieving HbA1c <7% was 22.4%, 22.8% and 9.1% respectively.

The Delegate noted that these absolute mean differences are small but consistent with the other studies. These patients were overweight at baseline: mean BMI was 28.8-29.1 kg/m2 in the study arms. Weight gain occurred in all groups in both phases, more so with saxagliptin, an effect that is thus not attributable to glibenclamide.

Of 768 randomised and treated subjects, all entered the LT phase. At least 95% of subjects in each arm provided data (albeit using LOCF methodology) at Week 50, and at least 60% at Week 63. Subjects who were not rescued received continued fixed dosing; rescued patients could receive glibenclamide 20 mg per day. Rescue with open-label metformin was allowed in previously un-rescued subjects. At Week 50 (LOCF), mean adjusted change in HbA1c was -0.25% (saxagliptin 2.5), -0.33% (saxagliptin 5) and +0.29% (glibenclamide); the respective results for the proportion of subjects who discontinued for lack of glycaemic control or who were rescued for meeting pre-specified criteria was 48.8%, 49.8% and 67%; for achieving the glycaemic response threshold of ≤7% (HbA1c) 14.4%, 14% and 7.5%.

Evaluator's Conclusions Regarding Efficacy

The pivotal studies are internally valid. It is reasonable to accept 5 mg as the proposed dose despite the lack of consistency in dose response. However, "Phase III monotherapy studies confirmed that saxagliptin treatment was superior to placebo in treatment of treatment-naïve T2DM subjects. In practice, a treating doctor will not be reassured by superiority of saxagliptin over placebo. Either superiority over a carefully structured intensive programme of diet and exercise improvements, or superiority over currently used pharmacotherapies, would be reassuring. The former comparison was not made. The latter comparison was made in Study CV181039 (where a 10 mg saxagliptin monotherapy dose rather than a 5 mg dose was chosen for study). "

HbA1c is accepted as a reasonable primary endpoint variable albeit a surrogate for want of clinical endpoints. By this measure, the treatment effect is small: "The small treatment effect in many saxagliptin studies should be viewed in the context of the 1.0-1.5% decrease in HbA1c often obtainable through lifestyle interventions in T2DM patients (Therapeutic Guidelines, 2009)."[2]

In monotherapy, there was an uneven effect size. "A difference between study populations or methodologies is evident in examination of the primary endpoint: in CV181039, saxagliptin (10 mg) alone decreased HbA1c by 1.69% at 24 weeks, whereas in the monotherapy study with a 10 mg arm, the decrease was 0.54%. One explanation for this stark difference is that in CV181039, subjects generally had a higher baseline HbA1c; treatment effect size is related to baseline HbA1c. Whether this can account for the size of the difference (1.69% vs 0.54%) is unclear."

No comparison with metformin monotherapy was presented. This is seen as a significant developmental weakness.

External validity is constrained by a lack of experience in patients with unstable cardiovascular disease. No Australian indigenes and no adolescents were studied.

Efficacy declines with time and it is not clear what the long term role of saxagliptin might be.

Safety

In the 120 day safety update, the pooled data suggest the common adverse events are:

- nasopharyngitis [8.3% for 2.5 mg; 9.5% for 5 mg; 14.3% for 10 mg; 9.9% in the placebo arm]

- influenza [7.4%, 6.8%, 12.5% and 7.6%]
- sinusitis [4.4%, 3.6%, 8.6% and 3.0%]
- tooth infection [1.1%, 1.0%, 2.2% and 1.0%]
- myalgia [3.1%, 2.0%, 3.6% and 2.5%]
- headache [8.6%, 8.5%, 14% and 8.9%]
- falls [0.6%, 1.0%, 2.9% and 0.9%]
- rash [2.0%, 2.8%, 5.4% and 1.4%]
- contact dermatitis [1.7%, 1.0%, 2.5% and 0.6%]
- blood pressure increased [0.7%, 0.7%, 2.2% and 0.3%]
- haematuria [0.5%, 0.8%, 2.5% and 1.0%]
- depression [1.5%, 2.7%, 4.3% and 1.4%]
- anxiety [1.5%, 2.2%, 2.9% and 1.1%]

There were increases across all saxagliptin doses relative to placebo for chest pain of unspecified origin [2.7%, 2.0%, 1.8% and 1.5%] and blood CK increased [2.0%, 2.7%, 2.2% and 1.6%].

Deaths were reported on study, but "Overall, there was no indication that saxagliptin was associated with increased mortality." There is a signal of increased hypoglycaemia when saxagliptin is used with sulphonylureas.

Cutaneous adverse events were more frequent with saxagliptin than placebo. There are weak signals concerning infections and lymphopenia, fractures, and psychiatric adverse events.

Risk-Benefit Analysis

Delegate Considerations

On efficacy grounds, the evaluator recommended approval for marketing for the initial combined therapy with metformin and second line combination therapy at the dose requested by the sponsor. First line monotherapy was rejected due to probable inferiority to metformin despite adequate tolerability.

Safety signals of note include, "…a sustained decrease in lymphocyte counts (marked in some subjects), has a poorly characterised effect on lymphocyte function and is associated with a slightly higher overall risk of infections. There were also modest safety signals for rash (including contact dermatitis), hypertension, elevations in CK, depression, anxiety, fractures and hypersensitivity."

Regarding registration, the evaluator opposed registration for monotherapy but found sufficient evidence to support first line dual therapy in treatment naïve patients, "For treatment-naïve patients, net benefit appears to be greatest with initial combination treatment with saxagliptin (5 mg) and metformin." Therefore, for treatment-naïve subjects, approval of the initial combination indication was recommended but not the initial saxagliptin indication. "Use of initial combination therapy is not common practice, but results of CV181039 support this approach."

Add-on to other agents, as a second agent, was supported by the submitted studies. The actual utility of saxagliptin is as yet undetermined.

The evaluator's proposed indication was:

Initial combination

Onglyza is indicated for use as initial combination therapy with metformin, in patients with type 2 diabetes mellitus, to improve glycaemic control as an adjunct to diet and exercise, where diet and exercise alone does not improve glycaemic control.

Add-on combination

Onglyza is indicated in patients with type 2 diabetes mellitus, to improve glycaemic control, in combination with metformin, a sulfonylurea, or a thiazolidinedione, as an adjunct to diet and exercise, when the single agent alone does not provide adequate glycaemic control.

The Delegate commented that preclinical studies have not, so far, predicted significant human toxicities. Support for combinations with pioglitazone or glibenclamide must come from human derived data.

Most of the sub-indications are supported by one pivotal study. There is an applicable TGA-adopted EU guideline.[29] The intent of the guideline is clear – replication of studies is needed unless the results are statistically compelling and clinically relevant. The Australian Drug Evaluation Committee (ADEC) was therefore asked to comment on the clinical relevance of saxagliptin. It is arguable that the therapeutic effect has been demonstrated with reasonable consistency across a spectrum of patients with diabetes mellitus type 2 albeit somewhat healthier than those commonly seen in clinical practice.

Saxagliptin has been shown to be of moderate efficacy: poor glycaemic control and a higher BMI at baseline independently were associated a subsequent need for rescue therapy. It might have a role as a therapeutic alternative to metformin monotherapy in patients who do not tolerate metformin but it has not been studied in such patients.

The first line combination study suggested that efficacy for metformin monotherapy was better than saxagliptin monotherapy and that both agents, taken together, offer an advantage over supramaximal doses of saxagliptin and titrated metformin. That is, some patients, will respond better to first line combination therapy - those with high initial HbA1c levels: the study enrolled patients with a baseline HbA1c in the range HbA1c ≥8% but ≤12%. Subgroup analysis of efficacy was notable for greater HbA1c reductions with increasing baseline HbA1c strata. It is therefore arguable that first line combination therapy would likely be offered to patients with high initial HbA1c levels and diabetic symptoms. The first-line monotherapy indication is supported by two studies of adequate size. An appropriate active comparator (metformin) was not used and this is a significant external validity problem for Australian practice. The first line combination study suggests that even saxagliptin 10 mg is inferior to metformin. These issues led the Delegate to ask the Committee's advice.

Similarly, the add-on study to glibenclamide was conducted in a patient sample (overweight) that might more typically have received metformin in Australia. Taken with the higher risk of hypoglycaemia with this combination, and no nonclinical support, the Committee may have reservations.

The Delegate agreed with the evaluator that the data to support first line monotherapy are weak. The problem with first line combination therapy with metformin is that its durability is uncertain. No advantage may be offered beyond initial tolerability but this is unknown at present.

The Delegate proposed that the application be approved and that the registered indication should be:

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

Initial combination - Onglyza is indicated for use as initial combination therapy with metformin, in patients with type 2 diabetes mellitus, to improve glycaemic control as an adjunct to diet and exercise, when dual saxagliptin and metformin therapy is appropriate (that is, high initial HbA1c levels and poor prospects for response to monotherapy).

The application to register the indication:

Monotherapy - Onglyza is indicated in patients with type 2 diabetes mellitus, to improve glycaemic control, as an adjunct to diet and exercise

should be rejected due to inadequate efficacy.

Response from Sponsor

The sponsor accepted the Delegate's indications and indicated that it wished to withdraw the proposed indication for the use of Onglyza as monotherapy. Other matters raised by the Delegate were discussed.

2.5 mg and 5 mg Dose Response

The Delegate raised some concerns about there being little evidence in dose response between the 2.5 mg and 5 mg Onglyza presentations. The intended daily dose of Onglyza is 5 mg. This dose was demonstrated to be appropriate based on the results from the 8 clinical studies in the saxagliptin Phase IIb and III program in over 4600 subjects. Combined with the results from clinical pharmacology studies, these data support the oral dose of saxagliptin 5 mg once daily in a wide range of patients with T2DM, in either monotherapy, add-on combination therapy with a TZD, a sulfonylurea (SU) or metformin, or initial combination therapy with metformin. In the Phase I and Phase IIa studies, administration of saxagliptin 5 mg was associated with greater inhibition of plasma DPP4 activity at the trough of the dosing interval compared to 2.5 mg. Clinically meaningful and statistically significant decreases in HbA1c, FPG and PPG were also seen at all doses in the Phase IIb/Phase III studies; maximal reductions in HbA1c and FPG were generally seen with the 5 mg dose.

The difference in efficacy between 2.5 mg and 5 mg was most clearly seen in the three add-on studies, (CV181014, CV181013, CV181040), indications for which the use of saxagliptin is proposed. Although these studies were not designed to make statistical comparisons between dose groups, a consistent numerically greater effect on these parameters was seen in 5 mg compared to 2.5 mg as referenced below:

• HbA1c, FPG, PPG: The 5 mg dose achieved greater reductions from baseline compared to the 2.5 mg in all the add-on studies.

• Patients at treatment target: the proportion of subjects who achieved HbA1c <7% was greater for the 5 mg saxagliptin dose compared with 2.5 mg (2 of 3 add-on studies)

The clinical safety profile of saxagliptin has been consistently confirmed across a large and diverse development program. The safety profiles of the 2.5 mg dose and the 5 mg dose are comparable and given the demonstrated efficacy of the 5 mg dose of saxagliptin this daily dose is considered to provide the optimal benefit:risk ratio in subjects with T2DM. In summary, the sponsor considered that the proposed daily dose of 5 mg was appropriate.

Indication: Add-on Combination Therapy

The sponsor believed that the studies presented for add-on therapy adequately demonstrate the clinical relevance of Onglyza as an add-on therapy.

