



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Saxagliptin

Proprietary Product Name: Onglyza

Sponsor: Bristol-Myers Squibb/AstraZeneca

June 2012

TGA Health Safety
Regulation

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I. Introduction to Product Submission

Submission Details

| | |
|------------------------------------|---|
| <i>Type of Submission</i> | Major Variation (New Strength, New Patient Group and Change in Dosage). |
| <i>Decision:</i> | Withdrawn ¹ |
| <i>Date of Decision:</i> | 20 December 2012 |
| <i>Active ingredient(s):</i> | Saxagliptin |
| <i>Product Name(s):</i> | Onglyza |
| <i>Sponsor's Name and Address:</i> | Bristol-Myers Squibb 556 Princes Highway, Noble Park VIC 3174 |
| <i>Dose form(s):</i> | Tablet |
| <i>Strength(s):</i> | 2.5 mg |
| <i>Container(s):</i> | Blister pack |
| <i>Pack size(s):</i> | 7 and 28 |
| <i>Route(s) of administration:</i> | Oral (PO) |
| <i>Dosage:</i> | 2.5 mg/day ² |
| <i>ARTG Number (s)</i> | Not applicable |

Product Background

Diabetes is a leading cause of morbidity and early death in the world. In Australia, approximately 7.4% of the population aged 25 or over have Type II Diabetes. In addition, prevalence increases progressively with age, so that it is estimated that more than 20% of the population aged over 60 have Type II Diabetes³.

Improving glycaemic control in people with Type II Diabetes is associated with reduced morbidity and mortality. The current National Health and Medical Research Council (NHMRC) guidelines for Type II Diabetes Mellitus⁴ state that if glycaemic targets are not achieved using lifestyle management within 2 to 3 months, anti-hypoglycaemic agents should be initiated. In addition, it is generally accepted that despite an adequate initial treatment more than one medication is usually required over time, as Type II Diabetes is a progressive disease.

¹ The majority of the application was withdrawn by the sponsor prior to a decision by the TGA. The approval was limited to a minor change to the PI.

² The registered dose is 5 mg once daily. This employs Onglyza (saxagliptin) 5 mg tablets.

³ Shaw JE & Chisholm DJ. Epidemiology and prevention of type 2 diabetes and the metabolic syndrome. Med J Aust. 2003 Oct 6;179(7):379-83.

⁴ Diabetes Australian Guideline Development Consortium. National evidence based guidelines for the prevention, diagnosis and management of type 2 diabetes mellitus. Diabetes Australia and the NHMRC, Canberra 2009. Available at <http://www.diabetesaustralia.com.au/For-Health-Professionals/Diabetes-National-Guidelines/>

Onglyza (saxagliptin) 5 mg tablets are currently approved for use as an adjunctive treatment in patients with Type II Diabetes. The original Onglyza application proposed both 5 mg and 2.5 mg tablets for registration. However, at that time the Australian Drug Evaluation Committee (now called Advisory Committee on Prescription Medicines (ACPM)) considered that there were insufficient data to support the registration of the 2.5 mg tablet for use in moderate or severe chronic kidney disease and the 2.5 mg tablet was withdrawn from the previous application which sought to register both the 2.5 and 5 mg strengths (referred to throughout this report as the "original application").

This AusPAR describes the current application in which the sponsor again proposes 2.5 mg tablets for patients with Type II diabetes (T2DM) and renal impairment. To support the use of saxagliptin in patients with renal impairment, the sponsor conducted a Phase III study of 2.5 mg saxagliptin in patients with moderate, severe and end stage renal disease.

Regulatory Status

The foreign status of this application is, as at the time of this application, summarised in Table 1.

Table 1 Submission and approval status: Saxagliptin for the treatment of patients with type 2 diabetes and renal impairment

| Country | Submission date | Approval date | Comment |
|-----------------------------|-----------------|---|--|
| Canada | 29-NOV-2010 | Under evaluation (Expected NOV-2011) | For use in patients with renal impairment: The dose of ONGLYZA is 2.5 mg once daily for patients with moderate or severe renal impairment, or with end-stage renal disease (ESRD) requiring haemodialysis. Claim for dose adjustment for patients with end-stage renal disease (ESRD) was withdrawn 11-OCT-2011. |
| European Union ^a | 05-MAR-2010 | 28-FEB-2011 | For use in patients with renal impairment: The dose of Onglyza should be reduced to 2.5 mg once daily in patients with moderate or severe renal impairment, or with end-stage renal disease (ESRD) requiring haemodialysis (creatinine clearance [CrCl] ≤50 ml/min). Claim for dose adjustment for patients with end-stage renal disease (ESRD) was withdrawn 15-SEP-2010. |
| New Zealand | 18-AUG-2011 | Under evaluation | 2.5 mg variation for use in Renal patients has not yet been submitted. |
| Switzerland | 29-DEC-2010 | Under evaluation | Use in moderate renal impairment approved with initial submission FEB 2010. Use in severe renal impairment only proposed in submission. |
| United States | 19-APR-2010 | 18-FEB-2011 | Dose adjustment to 2.5 mg for patients with moderate, severe or end-stage renal disease was approved in original application, 31-JUL-2009. Current submission adds a description of study D1680C00007 to the Clinical Studies section of the US PI. |

^a Centralised Procedure Rapporteur (Netherlands) and co-rapporteur (Norway).

Australian marketing approval for the Onglyza 5 mg tablet was granted on 7 March 2011.

The currently registered Indications are as follows:

Add-on combination

Onglyza is indicated in patients with Type II 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 II 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).

Product Information

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

II. Quality Findings

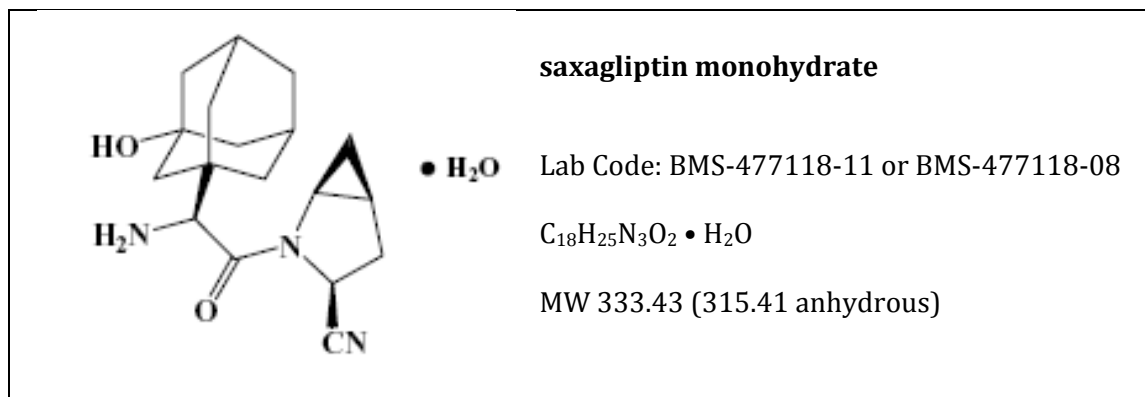
No new quality data were provided with this application.

Drug Substance (active ingredient)

Saxagliptin is an inhibitor of dipeptidyl-peptidase 4 (DPP-4). It is chiral (presented as a single enantiomer). Only one polymorphic form is known. Solubility is high, particularly in acid (127 mg/mL at pH 1; 19 mg/mL at pH 7.8).

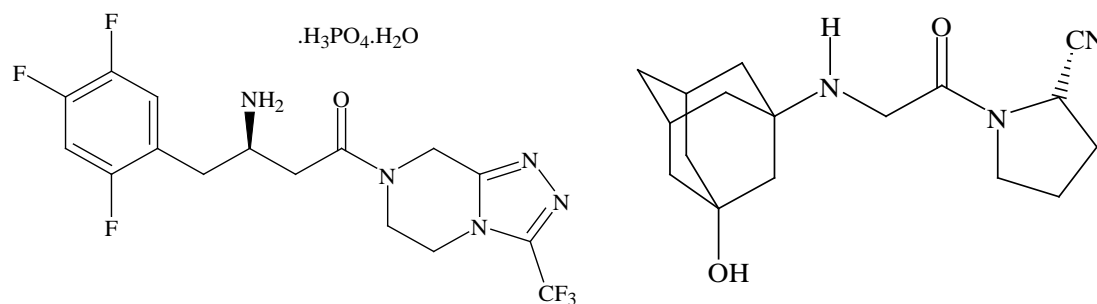
Figure 1A shows the chemical structure of saxagliptin.

Figure 1A. Chemical structure.



Related Drugs

Sitagliptin is another DPP-4 inhibitor, registered in Australia as Januvia 25, 50 and 100 mg tablets by Merck Sharp & Dohme. Sitagliptin has a quite different structure (see below Figure 1B). *Galvus* vildagliptin 50 and 100 mg tablets are approved in Europe. The structure of vildagliptin is more closely related to saxagliptin; the proposed saxagliptin doses are notably lower.

Figure 1B. Chemical structure of sitagliptin and vildagliptin.

sitagliptin phosphate monohydrate
(*Januvia* 25, 50, 100 mg tablets
Merck Sharp & Dohme)

vildagliptin
(50, 100 mg tablets in EU)

Saxagliptin is synthetic. Impurity levels are low: there are three specified impurities. Particle size is not controlled because the drug is dissolved during tablet manufacture.

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. The 2.5 mg and 5 mg tablets differ only in the amount of drug which is incorporated within the tablet and in the outer coat colour and markings (2.5 mg yellow with '2.5' and '4214' printed in blue; 5 mg pink with '5' and '4215' printed in blue).

It was recommended that as a specific condition of registration the 2.5 mg tablets must meet an agreed dissolution limit whenever tested through the shelf life.

The data are sufficient to support the same shelf life as earlier approved for the 5 mg tablets (24 months, store below 30°C in aluminium (Al)/Al blister packs).

Biopharmaceutics

The sponsor undertook an absolute bioavailability study during the course of the evaluation of the 5 mg tablets. The absolute oral bioavailability of saxagliptin was approximately 50% (confidence interval (CI) 48-53%).

Clinical Trial Formulations

The first clinical trials used 2.5, 5 and 20 mg capsules containing saxagliptin benzoate (Phase I and II studies up to the end of Phase IIb: CV181001, CV181002, CV181008, CV181010). Saxagliptin benzoate was not suitable to make tablets.