In relation to the saxagliptin + metformin add-on study the Delegate indicated that for the primary outcome there was a modest treatment effect, with each comparison to placebo being statistically significant ($p<0.0001$). The saxagliptin add-on to metformin study (CV181014) demonstrated clinically relevant reduction in HbA1c, FPG, PPG and increased proportion of patients with an HbA1c level below 7% efficacy after 24 weeks of treatment together with low risk of hypoglycaemia or other safety concerns. Add on to metformin represents the anticipated most common treatment modality for saxagliptin.

The Delegate raised concerns in the TZD + saxagliptin add-on study (Study CV181013) that the absolute differences in HbA1c levels between TZD+placebo and saxagliptin+TZD were small. However, the saxagliptin add-on to TZD study demonstrated that glycaemic control improved early in the course of saxagliptin treatment and a clear divergence between the saxagliptin and placebo treatment groups by LOCF analysis (result -0.63% (-0.84, -0.42)) at week 24 in the 5 mg dose. The Delegate also commented that "the results show that pioglitazone was still somewhat effective as monotherapy". However, the patients enrolled in this study were not treatment-naïve and had been on stable medication for at least 3 months in addition to compliance with lifestyle requirements, therefore the initial reduction of HbA1c observed in the placebo group should not be necessarily interpreted as a result of newly instituted TZD monotherapy efficacy. The initial reduction of HbA1c in the control group might be a residual effect of late changes in background TZD medication close to the 3 months stable treatment period before randomization or simply improved compliance with background treatment and lifestyle recommendations due to study participation. Overall, the TZD + saxagliptin add on study clearly demonstrated a positive clinical effect in reducing HbA1c levels.

The Delegate raised concerns of (i) possible weight gain side effect with saxagliptin + SU add-on therapy and (ii) that there may be higher risk of hypoglycaemia in this population . Although statistically significant weight gain was observed for saxagliptin compared to the placebo+uptitrated SU group, the magnitude of the change was small (0.8 kg in the saxagliptin 5 mg; 0.3 kg in the placebo+uptitrated SU treatment group) and the clinical significance of this difference is unclear. For all reported hypoglycaemia, the incidence for saxagliptin 5 mg was 14.6% and for placebo was 10.1%; the difference was not statistically significant. The incidence of confirmed hypoglycaemia was uncommon for saxagliptin 5 mg (0.8%) and placebo (0.7%). The study protocol included an exclusion criterion of any anti-hyperglycaemic therapy other than a SU within 12 weeks prior to enrolment, and patients were required by inclusion criteria to be on stable treatment with a submaximal dose of a SU for >2 months. This is because patients are often not treated with higher doses of SU due to fear of hypoglycaemia. The addition of saxagliptin to a mid-dose of SU compared with up-titration to a maximal dose of SU demonstrated clinically and statistically relevant reductions which were more pronounced with the 5 mg dose than with the 2.5 mg dose. Overall, the SU + saxagliptin add on study clearly demonstrated clinical effect in reducing HbA1c levels.

Indication: Initial Combination Therapy

The sponsor agreed with the Delegate's proposal for Initial Combination Therapy (ICT) to be indicated for previously untreated patients who have high initial HbA1c levels, for example greater than 8% or those patients considered unlikely to respond to therapy with a single agent based on the physician's clinical judgment.

Study CV181039 demonstrated in treatment naive subjects with T2DM, initial combination therapy with saxagliptin 5 mg + metformin or saxagliptin 10 mg + metformin resulted in glycaemic improvement that was both statistically and clinically significant compared with either saxagliptin or metformin monotherapy, as evidenced by the primary endpoint (change from baseline HbA1c) and the secondary endpoints (change from baseline FPG, change from baseline PPG area under the concentration-time curve [AUC], and the proportion of subjects achieving HbA1c levels <7.0% and ≤6.5%). Greater magnitudes of HbA1c reductions were observed with increasing baseline HbA1c strata.

The proportion of subjects reporting AEs and SAEs or discontinuing due to an AE in the saxagliptin plus metformin combination groups was similar to either saxagliptin or metformin monotherapy. The frequency of hypoglycaemia with saxagliptin + metformin combination therapy was similar to saxagliptin monotherapy and metformin monotherapy even with significantly greater glycaemic efficacy demonstrated by initial combination treatment. Similar degrees of weight loss were

observed in subjects receiving saxagliptin + metformin combination therapy and saxagliptin monotherapy and metformin monotherapy. Thus, these efficacy benefits were gained without additional side effects. In summary, study CV181039 demonstrates that ICT in treatment-naïve patients was clinically meaningful at lowering HbA1c levels in patients with high baseline HbA1c levels.

The Delegate raised concerns about lack of long-term data in ICT study CV181039. Only an interim cut of data for Study CV181039 was available at the time of submission. Of the pivotal studies, this study was the last to complete the 24-week short-term (ST) period, which resulted in limited data beyond the 24 week ST period at the time of initial submission. The sponsor stressed that the limited follow-up data were not due to high pre-term drop out rates. The study has since completed and the treatment effect was seen to be maintained long term (LT) up to 76 weeks. The clinical study report containing the long-term (LT) data will be soon finalized and can be provided to the TGA post approval.

Size of Effect

The Delegate commented about the size of effect in HbA1c levels in the studies that have been presented. According to the National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes, the preferred treatment regime is diet and exercise before moving onto drug therapy. It was noted that the patients in the core Phase III program had inadequate glycaemic control despite life style advice and for the add on treatment studies a stable background oral antidiabetic treatment. In general, the magnitude of HbA1c reduction with antidiabetic treatment is dependent on the baseline levels. This is clearly the case for DPP-4 inhibitors, which increase insulin secretion via a mode of action that is glucose dependent. This mode of action leads to smaller mean HbA1c reductions when baseline levels are low, while on the other hand the risk for marked hypoglycaemia is minimized. Thus, considering the mean baseline HbA1c levels in the three add-on Phase III studies, the statistically significant HbA1c reductions of 0.63 - 0.83% for saxagliptin 5 mg compared to placebo are considered clinically meaningful, as is the significant reduction of 0.54% compared to metformin monotherapy in the study demonstrating efficacy of ICT.

Durability

The Delegate raised concerns of durability of effect not being demonstrated in either ICT or add-on therapy. The objective of the LT period was primarily to gain long-term safety data, and secondarily to get an appreciation of treatment durability. The sponsor considered that durability is defined as sustained effect of saxagliptin therapy, as opposed to the prevention of disease progression.

The sponsor believed that the durability of saxagliptin in both ICT and add-on therapy has been adequately demonstrated. The LT clinical effect of saxagliptin has been observed for up to 102 weeks at the time of submission. Consideration needs to be given to the strict discontinuation criteria for lack of glycaemic control included in the study designs for ethical reasons. Subjects that met rescue criteria were reported as early discontinuations for the reason of “lack of efficacy”.

There also has to be a distinction made between prevention of disease progression vs maintaining improved glycaemic control. Prevention of disease progression is difficult to demonstrate with the design of the Phase III program, primarily due to the change in rescue criteria over time. A patient may have had a marked improvement in glycaemic control, but still at some point in time be above the threshold for rescue treatment, and be withdrawn for “lack of glycaemic control”. This makes assessment of prevention of progression difficult, if not impossible. However, maintained improvement in glycaemic control can be assessed by comparing HbA1c levels between saxagliptin and control groups. A similar difference vs control seen during the LT, as seen at the time of the primary endpoint, Week 24, represents maintained (durable) antihyperglycaemic effect, even if there is a gradual increase in HbA1c in all treatment groups due to progression of the underlying diabetes disease.

Durability for the add-on to metformin study (CV181014) can be quantified by the difference in the adjusted mean change in HbA1c from baseline compared with placebo up to Week 102. At Week 50 (LOCF) was -0.63 (95% CI: -0.84, -0.43) and -0.74 (95% CI: -0.95, -0.54) and the difference in the adjusted mean change in HbA1c from baseline compared with placebo at Week 102 (LOCF) was -0.62 (95% CI: -0.84, -0.40) and -0.72 (95% CI: -0.94, -0.50) for the saxagliptin 2.5 and 5 mg treatment groups, respectively. The greatest reduction in HbA1c was seen in the 5 mg saxagliptin group. The HbA1c values in all saxagliptin treatment groups were well separated from that of the placebo plus metformin group through Week 102 (LOCF). The final report can be provided to the TGA post approval.

Durability for the add-on to TZD study (CV181013) can be quantified by the difference in the adjusted mean change in HbA1c levels from baseline in the saxagliptin 2.5 and 5 mg groups compared with placebo up to Week 50. The results were -0.46% (95% CI: -0.70, -0.21) and -0.65% (95% CI: -0.90, -0.41) for the 2.5 and 5 mg doses respectively. Data from week 76 have since been obtained, but were not available at time of submission. The Week 76 results are consistent with the Week 50 results and demonstrate sustained treatment effect of saxagliptin on HbA1c for the duration of the study. The final report can be provided to the TGA post approval.

Durability for the add-on to glibenclamide study (CV181040) can be quantified by the difference in the adjusted mean change from baseline in HbA1c in saxagliptin 2.5 mg and 5 mg groups compared with the uptitrated glibenclamide group at week 50. The results were -0.54% (95% CI: -0.71, -0.37) and -0.63% (95% CI: -0.79, -0.46) for the 2.5 and 5 mg doses respectively. Data from Week 76 has since been obtained, but were not available at time of submission. The Week 76 results are consistent and demonstrate sustained treatment effect of saxagliptin on HbA1c for the duration of the study. The final report can be provided to the TGA post approval.

Durability for the ICT study (CV181039) can be quantified by the difference in the adjusted mean change from baseline in HbA1c for saxagliptin 5 mg + metformin compared with metformin at Week 50. The results were -0.5 (-0.84, -0.16) for saxagliptin 5 mg + metformin versus metformin. Data from Week 76 has since been obtained, but were not available at time of submission. The Week 50 results and the final Week 76 results are consistent and demonstrate sustained treatment effect of saxagliptin on HbA1c for the duration of the study. The final report can be provided to the TGA post approval.

In summary, as demonstrated in LT studies, saxagliptin provides clinically significant improvement in glycaemic control as add on treatment to metformin, a TZD, a SU and as ICT with metformin in patients with T2DM and is well tolerated with a safety profile similar to placebo. The effect vs. control treatment is maintained without any new safety concerns during LT treatment for up to 102 weeks.

Patient Demographics

The Delegate raised concerns that "….the patients studied appeared healthier than many that will be encountered in clinical practice." The efficacy and safety of saxagliptin was established in a broad range of patients with T2DM, including patients who had inadequate glycaemic control on diet and exercise alone, or who had inadequate glycaemic control on metformin, SU or a TZD. There was a wide range of mean baseline HbA1c values across the six core Phase III studies (7.9% to 9.5%) that included a substantial number of patients with higher HbA1c values at baseline. Patients were included who had both shorter and longer duration of diabetes upon enrolment (mean duration across the Phase III studies of 1.7 to 6.9 years). Several subpopulations classified by age, gender, race, and ethnicity were well represented in the clinical program. Approximately two thirds of patients had a history of cardiovascular disease at baseline. Furthermore, the subjects that were enrolled in the add-on studies represent the typical subjects in clinical practice in that, in addition to

the required stable background treatment at enrolment, some have been treated with other oral antidiabetic drugs during the preceding year for varying duration, and others have not.