“Early clinical tablets” were 5 and 40 mg tablets made with saxagliptin free base monohydrate, although the drug is actually present as the hydrochloride salt in the tablets after acidic spray coating. New strengths, with some small formulation changes were introduced to give a “clinical tablet” or “Phase III” formulations (2.5, 5 and 10 mg tablets):

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. Dissolution data are very similar.

Bioequivalence

A direct bioequivalence comparison of the 2.5 and 5 mg tablets has not been undertaken. Both tablet strengths were used in pivotal clinical trials. Tablet dissolution of the 2.5 and 5 mg tablets are similarly rapid at pH 1.2, 4.5 and 6.8. Registration of the 2.5 mg tablets (with respect to biopharmaceutic aspects) is recommended on the basis of these data.

Advisory Committee Considerations

This re-submission has not been referred to the Pharmaceutical Subcommittee given earlier consideration of both strengths. The PSC ultimately recommended:

“The PSC agreed that the all issues of concern in relation to biopharmaceutic data raised at its 129th and 130th meetings held 23 November 2009 and 27 January 2010 respectively have been resolved to the satisfaction of the TGA.

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

[*Recommendation No 2188*]

Quality Summary and Conclusions

Registration was recommended with respect to chemistry and quality control and bioavailability aspects. Consistent with PSC resolutions (see No 2077), the evaluator recommended that a formal condition of registration is applied requiring tablets to meet the dissolution limit at expiry (see above).

III. Nonclinical Findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical Findings

Introduction

Following a previous ADEC recommendation that there were insufficient data to support registration of the 2.5 mg strength in the setting of moderate or severe renal failure (see *Product Background* above), such data were submitted with the current application in the form of pivotal Study D1680C00007, referred to throughout this application as Study 07.

Certification of good clinical practice and provision of detail on ethical clearances and other matters relevant to appropriate care of patients/subjects were included in each of the three studies and all appear quite satisfactory.

Pharmacokinetics

Introduction

Studies of the pharmacokinetics (PK) of saxagliptin must involve measurement in plasma, and in some studies urine, of both the parent drug and its metabolite BMS-510849 which has 50% of the biological activity of saxagliptin. This is particularly so as the concentrations of these 2 substances may be differentially affected by factors that included the level of renal function and coadministration of drugs affecting their metabolism by the cytochrome P450 system, both of which are relevant to this application.

The analytical methods and statistical analysis planning for the PK studies reported in this section are essentially identical with those used in the PK studies in the original application and need not be detailed again in this report. Likewise, the characteristics of absorption, distribution and elimination of saxagliptin have been fully described in the

original application and are only discussed in this report when relevant in relation to specific studies.

Absorption

Bioavailability

No new bioavailability data has been reviewed in the course of this evaluation. It is noted that the sponsor has applied for a biowaiver for not demonstrating *in vivo* bioequivalence of the 2.5 and 5 mg tablets.

As detailed above, the pharmaceutical composition of the 2 tablet strengths is identical. The sponsor has provided other evidence on physicochemical characteristics which appear to support the application for the waiver.

Dose proportionality across a range including the 2.5 mg dose has been demonstrated in studies reviewed in the evaluation of the original application, as discussed below.

The above is felt to constitute sufficient evidence of bioequivalence of the 2.5 with the 5 mg saxagliptin tablet, at least for the purpose of this evaluation.

Dose proportionality and time dependency

Relevant data previously evaluated are discussed below.

Pharmacokinetics in the target population

The target population for this application consists of patients with Type II Diabetes who have renal impairment. Relevant pharmacokinetic data are discussed below.

Pharmacokinetics in special populations

Children

No data (but see comments below regarding a study that is in progress).

Impaired renal function

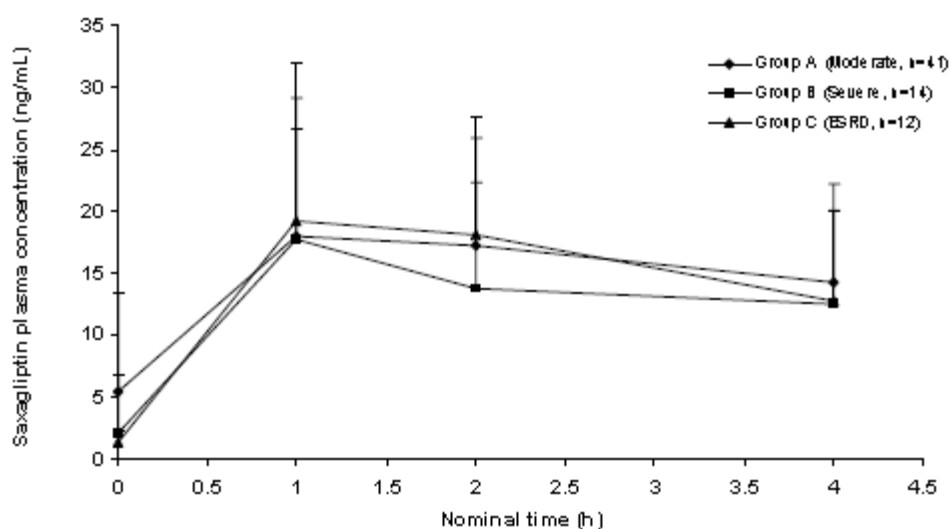
The effect of impaired renal function on the PK of saxagliptin was documented in Study CV181019, part of the original application and summarised in the clinical evaluation report (CER) of that application. These data are also summarised in the existing approved PI. They show that with mild renal impairment (creatinine clearance (CrCl) 50-80 mL/min), the AUC of saxagliptin is increased by 16% and the AUC of BMS-510849 is increased by 67% compared to values in healthy subjects. For moderate renal impairment (CrCl 30-50), these increases were 41% and 192%, respectively, and in severe renal impairment (CrCl <30), 108% and 345%, respectively. Note that these definitions of the various categories of impairment of renal function apply in all sections of this report.

PK data were also obtained in the course of the pivotal efficacy/safety Study D1680C00007 (Study 07) submitted with this application, which is summarised under the *Efficacy* and *Safety* sections below. The results for mean (standard deviation (SD)) plasma concentrations (ng/mL) of saxagliptin and BMS-510849 with administration of saxagliptin 2.5 mg daily at steady-state are shown below (Table 2).

Table 2. Plasma concentrations (ng/mL) of saxagliptin and BMS-510849 with administration of saxagliptin 2.5 mg daily at steady-state.

| | Baseline renal impairment | Pre-dose | | 1 hour post-dose | | 2-hours post-dose | | 4 hours post-dose | |
|-------------|---------------------------|----------|-------------------|------------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| | | n | Mean (SD) | n | Mean (SD) | n | Mean (SD) | n | Mean (SD) |
| Saxagliptin | Moderate | 41 | 5.44 (7.959) | 41 | 17.95 (11.201) | 41 | 17.27 (8.690) | 41 | 14.30 (7.935) |
| | Severe | 13 | 2.07 (4.706) | 14 | 17.76 (8.979) | 14 | 13.80 (8.516) | 14 | 12.58 (7.476) |
| | End-stage | 11 | 1.32 (1.012) | 12 | 19.26 (12.797) | 12 | 18.14 (9.556) | 12 | 12.80 (7.265) |
| BMS-510849 | Moderate | 39 | 9.77 (8.193) | 39 | 24.16 (12.423) | 39 | 30.71 (11.365) | 40 | 31.16 (11.327) |
| | Severe | 14 | 16.46 (16.368) | 14 | 35.27 (17.912) | 14 | 42.19 (20.989) | 14 | 42.96 (15.833) |
| | End-stage | 11 | 38.04 (24.346) | 11 | 49.18 (27.375) | 12 | 54.39 (33.605) | 12 | 57.96 (36.933) |

Comparison of these with existing data is difficult as calculation of PK parameters (C_{max} , AUC) was not undertaken; a sampling profile appropriate for this was not used. However, a semiquantitative evaluation is possible using the time concentration profiles as illustrated in Figure 2 below.

Figure 2. Time concentration profiles

Given that the time to peak plasma concentration (T_{max}) for saxagliptin is generally around 1 h, a C_{max} of between 15 and 20 ng/mL for saxagliptin is suggested. The CER of the original application reports dose proportionality in the 2.5-400 mg range for both C_{max} and AUC of saxagliptin in healthy subjects. The average C_{max} for saxagliptin approximates 20 ng/mL at 5 mg dose and 10 ng/mL at the 2.5 mg dose. The above data suggest a degree of increase in exposure of between 50 and 100% for the 2.5 mg dose with impaired renal function, similar to that reported for Study CV181019 in which a 10 mg dose was used, although without the progressive increase with degree of renal impairment. The lack of such a gradation seems implausible and probably reflects the relatively small numbers in this study, the restricted sampling profile and the high variances in the data.

For BMS-510849, post-dose plasma concentrations following the 2.5 mg dose at steady-state are generally in the range 30-50 ng/mL, similar to the levels observed in subjects with normal renal function following a 5 mg dose, including those in the saxagliptin only group in the study of interaction with rifampicin illustrated in Figure 3 below; the time concentration response is also extended, so that the AUC would be relatively more increased and overlaps the dosing interval. The degree of accumulation is clearly progressive with increasing severity of renal impairment and consistent with the data previously documented for the 10 mg dose in Study CV181019.

Impaired hepatic function

No data relevant to this application

Evaluator's overall comments on pharmacokinetics in special populations

For the severely renally impaired (as defined above) population taking the 2.5 mg saxagliptin dose in Study 07, there is an approximate 1.5-2 fold increase in exposure to saxagliptin and a 2-3 fold increase in exposure to the active metabolite BMS-510849 to what might be expected from previously evaluated population studies. The biological significance of the increased exposure to BMS-510849 is of relatively less significance as this metabolite has 50% of the potency of saxagliptin. Overall, the effect of this degree of impairment of renal function is therefore to increase the exposure to biologically active saxagliptin products following a 2.5 mg dose by approximately 100%; which, in the context of the demonstrated dose proportionality would predict that this dose would have a biological effect equivalent to the 5 mg dose in a person with normal renal function. For those with moderate or end stage renal dysfunction, as already defined, the effect should be a little less and a little more, respectively, but well within what might be predicted for the dose range 2.5-10 mg.

Pharmacokinetic interactions with other medicinal products or substances

The application is accompanied by two drug interaction studies which support changes in the PI proposed in the application form (but not letter of application).

In-vivo pharmacokinetic interactions

Study CV181059 was a non randomised, open label, single sequence study. The primary objective was to assess the effect of rifampicin on the single dose pharmacokinetics of saxagliptin when the two drugs were co administered to healthy subjects. Secondary objectives were assessment of the effect of rifampicin on the pharmacokinetics of saxagliptin's metabolically active metabolite BMS-510849 and assessment of the safety and tolerability of the single 5 mg saxagliptin dose in the presence and absence of rifampicin in these subjects.

Pharmacodynamic responsiveness (DPP-4 inhibition) was also assessed in the presence and absence of rifampicin.

Background and rationale

Following oral dosage and absorption, saxagliptin is rapidly hydroxylated by cytochrome P450 3A4 (CYP3A4) to its active metabolite BMS-510849. Accordingly, drugs which influence the activity of CYP3A4 have the capacity to affect the pharmacokinetics of both saxagliptin and the active metabolite. The pharmacokinetics of both substances are reviewed in detail in the CER of the original application which refers to data on two CYP3A4 inhibitors, diltiazem and ketoconazole, which had the expected effect of increasing saxagliptin but reducing BMS-510849 exposure. The CER in the original application draws attention to the fact that the effect of CYP3A4/5 inducers had not been studied and that the sponsor's statement (reflected in the original PI) in this regard was

that "coadministration of saxagliptin and CYP3A4/5 inducers may result in decreased plasma concentrations of saxagliptin".

The presently submitted study with rifampicin, as an indicative CYP3A4/5 inducer, aims to redress this deficiency.

An important aspect of this issue is the eventual outcome on the pharmacodynamic response to saxagliptin. BMS-510849 is said to have 50% of the potency of saxagliptin; evidence for this was not available to this evaluation but it is widely quoted in the documentation and the original CER. Reciprocal changes in exposure to the metabolite and its parent substance brought about by changes in CYP3A4/5 therefore tend to have counterbalancing effects although conditions which differentially affect the clearance of the two substances could in theory result in a pharmacodynamic response which might be unchanged, reduced or possibly even increased. Evaluation of the pharmacodynamic as well as the pharmacokinetic changes following coadministration of saxagliptin with drugs which influence the CYP 450 system is therefore essential.

This interaction issue is, according to available information⁵, specific to saxagliptin. Other drugs in this class so far approved for use (sitagliptin, vildagliptin) are not substrates, inducers or inhibitors of the CYP 450 system.

Conduct of study

Fourteen healthy subjects (13 male) were enrolled and treated in an eight-day protocol during which they were confined to the centre. The majority (n=11) were African-American. The mean age was 33±7 years and the body mass index (BMI) was 26.3±2.7. Thirteen subjects completed the study, one withdrew consent prior to completion. Each subject received a single 5 mg oral dose of saxagliptin on Day 1 and then 600 mg once daily oral doses of rifampicin from Days 2 to 6 inclusive. A second 5 mg oral dose of saxagliptin was then given on Day 7 together with a 600 mg dose of rifampicin.

Blood and urine samples for PK and PD analysis were taken during the 24 h period following the test doses on Days 1 and 7.

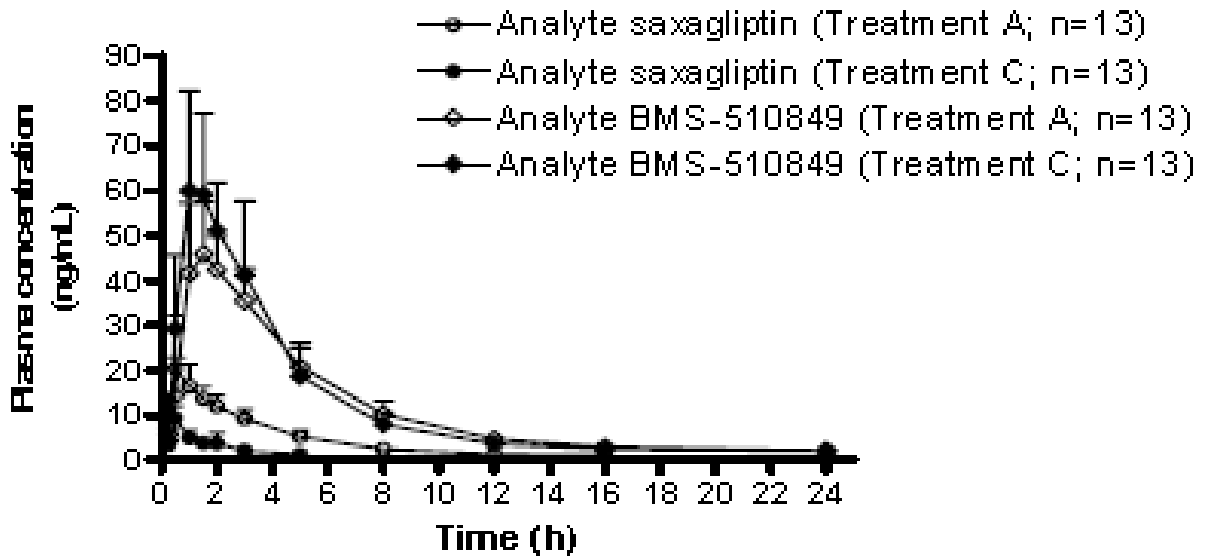
The study was commenced on 14 March 2008 and completed in 4 weeks.

Results

The PK profiles for saxagliptin and BMS-510849 in the presence or absence of rifampicin are displayed in the following figure (Figure 3). The time concentration profiles for saxagliptin are the lower two lines in the graphic.

⁵ Australian approved product information, Phoenix medical publishing, May 2011

Figure 3. PK profiles for saxagliptin and BMS-510849 in the presence or absence of rifampicin.



Treatment A is saxagliptin alone; treatment C, saxagliptin with rifampicin.

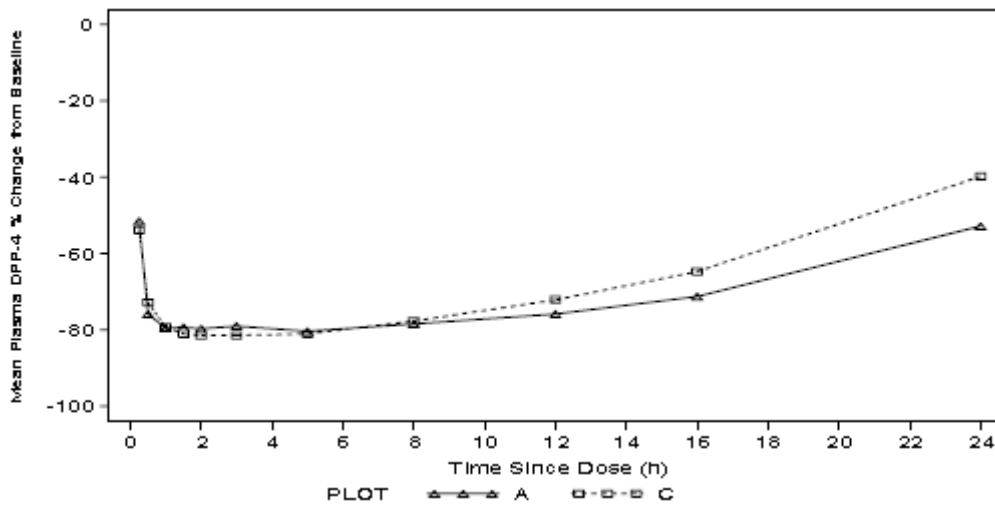
Overall, rifampicin had a much more marked effect on the PK of saxagliptin than on that of BMS-510849. For saxagliptin, C_{max} was reduced by 53%, the area under the plasma concentration time curve from time zero to infinity ($AUC_{(inf)}$) by 76% and area under the plasma concentration time curve over a dosing interval ($AUC_{(0-T)}$) by 80%. In contrast, for BMS-510849 the C_{max} was increased by 39% but the $AUC_{(inf)}$ and $AUC_{(0-T)}$ were only increased by 3% and 4%, respectively. For BMS-510849, comparison of the population means for the 2 treatments showed the 90% CI to be contained well within the 80-125% no-effect interval for $AUC_{(inf)}$ and $AUC_{(0-T)}$ but outside these limits for C_{max} and for all the saxagliptin parameters. The sponsor speculates on various possible explanations for these disparate results, including that rifampicin might have an effect in accelerating clearance of BMS-510849, and/or interfering with saxagliptin absorption; the latter possibility is supported by the finding that total dose recovery in urine (saxagliptin+ BMS-510849), was 41% following administration of saxagliptin alone but 30% following coadministration with rifampicin.

The above PK data have been combined into a calculation of "total active moieties". This consists of the molar saxagliptin exposure + 1/2 the BMS-510849 molar exposure, which makes allowance for the 50% reduction of biological potency of BMS-51049 with reference to saxagliptin. For this parameter, C_{max} was unchanged and the $AUC_{(inf)}$ was reduced by 27% when saxagliptin was coadministered with rifampicin.

Pharmacodynamic results

Pharmacodynamic (PD) response was assessed by measuring DPP-4 activity in plasma at all time points and expressing the data as % inhibition from baseline (the pre-dose value). The data are presented here rather than in the PD section because of the need, as outlined above, to view them in the context of the PK responses. The time course of the response is shown in the study report in Figure 4.

Figure 4. The time course of the response



Treatment C (upper line) is coadministration with rifampicin.

Inhibition of DPP-4 activity occurs rapidly in both treatment groups and to a similar level around 80%. However, the last 2 time points suggest that recovery may take place more quickly in the presence of rifampicin. Quantitative assessment of the data is shown in the following table (Table 3):

Table 3. Pharmacodynamic analysis.

| Pharmacodynamic Parameter | Treatment | |
|-------------------------------|-------------------------|--|
| | Saxagliptin 5 mg (n=13) | Saxagliptin 5 mg with Rifampin 600 mg (n=13) |
| % I _{max} | | |
| Mean (SD) | 83.07 (3.50) | 83.22 (2.14) |
| T _{max} (EFFECT) (h) | | |
| Median (Min, Max) | 2.00 (1.00, 8.00) | 2.00 (1.00, 12.00) |
| AUC(0-24h) (% inhibited.h) | | |
| Mean (SD) | 1711.61 (71.82) | 1603.97 (111.20) |
| T-HALF(EFFECT) (h) | | |
| Mean (SD) | 25.85 (10.64) | 14.46 (4.23) |

While reduction in overall PD effect (AUC) is only reduced by 6%, the half time of the effect is reduced by almost 50%. This difference has not been analysed statistically and in the study report is referred to as "unlikely to be of any clinical consequence".