Renally Impaired Patients

The sponsor acknowledged the Delegate's comments on there being no dedicated study for patients with moderate or severe renal impairment. However, in patients with mild renal impairment, exposure to both saxagliptin and BMS-510849 is less than 2-fold that observed in patients with normal renal function. Accordingly, a dose of 5 mg saxagliptin in subjects with mild renal impairment is recommended. A dose of 2.5 mg saxagliptin in moderate and severe renal impairment is associated with saxagliptin exposures that are similar to the expected usual clinical dose of 5 mg in patients with normal renal function, and will result in exposures to BMS-510849 that approach the exposures typically achieved with a 10 mg dose in patients with normal renal function. Thus, a 2.5 mg daily dose in moderate and severe renal impairment maintains systemic exposures to parent and metabolite within the current long-term clinical safety experience. The current data provided in the application supports the use of 2.5 mg in these patients and a further clinical study is underway in renally-impaired patients; these results can be provided to the TGA when the results are available.

Risk Management Plan (RMP)

The sponsor did not include a RMP in the submission, as it was not a mandatory requirement at the time of application. However, the Global RMP for Onglyza currently includes the following adverse events of interest: angioedema, raised transaminases, renal impairment, rash, and cutaneous lesions. It currently does not include fractures and pancreatitis, as these have only recently been identified as AEs of interest. However, the sponsor committed to updating the RMP before launch of the product to include these two additional AEs.

Cardiovascular Concerns

The Delegate raised concerns that patients with cardiovascular (CV) disease were not specifically targeted in the studies. The sponsor wished to clarify that in the saxagliptin clinical program, there was no exclusion of subjects based on atherosclerosis per se, hyperlipidaemia or hypertension. In general, the percentages of subjects with any CV medical history at baseline were similar between the saxagliptin (66.0%) and placebo/comparator (67.6%) treatment groups. An even distribution among the different treatment groups was evident for each of the specific CV diseases.

Using the Phase IIb/III dataset from the 4 Month Safety Update (4MSU) (data cut-off dates of 20 June 2008 to 01 July 2008), an evaluation of the safety profile in the subjects with CV disease history at baseline and subjects without CV disease history was performed. Based on an evaluation of AEs across the different Systems Organs Classes (SOCs), the AE profile in the subjects with CV diseases were similar in the saxagliptin and placebo/comparator group during the ST and LT treatment periods.

The overall frequencies of CV AEs in subjects with a history of CV disease were (1.4%) in the saxagliptin group and (1.9%) placebo/comparator group based on a pre-defined list of preferred terms selected from multiple Standardized MedDRA Queries.[32] Similar findings were observed in the subjects without a history of CV diseases; the frequency of CV AEs was (0.5%) in the saxagliptin group compared to (1.2%) in the placebo/comparator group. As expected, the frequency of any CV adverse events in the subjects with a history of CV disease is higher than the proportion of any CV adverse events in the subjects without a history of cardiovascular risk, regardless of treatment group.

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[32] MedDRA = Medical Dictionary for Regulatory Activities.

Based on an evaluation of AEs in the Phase II/3 clinical study data from the 4MSU, the AE profiles associated with saxagliptin was similar to that of placebo/comparator in the sub-analyses of the subjects with and without CV diseases. In addition to no signal of increased CV risk from the sub-analyses of pooled CV data from the core Phase III studies, the findings reassure the safety of saxagliptin in the population with CV history at baseline.

The sponsor was presently in the final stages of designing a CV outcome study for the saxagliptin program. This study will be a multicentre, randomised, double-blind, placebo-controlled Phase IV trial in patients with T2DM. This clinical study is CV event-driven, with an anticipated total duration of 5 years, with the primary objective to demonstrate a beneficial effect of saxagliptin on the incidence of major adverse CV events. The primary safety objective is to demonstrate that there is no unacceptable cardiovascular toxicity with saxagliptin treatment. In addition, the sponsor has planned a prospective epidemiology study of major CV outcomes. This epidemiology study will compare the risk of major CV events in new users of saxagliptin to new users of other oral antidiabetic drugs and has a total duration of 3 to 5 years.

Advisory Committee Considerations

The Australian Drug Evaluation Committee (ADEC), at its December 2009 meeting, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the delegate's proposal except that it recommended that the indication as an add-on combination should specify pioglitazone rather than a thiazolidinedione in general.

In making this resolution, the ADEC was satisfied on clinical grounds for recommendation of approval, however the Committee was mindful that the PSC has recommended rejection of Onglyza. The Committee expressed concern that no absolute bioavailability data have been submitted for this new chemical entity. The Committee did not accept the sponsor's argument that performance of absolute bioavailability was unwarranted and it was noted that the compound is highly soluble and that the intended route of administration is oral. In addition, the lack of bioavailability study between the clinical and commercial formulations was also considered to be suboptimal. The ADEC determined that there were insufficient data to support the approval of the 2.5 mg tablet as use of saxagliptin could not be supported in moderate or severe chronic kidney disease.

The specific conditions of registration should include:

- That the sponsor provide to the TGA, the absolute bioavailability data and the bioavailability study between the clinical and commercial formulations. Further consideration should be given to study examining the effect of food upon bioavailability

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Onglyza containing saxagliptin (as hydrochloride) 5 mg film-coated tablet, indicated for:

Add-on combination *- Onglyza is indicated in patients with type 2 diabetes mellitus, to improve glycaemic control, in combination with metformin, a sulfonylurea, or a thiazolidinedione, as an adjunct to diet and exercise, when the single agent alone does not provide adequate glycaemic control.*

Initial combination *- Onglyza is indicated for use as initial combination therapy with metformin, in patients with type 2 diabetes mellitus, to improve glycaemic control as an adjunct to diet and exercise, when dual saxagliptin and metformin therapy is appropriate. (that is, high initial HbA1c levels and poor prospects for response to monotherapy).*

It was noted that the application for the 2.5 mg strength had been withdrawn from the submission.

A specific condition of registration was that the tablets must meet an agreed dissolution limit whenever tested through the shelf life.

Attachment 1. Product Information

ONGLYZA ®

saxagliptin

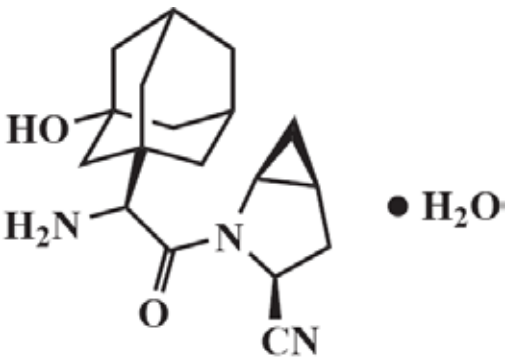
PRODUCT INFORMATION

NAME OF THE MEDICINE

ONGLYZA (saxagliptin) is an orally-active inhibitor of the dipeptidyl peptidase 4 (DPP-4) enzyme for the treatment of type 2 diabetes mellitus. Saxagliptin differs in chemical structure and pharmacological action from GLP-1 analogues, insulin, sulfonylureas or meglitinides, biguanides, peroxisome proliferators-activated receptor gamma (PPARγ) agonists, alpha-glucosidase inhibitors, and amylin analogues.

The chemical name of saxagliptin is (1S,3S,5S)-2-[(2S)-2-amino-2-(3-hydroxytricyclo [3.3.1.1^{3,7}] dec-1-yl)acetyl]-2-azabicyclo[3.1.0]hexane-3-carbonitrile, monohydrate.

The chemical structure of saxagliptin is:



CAS number: 945667-22-1

Molecular formula: $C_{18}H_{25}N_3O_2 \bullet H_2O$

Molecular weight: 333.43 (monohydrate)

DESCRIPTION

Saxagliptin is a white to light yellow or light brown powder. It is soluble in polyethylene glycol 400, acetone, acetonitrile, ethanol, isopropyl alcohol, methanol; sparingly soluble in water and slightly soluble in ethyl acetate.

Each film-coated tablet of ONGLYZA contains 5 mg of saxagliptin free base (as saxagliptin hydrochloride) and the following inactive ingredients: lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, polyvinyl alcohol, macrogol 3350, titanium dioxide, talc-purified, iron oxide red CI77491 (5 mg tablet only) and Opacode Blue (printing ink).

PHARMACOLOGY

Mechanism of Action

Saxagliptin is a member of a class of oral anti-hyperglycaemic agents called DPP-4 inhibitors. Saxagliptin is a reversible, competitive, DPP-4 inhibitor with nanomolar potency. Saxagliptin demonstrates selectivity for DPP-4 versus other DPP enzymes, with greater than 75 fold selectivity over DPP-8 and DPP-9. Saxagliptin has extended binding to the DPP-4 active site, prolonging its inhibition of DPP-4. Saxagliptin exerts its actions in patients with type 2 diabetes by slowing the inactivation of incretin hormones, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Concentrations of these active intact incretin hormones are increased by saxagliptin, thereby increasing and prolonging the actions of these hormones. Saxagliptin also inhibits the cleavage of other substrates *in vitro*, but the relevance or consequences of DPP4 inhibition for these substrates in patients is unknown.

Incretin hormones are released by the intestine throughout the day and concentrations are increased in response to a meal. These hormones are rapidly inactivated by the enzyme DPP-4. The incretins are part of an endogenous system involved in the physiologic regulation of glucose homeostasis. When blood glucose concentrations are elevated GLP-1 and GIP increase insulin synthesis and release from pancreatic beta cells. GLP-1 also lowers glucagon secretion from pancreatic alpha cells, leading to reduced hepatic glucose production.

Concentrations of GLP-1 are reduced in patients with type 2 diabetes, but saxagliptin increases active GLP-1 and GIP, potentiating these mechanisms. By increasing and prolonging active incretin concentrations, saxagliptin increases insulin release and decreases glucagon concentrations in the circulation in a glucose-dependent manner.

ONGLYZA improves glycemic control by reducing fasting and postprandial glucose concentrations in patients with type 2 diabetes through improvements in alpha and beta cell function as reflected by the actions described below.

<u>Fasting glucose-dependent insulin secretion</u>: ONGLYZA increases pancreatic beta-cell responsiveness to glucose in the fasting state and leads to enhanced insulin secretion and glucose disposal in the presence of elevated glucose concentrations.

<u>Postprandial glucose-dependent insulin secretion</u>: ONGLYZA increases pancreatic beta-cell responsiveness to glucose in the postprandial state and leads to enhanced postprandial insulin secretion and glucose disposal.

<u>Postprandial glucagon secretion</u>: In type 2 diabetes, paradoxical increases in glucagon secretion from alpha cells following meals stimulate hepatic glucose production and contribute to glycemic dysregulation. ONGLYZA moderates glucagon secretion and lowers postprandial glucagon concentrations.

Pharmacokinetics

The pharmacokinetics of saxagliptin has been extensively characterized in healthy subjects and patients with type 2 diabetes. Saxagliptin was rapidly absorbed after oral administration, with maximum saxagliptin plasma concentrations (C_{max}) usually attained within two hours after administration in the fasted state. The C_{max} and AUC values increased proportionally to the increment in the saxagliptin dose. Following a 5 mg single oral dose of saxagliptin to healthy subjects, the mean plasma $AUC_{(INF)}$ values for saxagliptin and its major metabolite were 78 ng·h/mL and 214 ng·h/mL, respectively. The corresponding plasma C_{max} values were 24 ng/mL and 47 ng/mL, respectively. The intra-subject coefficients of variation for saxagliptin C_{max} and AUC were less than 12%.

Following a single oral dose of 5 mg saxagliptin to healthy subjects, the mean plasma terminal half-life ($t_{1/2}$) for saxagliptin was 2.5 hours, and the mean $t_{1/2}$ value for plasma DPP-4 inhibition was 26.9 hours. The inhibition of plasma DPP-4 activity by saxagliptin for at least 24 hours after oral administration of ONGLYZA is due to high potency, high affinity, and extended binding to the active site. No appreciable accumulation was observed with repeated once-daily dosing at any dose level. No dose- and time-dependence was observed in the clearance of saxagliptin and its major metabolite over 14 days of once-daily dosing with saxagliptin at doses ranging from 2.5 mg to 400 mg.