Nevertheless, the apparent reduction in duration of PD response is consistent with the PK data in which the observed 27% reduction in combined exposure to saxagliptin and BMS-510489 occurs particularly in the second half of the 24 h dosing period as shown in Figure 3 above.

Study CV181067 was an open label, randomised, two-way crossover study conducted in healthy female subjects to assess the effect of saxagliptin on the pharmacokinetics of the components (ethinylestradiol (EE) and norgestimate (NGM)) of the oral contraceptive preparation Ortho-Cyclen.

Background and rationale

Saxagliptin and EE share a common metabolic pathway as substrates for CYP3A4. The metabolic pathways for NGM and its major active metabolites norelgestromin (NGMN) and norgestrel (NG) are described in the study report as being unknown. Although saxagliptin is described as not affecting CYP3A activity, the sponsor felt that the sharing of a common route of metabolism gave rise to some potential for an interaction between saxagliptin and EE in particular. The study is described as being intended to provide prescribers with some assurance about the interaction or lack of interaction, between saxagliptin and the components of at least this oral contraceptive preparation. Contraceptive failure due to drug interaction of this type is a previously described phenomenon.

It is noted that the particular oral contraceptive preparation employed in this study is not registered in Australia, nor is its progestogenic component NGM. However, the majority of available combined oral contraceptive preparations in Australia contain levonorgestrel which is closely related to NGM as indicated by its metabolites described above and all but a few contain EE as the estrogenic component. Given that on theoretical grounds the major potential is for interaction between saxagliptin and EE, and that the estrogenic component is more important for contraceptive efficacy as opposed to cycle control, the study findings do have relevance for Australian oral contraceptive users and deserve inclusion in the PI as requested.

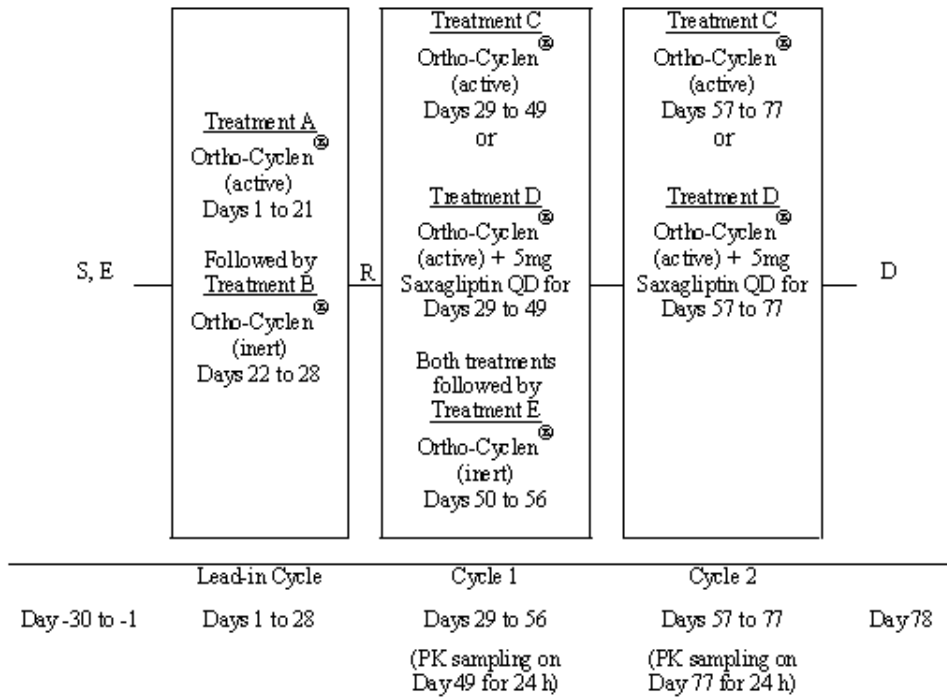
Conduct of study

The study was carried out on behalf of the sponsor between October 2008 and February 2009. It was designed to study 20 subjects in a two-way crossover sequence, with all subjects receiving both treatments: Ortho-Cyclen alone and Ortho-Cyclen plus saxagliptin. The study design is illustrated in the flow chart taken from the study report in Figure 5.

Of 53 enrolled subjects, 26 entered the lead-in cycle and received study medication. Six of these were discontinued once the planned 20 subjects had been randomised into Cycle 1. All of these were then crossed over in Cycle 2, that is, to the treatment which they did not receive in Cycle 1. Four subjects withdrew consent and discontinued during Cycle 2, so that 16 subjects completed the study. The reasons for consent being withdrawn by these 4 subjects were not given.

The subjects were healthy women of childbearing age already using Ortho-Cyclen or a similar oral contraceptive preparation. Summary statistics (given for those 26 who were treated) show average age of 30 (range 19-44) and a BMI of 24.7 (range 20.1-30.8) with approximately half being "White" or "Other" (mostly Hispanic) and a small number (3) African-American.

Blood samples for estimation of pharmacokinetic (PK) parameters were collected at frequent intervals (total 12 samples) on Day 21 of each treatment cycle as indicated in the above diagram, and analysed for EE, NGMN and NG. NGM itself was not measured; it is rapidly converted to the principal active metabolite NGMN by first-pass gastrointestinal tract (GIT)/hepatic metabolism and is usually below the limit of detection in plasma (sponsor's study report). PK parameters derived were C_{max} , T_{max} , trough plasma concentration (C_{min}) and $AUC_{(TAU)}$ (the area under the plasma concentration-time curve over 1 dosing interval (24 h)).

Figure 5. Study design

Abbreviations: D = study discharge, E = enrollment, R = randomization, S = screening

The principal statistical analysis consisted of estimating the ratio and variance of the population geometric means of C_{max} and AUC for EE, NGMN and NG. The hypothesis of a lack of effect of saxagliptin on these parameters was to be shown if the 90% CI for these parameters was contained within the limits of 80-125%.

Results

Summary statistics or PK parameters for the 3 component substances are shown in the following set of tables (in each case the C_{min} presented is the 24 h post dose value on Day 21) (Table 4abc):

Table 4a. Ethinylestradiol

| Pharmacokinetic Parameter | Treatment | |
|--------------------------------|-------------------|-------------------|
| | C (n=15) | D (n=15) |
| C_{max} (pg/mL) | | |
| Geometric Mean (CV %) | 158 (32) | 154 (24) |
| AUC(TAU) (pg h/mL) | | |
| Geometric Mean (CV %) | 1184 (28) | 1256 (25) |
| T_{max} (h) | | |
| Median (Min, Max) | 1.00 (1.00, 2.02) | 1.00 (0.50, 1.57) |
| C_{min} (pg/mL) ^a | | |
| Geometric Mean (CV %) | 23 (38) | 25 (35) |

Table 4b. Norelgestromin:

| Pharmacokinetic Parameter | Treatment | |
|--|-------------------|-------------------|
| | C (n=15) | D (n=15) |
| C _{max} (pg/mL) Geometric Mean (C.V. %) | 2192 (27) | 2386 (23) |
| AUC(TAU) (pg h/mL) Geometric Mean (C.V. %) | 16344 (32) | 17881 (26) |
| T _{max} (h) Median (Min, Max) | 1.00 (1.00, 2.02) | 1.00 (1.00, 2.00) |
| C _{min} (pg/mL) ^a Geometric Mean (C.V. %) | 354 (43) | 394 (35) |

Table 4c. Norgestrel:

| Pharmacokinetic Parameter | Treatment | |
|--|-------------------|--------------------|
| | C (n=15) | D (n=15) |
| C _{max} (pg/mL) Geometric Mean (C.V. %) | 2521 (66) | 2909 (56) |
| AUC(TAU) (pg h/mL) Geometric Mean (C.V. %) | 45224 (65) | 50564 (64) |
| T _{max} (h) Median (Min, Max) | 2.00 (1.00, 4.00) | 1.57 (1.00, 23.92) |
| C _{min} (pg/mL) ^a Geometric Mean (C.V. %) | 1642 (69) | 1823 (67) |

For EE, the point estimate (90% CI) for C_{max} was 0.982 (0.840-1.148) and for AUC 1.069 (0.977-1.169). For norelgestromin, the corresponding values were 1.090 (1.012-1.175) for C_{max} and 1.098 (1.002-1.203) for AUC. In both instances a lack of effect of saxagliptin on the PK parameters is clearly shown.

In the case of **norgestrel**, the ratio of means (Treatment D/Treatment C) was 1.165 with 90% CI of 0.922-1.472 for C_{max} and 1.127 with 90% CI 0.980-1.296 for AUC. These figures suggest a 13-17% increase in exposure to NG resulting from saxagliptin coadministration but as concluded in the study report, this cannot be regarded as a definite finding as the variances in the NG data were "unexpectedly high" (reason unexplained); certainly high enough to prohibit any test of statistical significance, as judged by the C.V. figures of approximately 60% and the graphic display of the data. All that can be concluded from this data is that a lack of effect of saxagliptin for this parameter was not shown.

Evaluator's overall comments on pharmacokinetic interactions

Study CV 181059 shows that, as an inducer of CYP 3A4, rifampicin significantly reduced levels of saxagliptin, an effect partly compensated for by an increase in its active metabolite but associated with some reduction in duration of PD response as assessed by DPP-4 inhibition. Whether this is "unlikely to be of clinical consequence", as claimed by the sponsor, is a matter of subjective judgement.

From *Study CV181067*, it can be concluded that there is no effect of saxagliptin on the PK of EE which is the most common component of oral contraceptive preparations available in Australia and also the component of the tested oral contraceptive preparation more likely on theoretical grounds to be so affected. If there is an effect on norgestrel, which appears

unlikely, it is to increase rather than decrease exposure, which would tend to be protective of contraceptive efficacy.

Exposure relevant for safety evaluation

The two studies in this section involved small numbers of healthy subjects exposed to a normal (5 mg) therapeutic dose of saxagliptin. In the case of Study CV181059, the 14 subjects each received two single 5 mg doses a week apart. In Study CV181067, between 16 and 20 women (depending on which treatment sequence was being taken by the 4 subjects who withdrew) were exposed to 21 days of this treatment. In both studies, full safety monitoring was undertaken and no adverse events of significance were reported.

Evaluator's overall conclusions on pharmacokinetics

The findings of Study CV181067 justify the proposed changes to the PI with regard to lack of significant effect of saxagliptin on oral contraceptive pharmacokinetics. Study CV181059 documents the interaction of saxagliptin with rifampicin, as an example drug for CYP3A4 induction in a way which might deserve more detailed description in the proposed PI (see recommendations below).

Pharmacodynamics

Pharmacodynamic (PD) data (DPP-4 inhibition) is included in Study CV181059 and is described and evaluated above along with the PK data from that study. The mechanism of action and overall pharmacology of saxagliptin was described fully in the CER of the original application and needs no further comment in this report.

Efficacy

Introduction

The main purpose of this application is to provide evidence of efficacy and safety in support of the use of a reduced (2.5 mg) dose of saxagliptin in the treatment of T2DM in patients with moderate, severe and end-stage degrees of renal impairment. This evidence is provided in the form of Study 07 which is pivotal to the application.

Main (pivotal) study

Study 07 (D1680C00007) had a short-term and Long-term Phase. The former was a 12 week, multicentre, randomised, parallel group, double-blind, placebo-controlled study of saxagliptin 2.5 mg compared with placebo in the treatment of adult patients with T2DM and moderate, severe and end-stage renal impairment. The moderate and severe impairment categories are as previously defined; "end-stage" comprised patients on haemodialysis. The Long-term Phase consisted of an additional 40 week randomised, parallel group, double blind, placebo controlled observation period.

Methods

Objectives

For the *Short-term period*, the stated efficacy objectives were:

1. Evaluation of efficacy of saxagliptin 2.5 mg in the renally impaired population described above, compared with placebo, by assessment of the absolute change from baseline in Hemoglobin A1C (HbA1c)⁶.
2. To similarly evaluate efficacy in this population by assessment of absolute change from baseline in fasting plasma glucose (FPG).
3. To characterise the pharmacokinetics of saxagliptin in this population by assessing the steady-state plasma concentration-time data of saxagliptin and BMS-510849 and to eventually pool these data with those of other studies to build a population exposure model.

Secondary objectives of the *Long-term extension* of the study included continuation of assessment of the efficacy measures (HbA1c and FPG) outlined above, together with assessment of the change from baseline in background antidiabetic therapy including the daily doses of existing therapy or addition of new therapy including both oral agents and insulin.

Study Participants

Criteria for inclusion of subjects were a diagnosis of T2DM, age 18 years or greater, and a documented history of CrCl < 50 mL/min within 3 months prior to enrolment; and at the first screening visit, HbA1c $\geq 7\%$ and $\leq 11\%$ together with C-peptide level ≥ 0.33 nmol/L (≥ 1.0 ng/mL) and an estimated CrCl < 50 mL/min. The purpose of the C-peptide level would be to exclude patients with Type I diabetes misdiagnosed as insulin requiring Type II Diabetes; "background" insulin use by study participants was not excluded. Some degree of beta cell function is obligatory for effective use of saxagliptin.

Treatments

Following randomisation, subjects were given 1 of 2 study treatments: either saxagliptin 2.5 mg (batch number H 2013-01-01-01) or a matching placebo tablet. Each subject continued the allocated treatment throughout both the Short and Long-term Phases without dosage adjustment.

Subjects continued their other diabetes therapy, which could consist of "background" insulin and/or oral hypoglycaemic agents with the exception of metformin (contraindicated with renal failure) and any form of incretin therapy including other DPP-4 inhibitors or glucagon-like peptide-1 receptor (GLP-1) agonist treatment. In the original protocol, thiazolidinedione use was also prohibited but a protocol amendment allowed this provided it was initiated, and stable, prior to study baseline. The term "background insulin" might be taken to mean daily long acting insulin, but in reality any form of insulin could be used. The sponsor's concept here being that saxagliptin is proposed to improve beta cell function and therefore increase endogenous insulin levels particularly in response to food, whereas exogenously administered insulin would be providing a baseline to this action. This is a rational approach as it has been shown in T2DM that improvement in glycaemic control by any means, including use of insulin, can have a beneficial effect on beta cell function.

Insulin was the most prevalent existing diabetes therapy, being used by 86% of saxagliptin subjects and 67% of placebo subjects in the safety analysis set. An oral agent was used by

⁶ Hemoglobin A1C is the amount of the protein hemoglobin that has combined with glucose in a person's body. Diabetics test their hemoglobin A1C levels to monitor the average amount of glycosylated hemoglobin (glucose attached to hemoglobin) that has been in their blood.

28% of saxagliptin and 37% of placebo subjects and only 2.4% of saxagliptin and 1.2% of placebo subjects received no antidiabetic therapy other than the study drug. This may seem an unusual distribution of therapies for Type II Diabetes but it reflects the difficulty of using oral hypoglycaemic agents in patients with advanced renal impairment; once metformin has to be discontinued insulin is often introduced, at which time other oral agents are often ceased, sometimes inappropriately.

The sponsor argues that using saxagliptin in this clinical setting along with other therapeutic agents represent a "real world" scenario. This is also a reasonable proposition, as all subjects could be regarded at entry as having by definition failed (HbA1c >7%) on their existing treatment and therefore meeting the criteria agreed by most relevant authorities for commencement of additional therapy.

Outcomes/endpoints

The primary criterion for the efficacy evaluation was change from baseline to Week 12 in HbA1c. A secondary criterion was change from baseline to Week 12 in fasting plasma glucose (FPG).

Pharmacokinetic endpoints have been described above and safety endpoints are described under *Safety* below.

Sample size

The study was designed to compare the magnitude of change in the efficacy parameters between the 2 treatment groups, saxagliptin and placebo, in the entire population. Power calculations were summarised as follows; 168 patients randomised and treated to yield 80% power to detect a 0.45% difference in HbA1c between the two randomized treatment groups in change from baseline to Week 12 in HbA1c at $p=0.05$, assuming a standard deviation of change from baseline in HbA1c of 1.0%.

The choice of target reduction in HbA1c (0.45%), and the assumed standard deviation, were based on the sponsor's experience of previously reported studies using saxagliptin.

At this sample size, and as can be seen in the flow diagram below (Figure 6), the numbers of subjects in some of the categories of renal dysfunction are small. As a result, statistically significant comparison between the treatment groups in the subcategories of renal dysfunction was not possible.

Randomisation

Randomisation was achieved by what is described as an "interactive voice response system" accessible by all the centres. This was carried out at the second study visit, following initial screening, giving of informed consent and the allocation of an identifying code. The voice response system was structured, using balanced blocks of allocation codes, so as to achieve balance of active and placebo subjects within each renal impairment category.

Blinding (masking)

Treatment packs containing either active or placebo tablets were separately randomised and provided in lots to the centres so that each subject could be provided with the appropriate treatment via the voice response system without the centre staff being aware of the treatment allocation.

Statistical methods

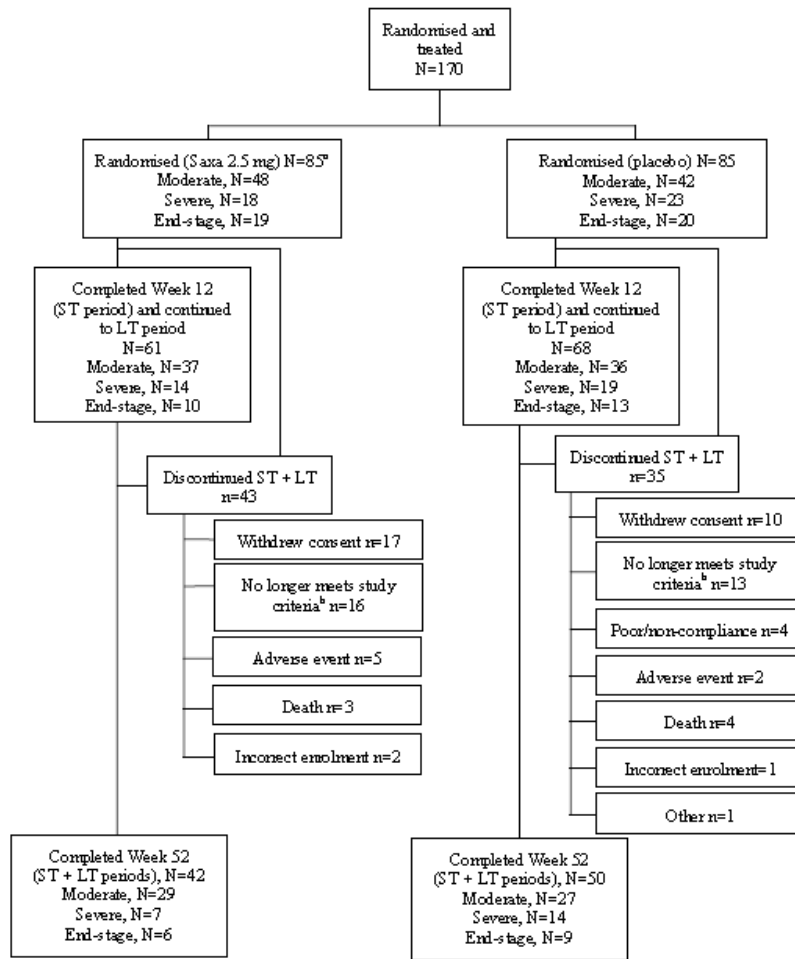
Statistical analyses were carried out using analysis of covariance (ANCOVA). For both primary and secondary efficacy endpoints, comparison between treatment groups used treatment group and baseline renal impairment category (moderate, severe or end stage) as fixed effects and the baseline value as a covariate. Point estimates and 95% confidence intervals (CI) were calculated for the absolute change from baseline in each treatment group (saxagliptin 2.5 mg or placebo), and also for the difference between the treatment groups in absolute change from baseline.

For each endpoint, statistical checks were made for significant potential confounding factors in the form of treatment-by-baseline HbA1c and treatment-by-baseline renal impairment category interactions.