Results from population-based exposure modelling indicate that the pharmacokinetics of saxagliptin and its major metabolite were similar in healthy subjects and in patients with type 2 diabetes.

Absorption

Based on food effects studies, ONGLYZA may be administered with or without food. However, in pivotal efficacy and safety studies ONGLYZA was generally taken prior to the morning meal. The amount of saxagliptin absorbed following an oral dose is at least 75%. The absolute oral bioavailability of saxagliptin is approximately 50% (90% CI of 48-53%). 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. The time for saxagliptin to reach C_{max} (T_{max}) was increased by approximately 0.5 hours with food compared with the fasted state. These changes were not considered to be clinically meaningful.

Distribution

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

Metabolism

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5). The major metabolite of saxagliptin is also a reversible, competitive DPP-4 inhibitor, half as potent as saxagliptin. It also demonstrates selectivity for

DPP-4 versus other DPP enzymes, with greater than 163 fold selectivity over DPP-8 and DPP-9.

Excretion

Saxagliptin is eliminated by both renal and hepatic pathways. Following a single 50 mg dose of ^{14}C-saxagliptin, 24%, 36%, and 75% of the dose was excreted in the urine as saxagliptin, its major metabolite, and total radioactivity, respectively. The average renal clearance of saxagliptin (~230 mL/min) was greater than the average estimated glomerular filtration rate (~120 mL/min), suggesting some active renal excretion. For the major metabolite, renal clearance values were comparable to estimated glomerular filtration rate. A total of 22% of the administered radioactivity was recovered in faeces representing the fraction of the saxagliptin dose excreted in bile and/or unabsorbed drug from the gastrointestinal tract.

Pharmacokinetics of the Major Metabolite

The C_{max} and AUC values for the major metabolite of saxagliptin increased proportionally to the increment in the saxagliptin dose. Following single oral doses of 2.5 mg to 400 mg saxagliptin in the fed or fasted states, the mean AUC values for the major metabolite ranged from 2-7 times higher than the parent saxagliptin exposures on a molar basis. Following a single oral dose of 5 mg saxagliptin in the fasted state, the mean terminal half-life ($t_{1/2}$) value for the major metabolite was 3.1 hours and no appreciable accumulation was observed upon repeated once-daily dosing at any dose.

Special Populations

Renal Impairment

A single-dose, open-label study was conducted to evaluate the pharmacokinetics of saxagliptin (10 mg dose) in subjects with varying degrees of chronic renal impairment compared to subjects with normal renal function. The study included patients with renal impairment classified on the basis of creatinine clearance as mild (>50 to ≤80 mL/min), moderate (30 to ≤50 mL/min), and severe (<30 mL/min), as well as patients with End Stage Renal Disease (ESRD) on haemodialysis. Creatinine clearance was estimated from serum creatinine based on the Cockcroft-Gault formula:

Males: $$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)} \times 1.2}{[\text{serum creatinine (micromol/L)}]}$$

Females: 0.85 × value calculated using formula for males

The degree of renal impairment did not affect the C_{max} of saxagliptin or its major metabolite. In subjects with mild renal impairment, the AUC values of saxagliptin and its major metabolite were 1.2- and 1.7-fold higher, respectively, than AUC values in subjects with normal renal function. Increases of this magnitude are not clinically relevant, therefore dosage adjustment in patients with mild renal impairment is not recommended. In subjects with moderate or severe renal impairment or in subjects with ESRD on haemodialysis, the AUC values of saxagliptin and its major metabolite were up to 2.1- and 4.5-fold higher,

respectively, than AUC values in subjects with normal renal function. See Dosage and Administration.

Hepatic Impairment

There were no clinically meaningful differences in pharmacokinetics for subjects with mild, moderate, or severe hepatic impairment; therefore, no dosage adjustment for ONGLYZA is recommended for patients with hepatic impairment. In subjects with hepatic impairment (Child-Pugh classes A, B, and C), mean C_{max} and AUC of saxagliptin were up to 8% and 77% higher, respectively, compared to healthy matched controls following administration of a single 10 mg dose of saxagliptin. The corresponding C_{max} and AUC of the major metabolite were up to 59% and 33% lower, respectively, compared to healthy matched controls. These differences are not considered to be clinically meaningful.

Elderly Patients

No dosage adjustment of ONGLYZA is recommended based on age alone. Elderly subjects (65-80 years) had 23% and 59% higher geometric mean C_{max} and geometric mean AUC values, respectively, for parent saxagliptin than young subjects (18-40 years). Differences in major metabolite pharmacokinetics between elderly and young subjects generally reflected the differences observed in parent saxagliptin pharmacokinetics. The difference between the pharmacokinetics of saxagliptin and the major metabolite in young and elderly subjects is likely to be due to multiple factors including declining renal function and metabolic capacity with increasing age. Age was not identified as a significant covariate on the apparent clearance of saxagliptin and its major metabolite in an exposure modelling analysis.

Paediatric and Adolescent

Pharmacokinetics in the paediatric population have not been studied.

Gender

No dosage adjustment is recommended based on gender. There were no differences observed in saxagliptin pharmacokinetics between males and females. Compared to males, females had approximately 25% higher exposure values for the major metabolite than males, but this difference is unlikely to be of clinical relevance. Gender was not identified as a significant covariate on the apparent clearance of saxagliptin and its major metabolite in an exposure modelling analysis.

Race

No dosage adjustment is recommended based on race. An exposure modelling analysis compared the pharmacokinetics of saxagliptin and its major metabolite in 309 white subjects with 105 non-white subjects (consisting of 6 racial groups). No significant difference in the pharmacokinetics of saxagliptin and its major metabolite were detected between these two populations.

Body Mass Index

No dosage adjustment is recommended based on body mass index (BMI). BMI was not identified as a significant covariate on the apparent clearance of saxagliptin or its major metabolite in an exposure modelling analysis.

Pharmacodynamics

General

In patients with type 2 diabetes, administration of ONGLYZA led to inhibition of DPP-4 enzyme activity for a 24-hour period. After an oral glucose load or a meal, this DPP-4 inhibition resulted in a 2- to 3-fold increase in circulating levels of active GLP-1 and GIP, decreased glucagon concentrations, and increased glucose-dependent beta-cell responsiveness, which resulted in higher insulin and C-peptide concentrations. The rise in insulin and the decrease in glucagon were associated with lower fasting glucose concentrations and reduced glucose excursion following an oral glucose load or a meal.

Cardiac Electrophysiology

In a clinical trial designed to study the effect of ONGLYZA on QTc interval, dosing with ONGLYZA was not associated with clinically meaningful prolongation of QTc interval or heart rate at daily doses up to 40 mg (8 times the Recommended Human Dose (RHD) of 5 mg/day). In a randomized, double-blind, placebo-controlled, four-way crossover, active comparator study, 40 healthy subjects were administered doses of saxagliptin up to 40 mg, placebo once daily for four days, or a single dose of moxifloxacin 400 mg as a positive control. Following the 40 mg dose, the maximum increase in the placebo-corrected mean changes in QTc interval and heart rate from baseline were 2.4 msec at 24 hours post-dose and 4.5 beats per minute at 4 hours post-dose, respectively.

CLINICAL TRIALS

ONGLYZA has been studied as monotherapy and in combination with metformin; glibenclamide; and the thiazolidinediones, pioglitazone and rosiglitazone. ONGLYZA has not been studied in combination with insulin or in triple combination therapy. ONGLYZA has been studied with antidiabetic medicinal products as described below.

ONGLYZA should be used as part of combination treatment with other oral diabetic agents. Results from long-term studies of ONGLYZA on overall morbidity and mortality outcomes are not available.

There were 4148 patients with type 2 diabetes randomized, including 3021 patients treated with ONGLYZA, in six double-blind, controlled clinical safety and efficacy studies conducted to evaluate the effects of ONGLYZA on glycemic control. In these studies, the mean age of patients was 54 years, and 71% of patients were white, 16% were Asian, 4% were black, and 9% were of other racial groups. Mean duration of diabetes ranged from 1.7 years to 6.9 years, mean weight ranged from 76 kg to 90 kg, and mean BMI ranged from 29 to 32 mg/kg^2.

An additional 423 patients, including 315 who received ONGLYZA, participated in a placebo-controlled, dose-ranging study of six to twelve weeks in duration.

In these six double-blind studies, ONGLYZA was evaluated at doses of 2.5 mg, 5 mg, and 10 mg once daily. Treatment with ONGLYZA at all doses produced clinically relevant and statistically significant improvements in haemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and postprandial glucose (PPG), including 2-hour PPG following standard oral glucose tolerance test (OGTT), compared to control. Reductions in HbA1c were seen across subgroups including gender, age, race, and baseline BMI. Overall, the 10 mg daily dose of saxagliptin did not provide greater efficacy than the 5 mg daily dose. The ONGLYZA 5 mg daily dose generally provided greater reductions in HbA1c and PPG compared to the ONGLYZA 2.5 mg daily dose.

Combination Therapy

Add-On Combination Therapy with Metformin

A total of 743 patients with type 2 diabetes participated in this randomized, double-blind, placebo-controlled study of 24-week duration, to evaluate the efficacy and safety of ONGLYZA in combination with metformin in patients with inadequate glycemic control (HbA1c ≥7% and ≤10%) on metformin alone. Patients were required to be on a stable dose of metformin (1500 mg to 2550 mg daily) for at least 8 weeks to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, two-week, dietary and exercise placebo lead-in period during which patients received metformin at their pre-study dose, up to 2500 mg daily, for the duration of the study. Following the lead-in period, eligible patients were randomized to 2.5 mg, 5 mg, or 10 mg of ONGLYZA or placebo in addition to their current dose of open-label metformin. Patients who failed to meet specific glycemic goals during the study were treated with pioglitazone rescue therapy, added on to placebo or ONGLYZA plus metformin. Dose titrations of ONGLYZA and metformin were not allowed in this study.