Results

Participant flow

Altogether, 572 subjects were enrolled and all but 11 entered the lead-in period which involved the information giving and consent process and the initial screening investigations. Of the 561 subjects, 170 were randomised, 85 to active treatment and 85 to placebo. The subsequent progress of these randomised subjects is shown below in Figure 6. It is not clear from the study report what the basis was for the remaining enrolled subjects, numbering 376, being excluded or perhaps simply not chosen. In the sponsor's study report they are simply classified as "incorrect enrolment".

Figure 5. Progress of randomised subjects.

Conduct of the study

The study was carried out in 69 centres; 7 in the USA and the remainder in 12 (mostly Eastern) European countries, which contributed most of the subjects; only 22 of the original 561 coming from the US centres. Patient enrolment commenced in January 2008 and the study was completed in March 2010.

Recruitment

Subjects were recruited from the patient base of the various centres described above. The European centres were mostly renal or endocrine departments of clinical research institutions whereas the US centres appear to be specialist private practices.

Baseline data

Of the 170 randomised subjects, 97 were female and 73 male. The median age was 68 years (range 42-86). All were classified as being White, with the great majority coming from Eastern Europe. There were 8 from Germany and 3 from the US. Some 50.6% of the patients were obese (body mass index (BMI) ≥ 30). At baseline, 90 subjects had moderate and 41 had severe renal impairment as defined above. A further 39 had end-stage renal failure (receiving haemodialysis). The median duration of diabetes was 15.4 years and baseline HbA1c 8.1% (range 5.0-11.3); the lower end of the range of HbA1c values

indicates some protocol deviations in this respect. At baseline all of these characteristics were distributed reasonably evenly between the active and placebo treatment groups.

The diabetes treatments being used by subjects at baseline have already been described. As already described, more subjects in the saxagliptin treatment group (86%) were using insulin than was the case in the placebo group (67%). In both treatment groups, there was considerable use of a variety of other medications characteristic of this group of chronically ill patients.

Numbers analysed

Several subsets of the study patients are defined and used in various parts of the statistical analysis and study report. The *randomised analysis set* ($n=170$) includes all subjects with a randomisation code who took at least one dose of double-blind treatment and this would correspond to the intent to treat (ITT) population as usually defined. The *full analysis set (FAS)* ($n=164$) was a subset of the above with reportable efficacy data both at baseline and post treatment; if end of study (12 week) data for the primary efficacy variable was missing, it was replaced by the last observation after baseline (last observation carried forward, LOCF). The *per protocol analysis set* ($n=150$) was a further subset of the FAS, excluding subjects with significant protocol deviations; mainly non-compliance with entry criteria or study medication. The *safety analysis set* ($n=170$) comprised subjects in the randomised analysis set who had taken at least one dose of study medication.

Of the 170 randomised subjects, 129 completed the 12 week short-term period and entered the Long-term Phase of the study. The reasons behind 41 (24%) of the subjects dropping out are detailed in the study report and comprise a combination of various protocol deviations, incorrect use of other anti-diabetes medications and poor compliance with study medication.

A further 37 subjects dropped out during the subsequent 40 week long-term period which was completed by 42 saxagliptin and 50 placebo subjects as shown above in Figure 6. Most of these discontinuations were due to changes in the health or treatment on the subjects so that they no longer met study criteria; for example progression to dialysis led to exclusion. There were 7 deaths. Overall, the difficulty with maintaining the numbers in this study, including no doubt the high dropout during the lead-in period, reflects the unstable health and rapidly changing management requirements of such a seriously ill group of patients of relatively advanced age.

Outcomes and estimation

Results for the primary efficacy parameter, change in HbA1c from baseline to Week 12, are shown below in Table 5.

Table 5. Change in HbA1c from baseline to Week 12.

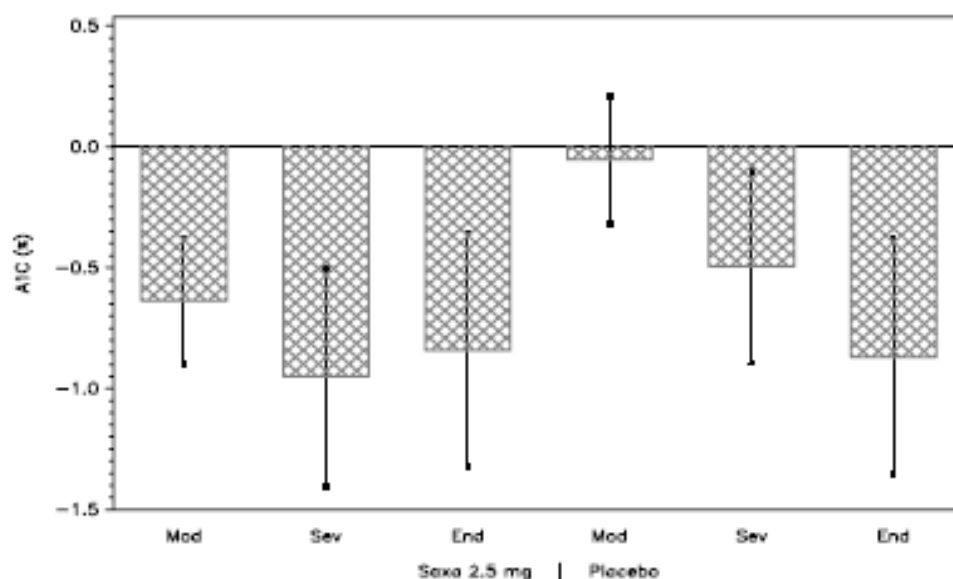
| Measure of HbA1c (%) | Saxa 2.5 mg (N=81) | Placebo (N=83) |
|---|-----------------------|-------------------|
| Baseline mean (SE) | 8.45 (0.135) | 8.09 (0.119) |
| Week 12 mean (SE) | 7.63 (0.132) | 7.80 (0.137) |
| Mean change from baseline (SE) | -0.82 (0.114) | -0.29 (0.122) |
| Mean adjusted change from baseline (SE) | -0.86 (0.112) | -0.44 (0.109) |
| 95% two-sided CI | (-1.08 to -0.64) | (-0.66 to -0.23) |
| Difference versus placebo ^a | | |
| Mean (SE) ^b | -0.42 (0.151) | |
| 95% two-sided CI | (-0.71 to -0.12) | |
| p-value | 0.007 | |

^a Difference in adjusted change from baseline for saxagliptin versus placebo.

^b Estimate=(adjusted mean change for saxagliptin)-(adjusted mean change for placebo)

A modest but statistically significant treatment effect of saxagliptin 2.5 mg, reducing HbA1c by 0.42%, can be seen.

For reasons of sample size already discussed, statistical analysis of the change from baseline in the various subcategories of renal impairment was not possible and only descriptive statistics are given. The changes in the various categories are best appreciated from Figure 7 below.

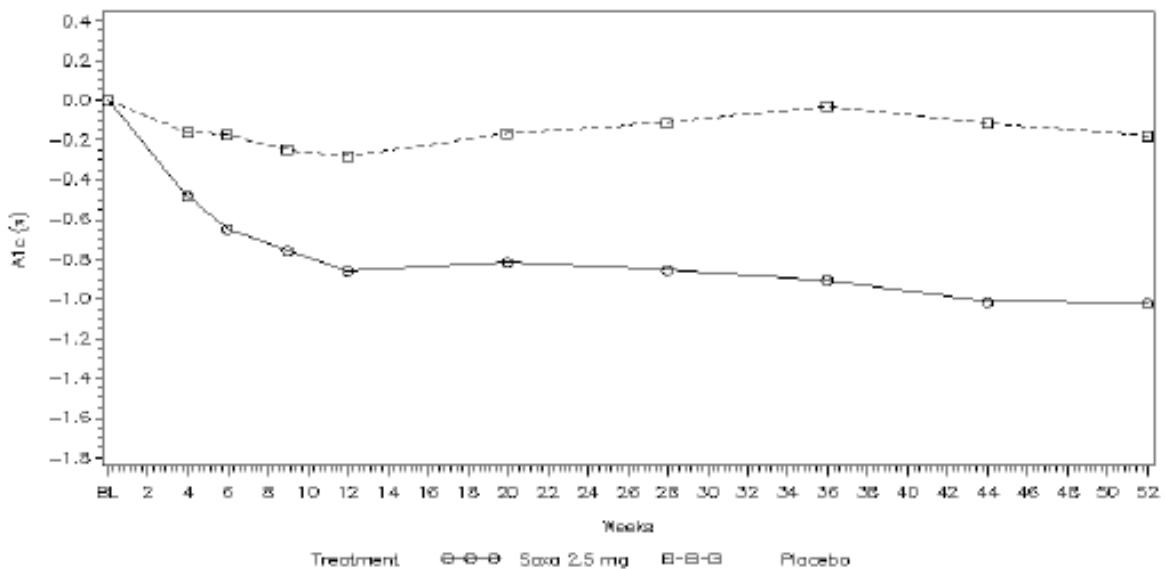
Figure 7. Changes in HbA1c by renal impairment subcategory.

The data are displayed as mean change from baseline, with 90% CI. In the moderately impaired category, mean reduction of HbA1c was 0.64% for the saxagliptin treatment group and 0.05% for the placebo group; in the severely impaired category it was 0.95% for saxagliptin and 0.50% for placebo; and in the end-stage renal impairment group it was 0.84% for saxagliptin and 0.87% for placebo. Given the relatively small number of subjects in these groups, the results in the moderate and severely impaired categories are consistent with the statistically significant change demonstrated in the overall study population. In the *end-stage renal impairment group*, HbA1c improved as much in the actively treated subjects as in the overall group but there was a similar improvement in

the placebo treated subjects. Possible reasons for this are the subject of a lengthy discussion in the sponsor's study report which includes narratives on the individual subjects. A substantial number of these were on multiple insulin injection regimens and were experiencing hypoglycaemic episodes which would contribute to the reduction in HbA1c. The lack of difference between the groups could not be explained by the fact that more saxagliptin than placebo subjects were being treated with insulin; an apparent response to saxagliptin was just as likely to occur in insulin treated subjects as in non-insulin treated subjects. Given that the end-stage group comprised only 10 actively treated and 13 placebo subjects and the multiple confounding factors involved, the failure to demonstrate difference from placebo should not be regarded as a significant negative finding but neither has a beneficial effect been demonstrated.

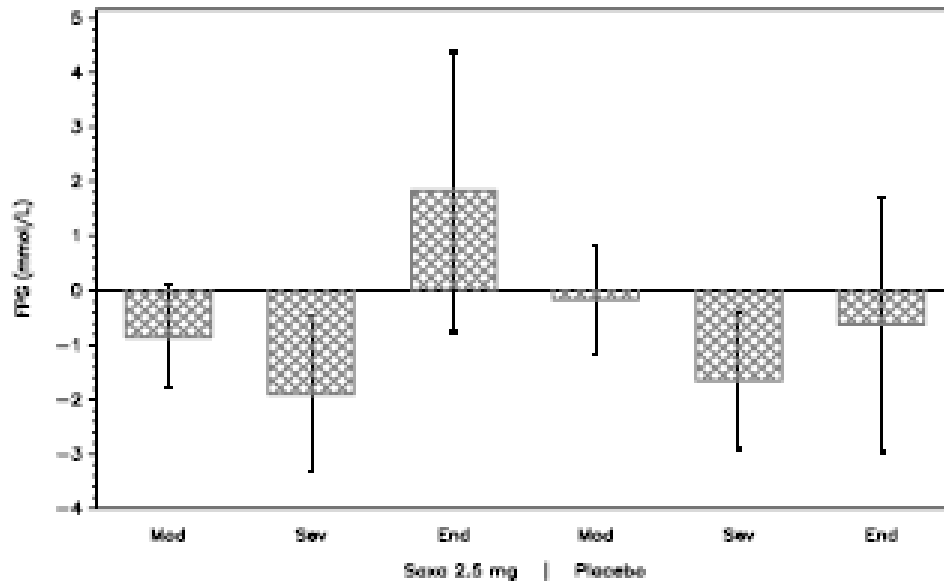
In the *Long-term follow-up (Week 12-52) Phase of Study 07*, the difference in HbA1c between active and placebo treatment groups was maintained. The difference in the adjusted mean change in HbA1c from baseline in the saxagliptin group compared with placebo was -0.73% (95% CI: -1.11 to -0.34) at Week 52 ($p < 0.001$). There was a similar finding at 28 weeks. The response is best illustrated by the following graph (as shown as Figure 8 below:

Figure 8. Change in HbA1c over 52 weeks in the saxagliptin and placebo groups.



The differences between saxagliptin and placebo treated subjects were also maintained in the various categories of renal impairment with much the same pattern as in the short term study and with a slight numerical increase in the active-placebo difference (descriptive statistics only): in the moderately impaired category, the mean reduction of HbA1c was 0.94% for the saxagliptin treatment group and 0.19% for the placebo group; in the severely impaired category it was 0.81% for saxagliptin and 0.49% for placebo; and in the end stage renal impairment group it was 1.13% for saxagliptin and 0.99% for placebo.

Statistical analysis of the difference between active and placebo treatment groups for the change in *fasting blood glucose* from baseline to Week 12 was complicated by the finding of a statistically significant treatment-by-baseline renal impairment category interaction, contributed to by differential drop out in the 3 categories. These data are therefore presented for the subcategories only in descriptive form. There is no clear pattern of response, as illustrated in Figure 9 below.

Figure 9. Fasting Blood Glucose results by renal impairment subcategory.

In the *Long-term Phase*, between the treatment groups as a whole, there was a numerically larger reduction in FPG in the saxagliptin group compared to the placebo group from baseline to Week 52 of 0.81 mmol/L, although with wide confidence limits (95% CI) of -2.24 to 0.61 mmol/L. In the end-stage renal impairment category there were several saxagliptin patients but no placebo patients who showed substantial *increases* in FPG, an outcome unlikely to be due to the study drug. These aberrations, along with other variances in the data and the small numbers of completing subjects, make these data difficult to interpret and it is not possible to reach any firm conclusion regarding the effect of the treatment on fasting glycaemia.

Clinical studies in special populations

Paediatric use

No data from paediatric patients have been included. A sponsor statement was included which postulated that saxagliptin may have a role in paediatric patients with Type II Diabetes and stating that a paediatric development program had been planned but the study design was not finalised. Elsewhere in the documentation there is reference to such a study now being in progress.

Evaluator's overall conclusions on clinical efficacy

The therapeutic model for pivotal Study 07 was use of saxagliptin as add-on therapy to the subject's existing diabetes treatment which in the majority of subjects consisted of insulin although there was also some usage of sulphonylureas, thiazolidinediones and other oral agents. The mean improvement in HbA1c resulting from the addition of saxagliptin was 0.42% which, as already concluded, is a modest improvement but clinically significant. Supportive studies for the original application in which saxagliptin was used as add-on therapy in combination with metformin, a sulphonylurea or a thiazolidinedione showed HbA1c improvements attributable to the saxagliptin therapy of 0.8, 0.7 and 0.6%, respectively; add-on therapy to insulin has not otherwise been studied.

The failure to demonstrate improvement in the secondary efficacy parameter of FPG is not regarded as a matter of concern as the small numbers of subjects, dropout rates and the use of concomitant antidiabetic medications, particularly insulin, were significant interfering factors. Furthermore, the mechanism of action of DPP-4 inhibitors in

enhancing meal related insulin secretion is intrinsically more likely to influence postprandial glycaemia, and therefore overall diabetes control as reflected by HbA1c, rather than fasting glycaemia.

The fact that the efficacy data for renally impaired subjects is mostly in the setting of use with insulin does create some difficulty in interpretation; this is not presently an approved or claimed indication and there is no similarly structured study in subjects with normal renal function with which the results of Study 07 can be compared. In principle, it would seem most likely that concomitant use of insulin would tend to mask beneficial effect of saxagliptin although, as discussed above, the use of this drug in combination with insulin is a rational approach provided there is evidence of residual beta cell function (as was a required entry criterion for this study).

Data from Study 07 which is particularly relevant to this evaluation was the PK data which showed (see discussion above) that exposure to the 2.5 mg dose of saxagliptin in these renally impaired subjects approximated that seen with 5 mg dosage in healthy subjects, even in those with end-stage disease on haemodialysis which had not previously been demonstrated.

Despite the limitations of the data, it is therefore concluded that efficacy of saxagliptin is maintained despite progressive impairment of renal function and that the 2.5 mg dosage is appropriate, particularly as:

- a) drug exposure with the 2.5 mg dosage was equivalent to that with the recommended 5 mg dosage in subjects with normal renal function; and
- b) there is no *a priori* reason to believe that diminishing renal function would in itself impair the action of saxagliptin.

Safety

Introduction

Apart from the small number (34) of patients evaluated for safety in the PK studies, as detailed above, the safety data available for this evaluation is contained in Study 07. For both the Short and Long-term Phases, the safety data collected and evaluated by comparison with placebo comprise: adverse events (AEs), including severe adverse events (SAEs) and AEs of special interest; laboratory values including estimation of CrCl (Cockcroft-Gault equation), estimated glomerular filtration rate (eGFR), and urinary albumin:creatinine ratio; electrocardiogram (ECG); vital signs; body weight; physical examination; and doubling of serum creatinine or progression to end-stage renal impairment.

The therapeutic effect of saxagliptin, and related drugs, in enhancing GLP-1 and hence insulin secretion particularly in response to food, is mediated by its action in inhibiting DPP-4. As is well documented and summarised in the clinical evaluation of the original submission, inhibition of other functions of DPP-4 or "off target" inhibition of related enzymes including DPP-8 and DPP-9, is a potential source of a specific range of AE resulting from use of this class of drugs. Lymphopenia and a small increase in the incidence of upper respiratory, and possibly urinary tract infections, are documented examples. These aspects have received close attention in the evaluation of the original application. It is unlikely that the relatively small quantum of drug exposure in the studies submitted with this application will add much to the overall safety profile of saxagliptin and the focus of this evaluation should be on observation of any qualitative change in the pattern of AE or the emergence of any specific AE, to which subjects with renal impairment might prove susceptible.

Patient exposure

In Study CV181059, 14 healthy subjects each received two single 5 mg saxagliptin doses. In Study CV181067, 20 healthy women received 5 mg daily for 21 days. In Study 07, 85 subjects in various categories of renal failure commenced active treatment with 5 mg saxagliptin; of these, 61 patients completed 12 weeks of treatment and 42 patients completed 52 weeks of treatment. Absolute exposure in patient-days of treatment has not been estimated. Excluding data from subjects who dropped out during the two phases of Study 07, this figure would be 20,834 patient-days.

Adverse events

The overall AE experience during the Short-term Phase of Study 07 is illustrated in Table 6 below.

Table 6. Overall AE incidence in Short-term Phase of Study 07.

| Category of AE | Saxa 2.5 mg (N=85) | | Placebo (N=85) | |
|--|-----------------------|--------|-------------------|--------|
| | n | (%) | n | (%) |
| At least 1 AE | 49 | (57.6) | 46 | (54.1) |
| At least 1 AE related to study medication | 9 | (10.6) | 6 | (7.1) |
| Deaths | 0 | | 0 | |
| At least 1 SAE | 12 | (14.1) | 7 | (8.2) |
| At least 1 SAE related to study medication | 1 | (1.2) | 1 | (1.2) |
| Discontinued study medication due to AE | 5 | (5.9) | 1 | (1.2) |
| Discontinued study medication due to SAE | 3 | (3.5) | 1 | (1.2) |

The distribution of AEs between saxagliptin and placebo groups appears even except that there were 10 AEs of Nervous system disorders, including dizziness or headache, in the saxagliptin group compared to 4 such events in the placebo group. In addition, there were 3 episodes of hyperglycaemia in the saxagliptin group only. The latter is unlikely to be due to the study drug and perusal of the detail of the other minor AEs does not suggest relationship to the study drug.

During the *Long-term Phase of the study*, distribution of AE and SAE between active and placebo treatment groups was more even, as shown in Table 7 below.