In combination with metformin, ONGLYZA 5 mg provided significant improvements in HbA1c, FPG, and PPG compared with the placebo plus metformin group (Table 1). Reductions in HbA1c at Week 4 (

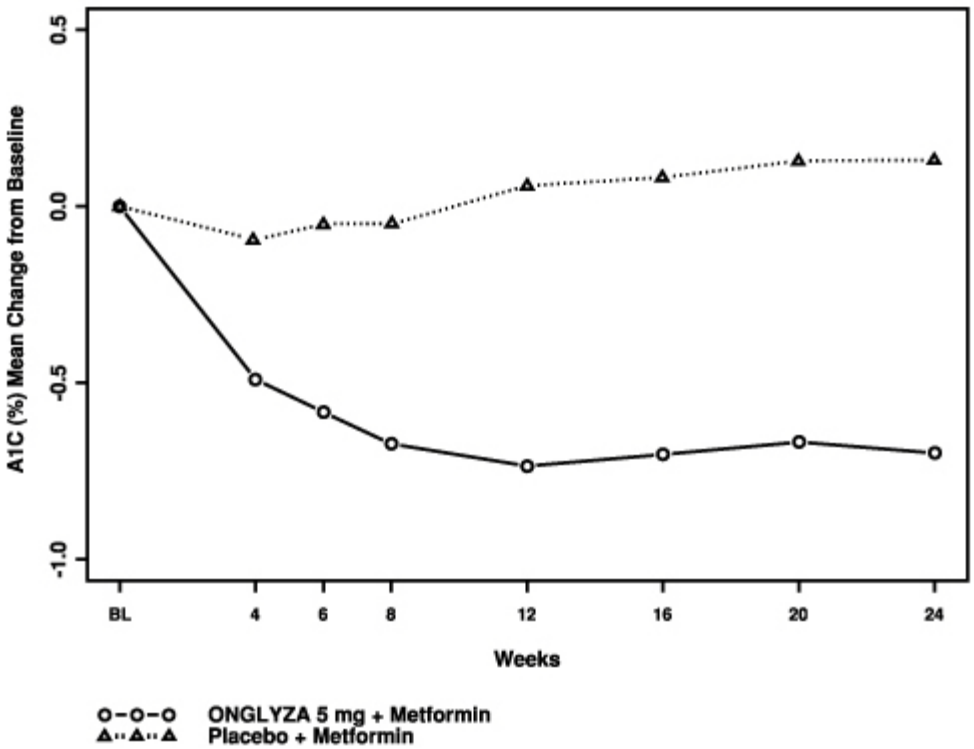
Figure 1) and FPG at Week 2 were seen in the ONGLYZA 5 mg plus metformin treatment groups relative to the placebo plus metformin group, the earliest time-points of assessment. The proportion of patients achieving HbA1c <7% (regardless of baseline value) was significantly greater in the ONGLYZA 5 mg plus metformin treatment groups compared with the placebo plus metformin group. Significant reductions in 2-hour PPG level following standard oral glucose tolerance test were observed in the ONGLYZA 5 mg plus metformin treatment group (-3.2 mmol/L) compared with the placebo plus metformin group (-1.0 mmol/L). The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting pre-specified glycemic criteria was higher in the placebo plus metformin group (27%) than in the ONGLYZA 5 mg plus metformin group (13%). Higher baseline HbA1c was associated with a greater adjusted mean change from baseline in HbA1c with ONGLYZA 5 mg plus metformin. The effect of ONGLYZA plus metformin on lipid endpoints in this study was similar to placebo. Similar reductions in body weight were observed in patients who received ONGLYZA plus metformin and placebo therapy (-0.9 kg and -0.9 kg, respectively).

Table 1 Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA 5 mg in combination with Metformin*

Efficacy Parameter	ONGLYZA 5 mg + Metformin	Placebo + Metformin
HbA1c (%)	**N=186**	**N=175**
Baseline (mean)	8.1	8.1
Change from baseline (adjusted mean†)	–0.7	0.1
Difference from placebo (adjusted mean†)	–0.8‡	
95% Confidence Interval	(−1.0, −0.6)	
Percent of patients achieving HbA1c <7%	44%‡ (81/186)	17% (29/175)
FPG (mmol/L)	**N=187**	**N=176**
Baseline (mean)	9.9	9.7
Change from baseline (adjusted mean†)	−1.2	0.1
Difference from placebo (adjusted mean†)	−1.3‡	
95% Confidence Interval	(−1.7, −0.9)	
3-hour PPG AUC (mmol•min/L)	**N=146**	**N=131**
Baseline (mean)	2721	2631
Change from baseline (adjusted mean†)	−532	−183
Difference from placebo (adjusted mean†)	−349‡	
95% Confidence Interval	(−478, −221)	

* Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy. † Least squares mean adjusted for baseline value. ‡ p-value <0.0001 compared to placebo + metformin

Figure 1 Mean Change from Baseline in HbA1c in a Placebo-Controlled Study of ONGYLZA in Combination with Metformin*



* Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy. Mean change from baseline (LOCF).

Controlled Long-Term Study Extension

Of the patients that started the 24-week treatment, 162 (84.8%) and 149 (83.2%) patients who were taking ONGLYZA 5 mg plus metformin and placebo plus metformin respectively entered a controlled double blind long-term study extension. Patients who received ONGLYZA in the initial 24-week study period maintained the same dose of ONGLYZA in the long-term extension. Treatment with ONGLYZA 5 mg plus metformin was associated with a greater reduction in A1C than in the placebo plus metformin group, and the effect relative to placebo was sustained at Week 50 and Week 102 compared to placebo. The A1C change for ONGLYZA 5 mg plus metformin (n=100 observed, n=187 LOCF) compared with placebo plus metformin (n=59 observed, n=175 LOCF) was -0.7% at Week 50. The A1C change for ONGLYZA 5 mg plus metformin (n=31 observed, n=184 LOCF) compared with placebo plus metformin (n=15 observed, n=172 LOCF) was -0.7% at Week 102.

Add-On Combination Therapy with a Sulfonylurea

A total of 768 patients with type 2 diabetes participated in this randomized, double-blind, placebo-controlled study of 24-week duration, to evaluate the efficacy and safety of ONGLYZA in combination with sulfonylurea (SU) in patients with inadequate glycemic control at enrollment (HbA1c ≥7.5% to ≤10%) on a submaximal dose of SU alone. Patients were required to be on a submaximal dose of SU for 2 months or greater to be enrolled in this study. In this study, ONGLYZA in combination with a fixed, intermediate dose of SU was compared to titration to a higher dose of SU.

Patients who met eligibility criteria were enrolled in a single-blind, 4-week, dietary and exercise lead-in period and placed on glibenclamide 7.5 mg once daily. Following the lead-in period, eligible patients with HbA1c ≥7% to ≤10% were randomized to either 2.5 mg or 5 mg of ONGLYZA plus 7.5 mg glibenclamide or placebo plus a 10 mg total daily dose of glibenclamide. Patients who received placebo were eligible to have glibenclamide up-titrated to a total daily dose of 15 mg. Up titration of glibenclamide was not allowed in patients who received ONGLYZA 2.5 or 5 mg. Glibenclamide could be down-titrated in any treatment group once during the 24-week study period due to hypoglycemia as deemed necessary by the investigator. Approximately 92% of patients in the placebo plus glibenclamide group were up-titrated to a final total daily dose of 15 mg during the study period. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue, added on to the ONGLYZA plus glibenclamide or the placebo plus up-titrated glibenclamide group. Dose titration of ONGLYZA was not permitted during the study.

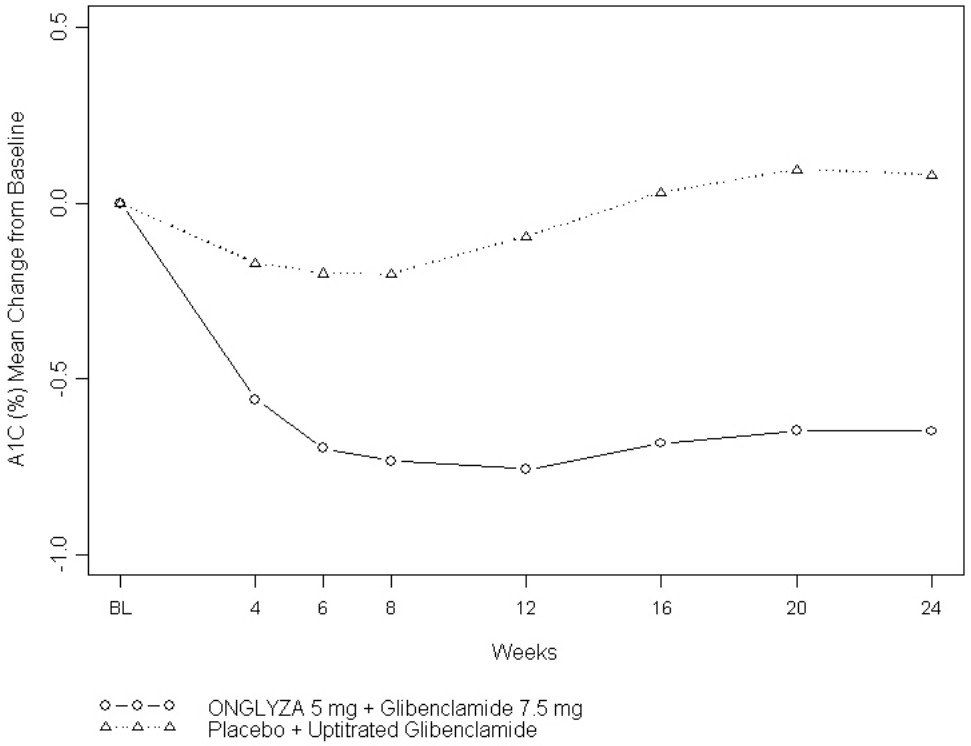
In combination with glibenclamide, ONGLYZA 5 mg provided significant improvements in HbA1c, FPG, and PPG compared with the placebo plus up-titrated glibenclamide group (Table 2). Reductions in HbA1c (Figure 2) at Week 4 and FPG at Week 2 were seen in the ONGLYZA 5 mg plus glibenclamide treatment group relative to the placebo plus up-titrated glibenclamide group, the earliest timepoints of assessment. The proportion of patients achieving HbA1c <7% (regardless of baseline value) was significantly greater in the ONGLYZA 5 mg plus glibenclamide treatment group compared with the placebo plus up-titrated glibenclamide group. Significant reductions in 2 hour PPG level following standard oral glucose tolerance test were observed in the ONGLYZA 5 mg plus glibenclamide treatment group (-1.9 mmol/L) compared with the placebo plus up-titrated glibenclamide (0.4 mmol/L). The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting pre-specified glycemic criteria was higher in the placebo plus up-titrated glibenclamide group (30%) than in the ONGLYZA 5 mg plus glibenclamide group (17%). Higher baseline HbA1c was associated with a greater adjusted mean change from baseline in HbA1c with ONGLYZA 5 mg plus glibenclamide. The effect of ONGLYZA plus glibenclamide on lipid endpoints in this study was similar to placebo. In this study, small increases in body weight were seen in patients treated with ONGLYZA 5 mg plus glibenclamide and with placebo plus up-titrated glibenclamide (0.8 kg versus 0.3 kg, p=0.012).

Table 2 Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA 5 mg in Combination with Glibenclamide*

Efficacy Parameter	ONGLYZA 5 mg + Glibenclamide 7.5 mg	Placebo + Up-Titrated Glibenclamide
HbA1c (%)	**N=250**	**N=264**
Baseline (mean)	8.5	8.4
Change from baseline (adjusted mean[†])	−0.6	0.1
Difference from placebo (adjusted mean[†])	−0.7[‡]	
95% Confidence Interval	(−0.9, −0.6)	
Percent of patients achieving HbA1c <7%	23%[‡] (57/250)	9% (24/264)
FPG (mmol/L)	**N=252**	**N=265**
Baseline (mean)	9.7	9.7
Change from baseline (adjusted mean[†])	−0.6	0.1
Difference from placebo (adjusted mean[†])	−0.6[§]	
95% Confidence Interval	(−0.9, −0.2)	
3-hour PPG AUC (mmol•min/L)	**N=195**	**N=204**
Baseline (mean)	2794	2875
Change from baseline (adjusted mean[†])	−278	66
Difference from placebo (adjusted mean[†])	−344[‡]	
95% Confidence Interval	(−433, −254)	

- Intent-to-treat population using last observation on study prior to metformin rescue therapy. [†] Least squares mean adjusted for baseline value. [‡] p-value <0.0001 compared to placebo + up-titrated glibenclamide. § p-value=0.0020 compared to placebo + up-titrated glibenclamide

Figure 2 Mean Change from Baseline in HbA1c in a Placebo-Controlled Study of ONGLYZA in Combination with Glibenclamide*



* Intent-to-treat population using last observation on study prior to metformin rescue therapy. Mean change from baseline (LOCF).

Controlled Long-Term Study Extension

Of the patients that started the 24-week treatment, 227 (89.7%) and 235 (88%) patients who were taking ONGLYZA 5 mg plus glibenclamide and placebo plus up-titrated glibenclamide respectively entered a controlled double blind long-term study extension. Patients who received ONGLYZA in the initial 24-week study period maintained the same dose of ONGLYZA in the long-term extension. The HbA1C change for ONGLYZA 5 mg plus glibenclamide (n=99 observed, n=243 LOCF) compared with placebo plus up-titrated glibenclamide (n=61 observed, n=253 LOCF) was -0.6% at Week 50.

Add on Combination Therapy with a Thiazolidinedione (TZD)

A total of 565 patients with type 2 diabetes participated in this randomized, double-blind, placebo-controlled study of 24-week duration, to evaluate the efficacy and safety of ONGLYZA in combination with a TZD (pioglitazone or rosiglitazone) in patients with inadequate glycemic control (HbA1c ≥7% to ≤10.5%) on TZD alone. Patients were required to be on a stable dose of pioglitazone (30 mg to 45 mg once daily) or rosiglitazone (4 mg once daily or 8 mg either once daily or in two divided doses of 4 mg) for at least 12 weeks to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, two-week, dietary and exercise placebo lead-in period during which patients received TZD at their pre-study dose for the duration of the study. Following the lead-in period, eligible patients were randomized to 2.5 mg or 5 mg of ONGLYZA or placebo in addition to their current dose of TZD. Patients who failed to meet specific glycemic goals during the study were treated with metformin rescue, added on to placebo or ONGLYZA plus TZD. Dose titration of ONGLYZA or TZD was not permitted during the study. A change in TZD regimen from rosiglitazone to pioglitazone at specified, equivalent therapeutic doses was permitted at the investigator's discretion if believed to be medically appropriate.

In combination with TZD, ONGLYZA 5 mg provided significant improvements in HbA1c, FPG, and PPG compared with the placebo plus TZD treatment group (Table 3). Reductions in HbA1c (Figure 3) at Week 4 and FPG at Week 2 were seen in the ONGLYZA 5 mg plus TZD treatment group relative to the placebo plus TZD group, the earliest timepoints of assessment. The proportion of patients achieving HbA1c <7% (regardless of baseline value) was significantly greater in the ONGLYZA 5 mg plus TZD treatment group compared with the placebo plus TZD group. Significant reductions in 2-hour PPG level following standard oral glucose tolerance test were observed in the ONGLYZA 5 mg plus TZD treatment group (-3.6 mmol/L) compared with the placebo plus TZD group (-0.8 mmol/L). The proportion of patients who discontinued for lack of glycemic control or who were rescued for meeting pre-specified glycemic criteria was 10% in the placebo plus TZD group and 6% for the 5 mg ONGLYZA plus TZD group. Higher baseline HbA1c was associated with a greater adjusted mean change from baseline in HbA1c with ONGLYZA 5 mg plus TZD. The effect of ONGLYZA plus TZD on lipid endpoints in this study was similar to placebo. Small increases in body weight were observed in the ONGLYZA 5 mg plus TZD and placebo treatment groups (1.4 kg and 0.9 kg, respectively.)

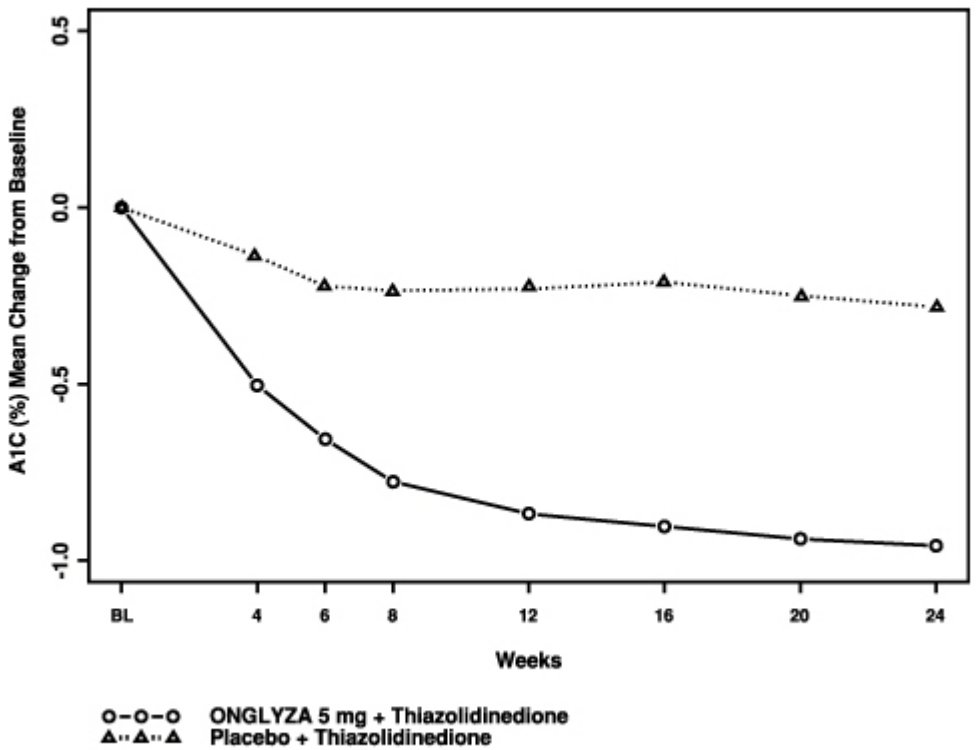
Table 3 Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA 5 mg in Combination with a Thiazolidinedione*

Efficacy Parameter	ONGLYZA 5 mg + TZD	Placebo + TZD
HbA1c (%)	**N=183**	**N=180**
Baseline (mean)	8.4	8.2
Change from baseline (adjusted mean[†])	−0.9	−0.3
Difference from placebo (adjusted mean[†])	−0.6[‡]	
95% Confidence Interval	(−0.8, −0.4)	
Percent of patients achieving HbA1c <7%	42%[§] (77/184)	26% (46/180)
FPG (mmol/L)	**N=185**	**N=181**
Baseline (mean)	8.9	9.0
Change from baseline (adjusted mean[†])	−0.9	−0.2

Efficacy Parameter	ONGLYZA 5 mg + TZD	Placebo + TZD
Difference from placebo (adjusted mean†)	−0.8‖	
95% Confidence Interval	(−1.3, −0.3)	
3-hour PPG AUC (mmol•min/L)	**N=131**	**N=123**
Baseline (mean)	2657	2623
Change from baseline (adjusted mean†)	−514	−149
Difference from placebo (adjusted mean†)	−365‡	
95% Confidence Interval	(−490, −240)	

* Intent-to-treat population using last observation on study prior to metformin rescue therapy. † Least squares mean adjusted for baseline value. ‡ p-value <0.0001 compared to placebo + TZD. § p-value=0.0013 compared to placebo + TZD ‖ p-value=0.0005 compared to placebo + TZD

Figure 3 Mean Change from Baseline in HbA1c in a Placebo-Controlled Study of ONGLYZA in Combination with a Thiazolidinedione*



* Intent-to-treat population using last observation on study prior to metformin rescue therapy. Mean change from baseline (LOCF).

Controlled Long-Term Study Extension

Of the patients that started the 24-week treatment, 150 (80.6%) and 145 (78.8%) patients who were taking ONGLYZA 5 mg plus TZD and placebo plus TZD respectively entered a controlled double blind long-term study extension. . Patients who received ONGLYZA in the initial 24-week study period maintained the same dose of ONGLYZA in the long-term extension. The HbA1C change for ONGLYZA 5 mg plus TZD (n=65 observed, n=135 LOCF) compared with placebo plus TZD (n=48 observed, n=130 LOCF) was –0.7% at Week 50.

Combination with Metformin as Initial Therapy

A total of 1306 treatment-naïve patients with type 2 diabetes participated in this randomized, double-blind, placebo-controlled study of 24-week duration, to evaluate the efficacy and safety of ONGLYZA as initial combination therapy with metformin in patients with inadequate glycemic control (HbA1c ≥8% to ≤12%) on diet and exercise alone. Patients were required to be treatment-naïve to be enrolled in this study.

Patients who met eligibility criteria were enrolled in a single-blind, one-week, dietary and exercise placebo lead-in period. Patients were randomized to one of four treatment arms: ONGLYZA 5 mg + metformin 500 mg, saxagliptin 10 mg + metformin 500 mg, saxagliptin 10 mg + placebo, or metformin 500 mg + placebo. ONGLYZA was dosed once daily. During Weeks 1 through 5, in the ONGLYZA 5 mg and the saxagliptin 10 mg plus metformin groups, and the metformin alone group, metformin was up-titrated based on FPG levels in 500 mg per day increments as tolerated to a maximum of 2000 mg per day. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue as add-on therapy.

Initial therapy with the combination of ONGLYZA 5 mg plus metformin provided significant improvements in HbA1c, FPG, and PPG compared with metformin alone (Table 4). Reductions in HbA1c at Week 4 and FPG at Week 2 were seen in the ONGLYZA 5 mg plus metformin treatment group relative to metformin alone, the earliest timepoints of assessment. The proportion of patients achieving HbA1c <7% (regardless of baseline value) was significantly greater in the ONGLYZA 5 mg plus metformin treatment group compared with metformin alone. Significant reductions in 2-hour PPG level following standard oral glucose tolerance test were observed in the ONGLYZA 5 mg plus metformin group (-7.7 mmol/L) compared with the metformin alone group (-5.4 mmol/L). Significant improvements in HbA1c, FPG, and PPG were also seen in the ONGLYZA 5 mg plus metformin group compared with the saxagliptin alone group. Higher baseline HbA1c was associated with greater adjusted mean change from baseline in HbA1c in all treatment groups. Similar effects on lipid parameters were observed in all treatment groups. Similar reductions in body weight were seen in the ONGLYZA 5 mg plus metformin and in the metformin alone groups (-1.8 kg and -1.6 kg, respectively) with a smaller reduction seen in the saxagliptin 10 mg group.

Table 4 Glycemic Parameters at Week 24 in a Placebo-Controlled Study of ONGLYZA 5 mg in Combination with Metformin as Initial Therapy and Metformin Alone*

Efficacy Parameter	ONGLYZA 5 mg + Metformin	Metformin
HbA1c (%)	**N=306**	**N=313**
Baseline (mean)	9.4	9.4
Change from baseline (adjusted mean†)	−2.5	−2.0
Difference from placebo (adjusted mean†)	−0.5‡	
95% Confidence Interval	(−0.7,−0.4)	
Percent of patients achieving HbA1c <7%	60%‡ (185/307)	41% (129/314)
FPG (mmol/L)	**N=315**	**N=320**
Baseline (mean)	11.0	11.0
Change from baseline (adjusted mean†)	−3.3	−2.6
Difference from placebo (adjusted mean†)	−0.7§	
95% Confidence Interval	(−1.1,−0.3)	
3-hour PPG AUC (mmol•min/L)	**N=142**	**N=135**
Baseline (mean)	3082	3216
Change from baseline (adjusted mean†)	−1170	−833
Difference from placebo (adjusted mean†)	−337‡	
95% Confidence Interval	(−468,−207)	

* Intent-to-treat population using last observation on study prior to pioglitazone rescue therapy. † Least squares mean adjusted for baseline value. ‡ p-value <0.0001 compared to metformin. § p-value=0.0002 compared to metformin

Controlled Long-Term Study Extension

Of the patients that started the 24-week treatment, 276 (86.3%) and 266 (81.1%) patients who were taking ONGLYZA 5 mg plus metformin and metformin respectively entered a controlled long-term study extension. Patients who received ONGLYZA in the initial 24-week study period maintained the same dose of ONGLYZA in the long-term extension. The HbA1c change for ONGLYZA 5 mg plus metformin (n=46 observed, n=100 LOCF) compared with placebo plus metformin (n=33 observed, n=91 LOCF) was –0.5% at Week 50 compared to placebo.

INDICATIONS

Add-on combination

ONGLYZA is indicated in patients with type 2 diabetes mellitus, to improve glycaemic control, in combination with metformin, a sulfonylurea, or a thiazolidinedione, as an adjunct to diet and exercise, when the single agent alone does not provide adequate glycaemic control.

Initial combination

ONGLYZA is indicated for use as initial combination therapy with metformin, in patients with type 2 diabetes mellitus, to improve glycemic control as an adjunct to diet and exercise, when dual saxagliptin and metformin therapy is appropriate. (i.e. high initial HbA1c levels and poor prospects for response to monotherapy).

CONTRAINDICATIONS

ONGLYZA is contraindicated in patients with a history of any serious hypersensitivity reaction to any component of ONGLYZA or to any other DPP-4 inhibitor.

PRECAUTIONS

General

ONGLYZA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. ONGLYZA has not been studied in combination with insulin.

Use in Patients with Renal Impairment

There is limited experience in patients with moderate or severe renal impairment and in patients with End Stage Renal Disease (ESRD) on haemodialysis. Therefore ONGLYZA should not be used in these patients. Assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter. The recommended clinical dose is unchanged in patients with mild renal impairment. (See Dosage and Administration.) ONGLYZA should not be used in more significant degrees of renal impairment.

Use with Medications Known to Cause Hypoglycaemia

The sulfonylurea class of antihyperglycaemic agents is known to cause hypoglycaemia. Therefore, a lower dose of sulfonylurea may be required to reduce the risk of hypoglycaemia when used in combination with ONGLYZA. (See Adverse Effects.)

Effects on ability to drive and to use machines

No studies on the effects on the ability to drive and use machines have been performed. However, when driving or operating machines, it should be taken into account that dizziness has been reported with saxagliptin.

Effects on fertility

In a rat fertility study, males were treated with oral gavage doses of 100, 200, and 400 mg/kg/day for two weeks prior to mating, during mating, and up to scheduled termination (approximately four weeks total) and females were treated with oral gavage doses of 125, 300, and 750 mg/kg/day for two weeks prior to mating through gestation day 7. No adverse effects on fertility were observed at 200 mg/kg/day (males) or 125 mg/kg/day (females) resulting in respective exposures (AUC) of approximately 670 (males) and 865 (females) times human exposure at the recommended clinical dose. At higher, maternally toxic doses (300 and 750 mg/kg/day), increased fetal resorptions were observed (approximately 2300 and 6810 times the recommended clinical dose). Additional effects on oestrous cycling, fertility, ovulation, and implantation were observed at 750 mg/kg/day (approximately 6810 times the recommended clinical dose).

Use in pregnancy – Category B3

Saxagliptin was not teratogenic at any dose evaluated in rats or rabbits. At high doses in rats, saxagliptin caused a minor developmental delay in ossification of the foetal pelvis at ≥240 mg/kg/day (≥1670 times the human exposure [AUC] at the recommended clinical dose). Maternal toxicity and reduced foetal body weights were observed at 900 mg/kg/day (>8860 times the recommended clinical dose). In rabbits, the effects of saxagliptin were limited to minor skeletal variations observed only at maternally toxic doses (200 mg/kg/day, exposures 1520 times the recommended clinical dose).

Saxagliptin administered to female rats from gestation day 6 to lactation day 20 resulted in decreased body weights in male and female offspring only at maternally toxic doses (≥250 mg/kg/day, exposures ≥1810 times the recommended clinical dose). No functional or behavioural toxicity was observed in the offspring of rats administered saxagliptin at any dose.

Saxagliptin and/or its metabolites cross the placenta into the fetus following dosing in pregnant rats.

There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ONGLYZA should be used during pregnancy only if clearly needed.

Use in lactation

Saxagliptin and/or its metabolites are secreted in the milk of lactating rats. It is not known whether saxagliptin is secreted in human milk. Caution should be exercised when ONGLYZA is administered to a nursing woman.

Paediatric use

Safety and effectiveness of ONGLYZA in paediatric patients have not been established.

Use in elderly

Of the total number of subjects (N=4148, of which 3021 received ONGLYZA) in six, double-blind, controlled clinical safety and efficacy studies of ONGLYZA, 634 (15.3%) patients were 65 years and over, of which 59 (1.4%) patients were 75 years and over. No overall differences in safety or effectiveness were observed between subjects 65 years and over, and younger subjects. While this clinical experience has not identified differences in responses between the elderly and younger patients, greater sensitivity of some older individuals cannot be ruled out. Experience in patients aged 75 years and older is very limited and caution should be exercised when treating this population.

Saxagliptin and its major metabolite are eliminated in part by the kidney. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function. (See Dosage and Administration)

Carcinogenicity

Two-year carcinogenicity studies were conducted in mice and rats. Saxagliptin did not induce tumours in mice treated at up to 600 mg/kg/day, producing exposure 1123-times that of humans at the recommended clinical dose. In rats, no increase in tumours was observed in males treated with saxagliptin at up to 150 mg/kg/day and females at up to 300 mg/kg/day (relative exposure at the highest doses, approximately 400 and 2465, respectively.

Genotoxicity

The mutagenic and clastogenic potential of saxagliptin was tested at high concentrations and exposures in a battery of genetic toxicity studies including an *in vitro* Ames bacterial assay, an *in vitro* cytogenetics assay in primary human lymphocytes, an *in vivo* oral micronucleus assay in rats, an *in vivo* oral DNA repair study in rats, and an oral *in vivo*/*in vitro* cytogenetics study in rat peripheral blood lymphocytes. Saxagliptin was not mutagenic or clastogenic based on the combined outcomes of these studies. The major metabolite was not mutagenic in an *in vitro* Ames bacterial assay.

Interactions with other medicines

The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5).

In *in vitro* studies, saxagliptin and its major metabolite neither inhibited CYP1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, or 3A4, nor induced CYP1A2, 2B6, 2C9, or 3A4. Therefore, saxagliptin is not expected to alter the metabolic clearance of coadministered drugs that are metabolised by these enzymes. Saxagliptin is neither a significant inhibitor of P-glycoprotein (P-gp) nor an inducer of P-gp.

The *in vitro* protein binding of saxagliptin and its major metabolite in human serum is below measurable levels. Thus, protein binding would not have a meaningful influence on the pharmacokinetics of saxagliptin or other drugs.

In studies conducted in healthy subjects, as described below, the pharmacokinetics of saxagliptin, its major metabolite, or the exposure to the total active components of saxagliptin (parent + metabolite), were not meaningfully altered by metformin, glibenclamide, pioglitazone, digoxin, simvastatin, diltiazem, ketoconazole, omeprazole, aluminium hydroxide + magnesium hydroxide + simethicone combination, or famotidine. Saxagliptin also did not meaningfully alter the pharmacokinetics of metformin, glibenclamide, pioglitazone, digoxin, simvastatin, diltiazem, or ketoconazole.

Metformin

Coadministration of a single dose of saxagliptin (100 mg) and metformin (1000 mg), an hOCT-1 and hOCT-2 substrate, decreased the C_{max} of saxagliptin by 21%; however, the AUC was unchanged. Saxagliptin did not alter the pharmacokinetics of metformin. Therefore, ONGLYZA is not an inhibitor of hOCT-1 and hOCT-2-mediated transport and meaningful interactions with other hOCT-1 and hOCT-2 substrates would not be expected.

Glibenclamide

Coadministration of a single dose of saxagliptin (10 mg) and glibenclamide (5 mg), a CYP2C9 substrate, increased the C_{max} of saxagliptin by 8%; however, the AUC of saxagliptin was unchanged. The plasma C_{max} of glibenclamide increased by 16%; however, the AUC of glibenclamide was unchanged. Therefore, ONGLYZA does not meaningfully inhibit CYP2C9-mediated metabolism and meaningful interactions with other CYP2C9 substrates would not be expected.

Pioglitazone

Coadministration of multiple once-daily doses of saxagliptin (10 mg) and pioglitazone (45 mg), a CYP2C8 (major) and CYP3A4 (minor) substrate, did not alter the pharmacokinetics of saxagliptin. The plasma C_{max} of pioglitazone increased by 14%; however, the AUC of pioglitazone was unchanged. Therefore, ONGLYZA does not meaningfully inhibit or induce CYP2C8-mediated metabolism and meaningful interactions with other CYP2C8 substrates would not be expected.

Digoxin

Coadministration of multiple once-daily doses of saxagliptin (10 mg) and digoxin (0.25 mg), a P-gp substrate, did not alter the pharmacokinetics of saxagliptin or digoxin. Therefore, ONGLYZA is not an inhibitor or inducer of P-gp-mediated transport and meaningful interactions with other P-gp substrates would not be expected.

Simvastatin

Coadministration of multiple once-daily doses of saxagliptin (10 mg) and simvastatin (40 mg), a CYP3A4/5 substrate, increased the C_{max} of saxagliptin by 21%; however, the AUC of saxagliptin was unchanged. Saxagliptin did not alter the pharmacokinetics of simvastatin. Therefore, ONGLYZA is not an inhibitor or inducer of CYP3A4/5-mediated metabolism and meaningful interactions would not be expected with other substrates of CYP3A4/5.

Diltiazem

Coadministration of a single dose of saxagliptin (10 mg) and diltiazem (360 mg long-acting formulation at steady state), a moderate inhibitor of CYP3A4/5, increased the C_{max} of saxagliptin by 63% and the AUC for the total active components of saxagliptin by 21%. The plasma C_{max} of diltiazem increased by 16%; however, the AUC of diltiazem was unchanged. Therefore, ONGLYZA would not be expected to meaningfully alter the pharmacokinetics of moderate CYP3A4/5 inhibitors and meaningful interactions with other moderate CYP3A4/5 inhibitors would not be expected.

Ketoconazole

Coadministration of a single dose of saxagliptin (100 mg) and ketoconazole (200 mg every 12 hours at steady state), a potent inhibitor of CYP3A4/5 and P-gp, increased the C_{max} for saxagliptin by 62% and the AUC for the total active components of saxagliptin by 13%. The plasma C_{max} and AUC of ketoconazole decreased by 16 and 13% respectively. Therefore, ONGLYZA would not be expected to meaningfully alter the pharmacokinetics of potent CYP3A4/5 and P-gp inhibitors and meaningful interactions would not be expected with other potent CYP3A4/5 and P-gp inhibitors.

CYP3A4/5 Inducers

The effects of CYP3A4/5 inducers on the pharmacokinetics of saxagliptin have not been studied. However, the coadministration of saxagliptin and CYP3A4/5 inducers such as carbamazepine, dexamethasone, phenobarbital, phenytoin, and rifampicin may result in decreased plasma concentrations of saxagliptin and increased concentrations of its major metabolite.

Omeprazole

Coadministration of multiple once-daily doses of saxagliptin (10 mg) and omeprazole (40 mg), a CYP2C19 (major) and CYP3A4 substrate, an inhibitor of CYP2C19, and an inducer of MRP-3, did not alter the pharmacokinetics of saxagliptin. Therefore, meaningful interactions of ONGLYZA with other CYP2C19 inhibitors or MRP-3 inducers would not be expected.

Aluminium hydroxide + magnesium hydroxide + simethicone

Coadministration of a single dose of saxagliptin (10 mg) and a liquid containing aluminium hydroxide (2400 mg), magnesium hydroxide (2400 mg), and simethicone (240 mg) decreased the C_{max} of saxagliptin by 26%; however, the AUC of saxagliptin was unchanged. Therefore, meaningful interactions of ONGLYZA with antacid and antigas formulations of this type would not be expected.

Famotidine

Administration of a single dose of saxagliptin (10 mg) three hours after a single dose of famotidine (40 mg), an inhibitor of hOCT-1, hOCT-2, and hOCT-3, increased the C_{max} of saxagliptin by 14%; however, the AUC of saxagliptin was unchanged. Therefore, meaningful interactions of ONGLYZA would not be expected with other inhibitors of hOCT-1, hOCT-2, and hOCT-3.

Other interactions

The effects of smoking, diet, herbal products, and alcohol use on the pharmacokinetics of saxagliptin have not been specifically studied.

The safety and efficacy of saxagliptin in combination with insulin, alpha-glucosidase inhibitors or orlistat has not been established.

ADVERSE EFFECTS

There were 4148 patients with type 2 diabetes randomized, including 3021 patients treated with ONGLYZA, in six, double-blind, controlled clinical safety and efficacy studies conducted to evaluate the effects of ONGLYZA on glycemic control.

In a pre-specified pooled analysis of two monotherapy studies, the add-on to metformin study, the add-on to TZD study, and the add-on to glibenclamide study, the overall incidence of adverse events in patients treated with ONGLYZA 5 mg was similar to placebo. In the 24-week short-term period, discontinuation of therapy due to adverse events occurred in 3.3% and 1.8% of patients receiving ONGLYZA 5 mg and placebo, respectively. In the 24-week short-term combined with the long-term extension period, discontinuation of therapy due to adverse events occurred in 6.7% and 4.6% of patients receiving ONGLYZA 5 mg and placebo, respectively.

The adverse reactions in this short-term pooled analysis reported (regardless of investigator assessment of causality) in ≥5% of patients treated with ONGLYZA 5 mg and more commonly than in patients treated with placebo are shown in the following table.

Table 5 Adverse Reactions (Regardless of Investigator Assessment of Causality) in Placebo-Controlled Studies* Reported in ≥5% of Patients Treated with ONGLYZA 5 mg and More Commonly than in Patients Treated with Placebo

	Number (%) of Patients	
	ONGLYZA 5 mg N=882	**Placebo N=799**
Upper respiratory tract infection	68 (7.7)	61 (7.6)
Urinary tract infection	60 (6.8)	49 (6.1)
Headache	57 (6.5)	47 (5.9)

* The 5 placebo-controlled studies include two monotherapy studies and one add-on combination therapy study with each of the following: metformin, thiazolidinedione, or glibenclamide

In this pooled analysis, less common adverse reactions that were reported in ≥2% of patients treated with ONGLYZA 5 mg and ≥1% more frequently compared to placebo included the following: sinusitis, gastroenteritis, and vomiting.

In the combined short-term and long-term extension periods of the placebo controlled studies, adverse reactions reported in ≥2% of patients treated with ONGLYZA 5 mg and ≥1% more frequently compared to placebo were: upper respiratory tract infection, urinary tract infection and gastroenteritis. Adverse events of uncertain causality that were reported in ≥2% of patients treated with ONGLYZA 5 mg and ≥1% more frequently compared to placebo include: abdominal pain, rash, blood creatine phosphokinase increased, hypertriglyceridaemia, anaemia, depression, and anxiety.

In short-term combined with long-term periods of pooled studies, the incidence rate of fractures was 1.0 and 0.6 per 100 patient-years, respectively, for ONGLYZA (pooled analysis of 2.5 mg, 5 mg, and 10 mg) and placebo. The incidence rate of fracture events in patients who received ONGLYZA did not increase over time. Causality has not been established and nonclinical studies have not demonstrated adverse effects of saxagliptin on bone.

A grouping of hypersensitivity-related events in the 5-study pooled analysis up to Week 24 showed an incidence of 1.5% and 0.4% in patients who received ONGLYZA 5 mg and placebo, respectively. None of these events in patients who received ONGLYZA required hospitalisation or were reported to be life-threatening by the investigators.

Adverse Reactions Associated with ONGLYZA and Concomitant Therapy

In the short-term 24-week add-on to glibenclamide study, the overall incidence of hypoglycaemia was higher for ONGLYZA 5 mg plus glibenclamide versus placebo plus up-titrated glibenclamide. The difference (14.6% versus 10.1%) was not statistically significant. The incidence of confirmed hypoglycaemia in this study, defined as symptoms of hypoglycaemia accompanied by a fingerstick glucose value of ≤2.8 mmol/L, was 0.8% for ONGLYZA 5 mg plus glibenclamide and 0.7% for placebo plus up-titrated glibenclamide. In the combined short-term and long-term extension period of the add-on to glibenclamide study, the overall incidence of hypoglycemia was 18.2% for ONGLYZA 5 mg and 12.0% for up-titrated glibenclimide; the incidence of confirmed hypoglycemia was 1.6% for ONGLYZA 5 mg and 1.9% for up-titrated glibenclimide. In a pooled analysis of the two monotherapy studies, the add-on to metformin study, and the add-on to TZD study (short-term 24 week), the overall incidence of adverse reactions of hypoglycaemia in patients treated with ONGLYZA 5 mg was similar to placebo (4.8% versus 4.3%). Adverse reactions of hypoglycaemia were based on all reports of hypoglycemia; a concurrent glucose measurement was not required.

In the add-on to TZD study, the incidence of peripheral oedema was higher for ONGLYZA 5 mg plus TZD versus placebo plus TZD (8.1% versus 4.3%). In the combined short-term and long-term extension period, the incidence of peripheral oedema was higher for ONGLYZA 5 mg plus TZD versus placebo plus TZD (13.4% versus 9.8%). In a pooled analysis of the two monotherapy studies, the add-on to metformin study and the add-on to SU study (short-term 24 week), the overall incidence of adverse reactions of peripheral oedema observed in patients treated with ONGLYZA 5 mg alone or in combination was similar to placebo (1.7% versus 2.4%).

In a 24-week, active-controlled study of initial therapy of ONGLYZA in combination with metformin, the adverse reactions reported (regardless of investigator assessment of causality) in ≥5% of patients are shown in Table 6. The incidence of hypoglycemia was 3.4% in patients given ONGLYZA 5 mg plus metformin, 1.5% in patients given saxagliptin 10 mg alone, and 4.0% in patients given metformin alone. In the combined short-term and long-term extension period, the incidence of hypoglycemia was 4.4% in patients given ONGLYZA 5 mg plus metformin, 1.8% in patients given saxagliptin 10 mg alone, and 5.2% in patients given metformin alone.

Table 6 Initial Therapy with Combination of ONGLYZA and Metformin: Adverse Reactions Reported (Regardless of Investigator Assessment of Causality) in ≥5% of Patients Treated with Combination Therapy of ONGLYZA 5 mg Plus Metformin (and Greater Than in Patients Treated with Saxagliptin 10 mg Alone and Metformin Alone)

	Number (%) of Patients		
	ONGLYZA 5 mg + Metformin* N=320	**Saxagliptin 10 mg N=335**	**Metformin* N=328**
Headache	24 (7.5)	21 (6.3)	17 (5.2)
Nasopharyngitis	22 (6.9)	14 (4.2)	13 (4.0)

* Metformin was initiated at a starting dose of 500 mg daily and titrated up to a maximum of 2000 mg daily.

In this study, less common adverse events that were reported in ≥2% of patients treated with ONGLYZA 5 mg and ≥1% more frequently compared to saxagliptin monotherapy and metformin included the following: bronchitis, dyspepsia, and back pain.

In the combined short-term and long-term extension period, adverse reactions in placebo controlled studies reported in ≥2% of patients treated with ONGLYZA 5 mg and ≥1% more frequently compared to saxagliptin 10 mg alone and metformin alone were: nasopharyngitis and headache. Hypertension, an adverse event of uncertain causality, was reported in ≥2% of patients treated with ONGLYZA 5 mg and ≥1% more frequently compared to placebo

No clinically meaningful changes in vital signs have been observed in patients treated with ONGLYZA 5 mg.

Laboratory Tests

Across clinical studies, the incidence of laboratory adverse events was similar in patients treated with ONGLYZA 5 mg alone or in combination compared to patients treated with placebo. A small decrease in absolute lymphocyte count was observed. From a baseline mean absolute lymphocyte count of approximately 2.2 x 10^9 c/L, a mean decrease of approximately 0.1 x 10^9 c/L relative to placebo was observed in a pooled analysis of five placebo-controlled clinical studies. Mean absolute lymphocyte counts remained stable and within the normal limits with daily

dosing up to 102 weeks in duration. In the short term period, the proportion of patients who were reported to have a lymphocyte count ≤750 cells/microL was 1.5% and 0.4% in the saxagliptin 5 mg and placebo groups, respectively. In the short-term combined with long-term extension period of the pooled studies, the proportion of patients who were reported to have a lymphocyte count ≤750 cells/microL was 1.6% and 1.0% in the saxagliptin 5 mg and placebo groups, respectively. 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.

DOSAGE AND ADMINISTRATION

Add-On Combination Therapy

The recommended dose of ONGLYZA is 5 mg once daily as add-on combination therapy with metformin, a thiazolidinedione, or a sulfonylurea. ONGLYZA can be taken with or without food.

Initial Combination Therapy

The recommended starting doses of ONGLYZA and metformin when used as initial combination therapy is 5 mg ONGLYZA plus 500 mg metformin once daily. Patients with inadequate glycemic control on this starting dose should further have their metformin dose increased according to approved metformin Product Information.

Renal impairment

Assessment of renal function is recommended prior to initiation of ONGLYZA and periodically thereafter. Renal function can be estimated from serum creatinine using the Cockcroft-Gault formula or Modification of Diet in Renal Disease (MDRD) formula.

ONGLYZA should not be used in patients with moderate or severe renal impairment and in patients with End Stage Renal Disease (ESRD) on haemodialysis, due to limited experience in these patients. In patients with mild renal impairment (creatinine clearance [CrCl] >50 mL/min), the recommended clinical dose is ONGLYZA 5 mg daily

Hepatic impairment

No dosage adjustment for ONGLYZA is necessary for patients with mild, moderate, or severe hepatic impairment.

Paediatric and adolescent

Safety and effectiveness of ONGLYZA in paediatric and adolescent patients have not been established.

Geriatric

No dosage adjustment for ONGLYZA is required based solely on age. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection in the elderly based on renal function. (See Precautions)

OVERDOSAGE

Once-daily, orally-administered ONGLYZA has been shown to be safe and well-tolerated, with no clinically meaningful effect on QTc interval or heart rate at doses up to 400 mg daily for two weeks (80 times the recommended human dose of 5 mg/day).

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. Saxagliptin and its major metabolite are removed by hemodialysis (23% of dose over four hours).

Contact the Poisons Information Centre for advice on management.

PRESENTATION AND STORAGE CONDITIONS

ONGLYZA (saxagliptin) 5 mg tablets are pink, biconvex, round, film-coated tablets with "5" printed on one side and "4215" printed on the other side, in blue ink.

ONGLYZA is available in blister packs of 7 and 28 tablets. Store below 30°C.

NAME AND ADDRESS OF SPONSOR

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ABN 33 004 333 322
556 Princes Highway
NOBLE PARK VIC 3174

Marketed in Australia by

Bristol-Myers Squibb Australia Pty Ltd
ABN 33 004 333 322
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NOBLE PARK VIC 3174

and

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POISON SCHEDULE OF THE MEDICINE

Prescription only medicine (Schedule 4)

DATE OF APPROVAL

Date of approval: 7 March 2011

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