Table 7. Overall AE incidence in Long-term Phase of Study 07.

| Category of AE | Saxa 2.5 mg (N=85) | | Placebo (N=85) | |
|--|-----------------------|--------|-------------------|--------|
| | n | (%) | n | (%) |
| At least 1 AE | 64 | (75.3) | 60 | (70.6) |
| At least 1 AE related to study medication | 9 | (10.6) | 11 | (12.9) |
| Deaths | 3 | (3.5) | 4 | (4.7) |
| At least 1 SAE | 23 | (27.1) | 24 | (28.2) |
| At least 1 SAE related to study medication | 1 | (1.2) | 2 | (2.4) |
| Discontinued study medication due to AE | 10 | (11.8) | 7 | (8.2) |
| Discontinued study medication due to SAE | 6 | (7.1) | 6 | (7.1) |

Adverse effects of special interest

Due to the known side effect profile of DPP-4 inhibitors, and saxagliptin specifically as documented in the clinical evaluation of the original application, monitoring was undertaken for "adverse events of special interest", including lymphopenia, thrombocytopenia, specific skin disorders, hypersensitivity, pancreatitis, infections and localised oedema as well as cardiovascular events and hypoglycaemic events. In the Short-term Phase of the study in the saxagliptin group, there were two cutaneous events, hyperhidrosis and skin ulcer, with three further episodes skin of ulceration (2 saxagliptin and 1 placebo) in the Long-term Phase. There were no defined lymphopenic or thrombocytopenic events although there were changes in lymphocyte and platelet count which are detailed below. There were even numbers between the treatment groups of cardiovascular events, including myocardial infarction, which occurred mostly in the Long-term Phase. Infection related events were evenly balanced between the two groups and included none which would be regarded as unusual in the clinical setting. Throughout the study, the incidence of hypoglycaemic events was similar between the groups. There were no episodes of hypersensitivity reactions or pancreatitis in the Short-term Phase. In the Long-term Phase, there were single episodes of each of these conditions, both of which occurred in placebo subjects.

Serious adverse events and deaths

As shown in Table 6, there is an apparent excess (12 versus 7) of SAEs in the saxagliptin group. These comprise a wide spectrum of complaints, including single subjects with congestive heart failure, non-specific abdominal complaints and respiratory and vascular disorders. There is no apparent qualitative difference in the nature of the SAEs between the treatment groups and given the relatively small numbers involved, the difference does not appear significant. During the Long-term Phase, the distribution of SAEs favoured the placebo group so that in the overall period of the study the numbers were even and the qualitative nature of the events remained similar with no apparent or likely relationship to the study medication.

During the Long-term Phase of the study, 7 subjects died (3 in the saxagliptin group and 4 in the placebo group) (Table 7). The deaths were due to cardiac or cerebrovascular events with the exception of two cases; one case of sepsis and another with severe liver disease and unexplained sudden death. These deaths are consistent with, and can be explained by, the health status and clinical background of the subject population.

Laboratory findings

With regard to *renal function*, there was some movement between the moderate and severe categories of renal impairment in either direction, involving 14 of the 170 subjects during the Short-term Phase of the study. The changes in renal impairment category were evenly distributed between the active and placebo treatment groups. No subject progressed to end-stage disease and none experienced a doubling of serum creatinine. During the Long-term Phase, 3 saxagliptin treated subjects experienced a doubling of serum creatinine but the only subjects to progress to end-stage disease were 2 in the placebo group. Particularly given the small numbers enrolled in the groups and the dropout rate, these findings cannot be regarded as significant between the treatment groups.

Changes in *lymphocyte counts* during the Short-term Phase appeared evenly balanced between the two treatment groups with similar numbers in each group experiencing 10% or 30% reductions in lymphocyte count from baseline, and more placebo than active subjects (12 versus 8) showing a $\geq 20\%$ reduction. The pattern after 52 weeks was similar, with a higher proportion of reductions at all levels in the placebo group. Given the proportion of dropout in the Long-term Phase, more notice should perhaps be taken of the Short-term Phase results.

For *platelet counts*, 17/60 (28%) of saxagliptin subjects and 11/64 (17%) placebo subjects showed a 10% or more reduction. Furthermore, 8/60 (13%) saxagliptin subjects compared to 4/64 (6%) placebo subjects showed a $\geq 20\%$ reduction. Three out of sixty subjects in each group showed $\geq 30\%$ reduction in platelet counts. In the Long-term Phase after 52 weeks, reductions in platelet count remained more prevalent in the saxagliptin group (19/37, 7/37, and 3/37 subjects, respectively, at the 10, 20 and 30% levels) than in the placebo group (15/44, 4/44 and 1/44 subjects, respectively). However, the mean absolute reduction in platelet count from baseline to Week 52 was only modest: -22.46×10^3 cells/ μL (95% CI: -36.64 to -8.28) in the saxagliptin group and -17.18×10^3 cells/ μL (95% CI: -27.45 to -6.91) in the placebo group. This difference does not appear statistically significant (although the subject numbers and dropout rate make any conclusion difficult) but it would not be clinically significant. No subject in either group experienced a thrombocytopenic event of predefined significance (count $< 50 \times 10^9$ cells/L).

There were no changes of apparent significance to the study or maldistribution between the treatment groups, in other laboratory parameters or ECG findings.

Safety in special populations

This report specifically addresses safety in the special population of patients with impaired renal function.

Immunological events

As outlined above, immunological events were specifically monitored in the safety evaluation, and apart from the changes in lymphocyte count referred to previously, no abnormalities of significance were observed.

Safety related to drug-drug interactions and other interactions

No adverse events of any significance were reported in Studies CV 181059 and CV 181067 in which interactions with rifampicin and Ortho-Cyclen were evaluated.

Discontinuation due to adverse events

In the Short-term Phase of Study 07, 5 saxagliptin subjects, as opposed to 1 placebo subject, withdrew following an SAE. These instances comprised congestive cardiac failure, an episode of myocardial infarction, gastrointestinal disorder, nausea, urinary tract

infection and a minor change in liver function. None of these conditions would be regarded as unusual in the subject population.

Post marketing experience

Some postmarketing data is referred to in the risk management plan; a report refers to the period between 31 July 2009 to 31 March 2010 during which the quantity of saxagliptin sold provides an estimate for the treatment of approximately 37,000 patients. There is no information about postmarketing experience with specific reference to the renally impaired population which is the subject of this report.

Evaluator's overall conclusions on clinical safety

The pattern of AE and SAE observed in both Short and Long-term Phases of Study 07 does not suggest any safety issue specific to patients with impaired renal function.

There is equivocal evidence (see above) of a treatment effect on platelet count. It is noted that in the original application which presented data on a much larger number of subjects, a slight decrease of around 4-5% in platelet count was also observed, which persisted for 24 months. It is noted that while the draft PI section on adverse effects notes the incidence of a small decrease in lymphocyte count, platelet count is not mentioned. While the observed abnormalities, if indeed real, are of no clinical significance, they should be the subject of continued long term monitoring in the periodic safety update reports (PSURs).

Clinical Summary and Conclusions

Clinical aspects

Pharmacokinetics

The proposed changes to the PI section on interactions with other medicines, with relation to oral contraceptive preparations and rifampicin, are supported as summarised above.

Pharmacodynamics

No pharmacodynamic issues are specifically relevant to this evaluation report.

Clinical efficacy

The efficacy of Onglyza (saxagliptin) 2.5 mg in the management of Type II Diabetes in patients with impaired renal function is adequately demonstrated by the data included with this submission, with the exception that there is some uncertainty about benefit for end stage renal disease patients as outlined above.

Clinical safety

No safety issues specific to patients with impaired renal function emerge from this evaluation. The safety profile of saxagliptin 2.5 mg in this clinical setting is discussed and summarised above.

Benefit risk assessment

A comprehensive risk management plan was submitted by the sponsor. It is presumed that such a document was not included in the original application as it is not referred to in the evaluation report thereof, and is therefore presented here in some detail. It includes the data from the pivotal Study 07 of this application but addresses the overall risk management strategy for saxagliptin use, not specifically its use in the population of renal impaired patients.

With regard to potential adverse effects of special interest, as discussed above, the plan does state that "pancreatitis, severe hypersensitivity reactions including severe cutaneous

adverse reactions and bone fractures have been added as important potential risks based on ongoing safety surveillance and postmarketing experience from other DPP4 inhibitors”.

The report identifies no area of risk specific to the renal subjects. Overall, the safety data reported in the risk management plan and the areas of Identified or Potential risk discussed correspond closely with those presented in detail the evaluation report of the original application. The classes of subjects/potential patients for which there is no or only limited information include particularly very young and very old subjects, pregnant and breastfeeding women and subjects who are immunocompromised or have significant hepatic or cardiac impairment. It notes that subjects with moderate or severe renal impairment were excluded from most studies but does refer to the pivotal Study 07 from this application as having been completed.

Benefits

Management of Type II Diabetes in the presence of advanced renal failure is difficult because of fluctuating metabolic demands and the contraindication to metformin which is otherwise the most useful single oral agent. The availability to the physician of an oral agent which is effective and does not promote weight gain, fluid retention or compromise renal function, will be beneficial for the patient. Excluding off-label use, this benefit will be somewhat restricted as the conditions for registration the sponsor has applied for do not permit monotherapy or use with insulin. Less than 30% of the patients who participated in pivotal Study 07 would qualify for the approved indications.

The documentation that Onglyza (saxagliptin) is unlikely to cause contraceptive failure if coadministered with oral contraceptive medications and unlikely to cause significant interaction with drugs which are inducers of the cytochrome P-450 enzyme system, is beneficial to users of these medications.

Risks

The documented side effect profile of saxagliptin, a generic to the class of DPP-4 inhibitor drugs, does not contain any additional demonstrated risks specific to patients with impaired renal function. Nevertheless, continued monitoring for potential adverse effects should be continued in this population as with use of the drug generally.

Safety specification

This is acceptable given the dose reduction to 2.5 mg in the target (renally impaired) population. Continued monitoring of safety parameters, including platelet count as noted above, should continue to occur as part of the PSUR program which the sponsor states it will undertake as part of its risk-benefit plan.

Balance

The balance of benefits and risks is favourable to extended use of Onglyza as requested in the application.

Conclusions

It is recommended that the conditions for registration of Onglyza (saxagliptin) be varied, as requested in this application, to permit the use of the 2.5 mg tablet in patients with Type II Diabetes and renal impairment.

Attention is drawn to the fact that approval of this application will effectively restrict the use of the 2.5 mg tablet to combination therapy with either a sulphonylurea or a thiazolidinedione, as use with metformin is contraindicated in all but mildly renally impaired patients, and there is no evidence to support monotherapy or use with insulin.

Conditions for registration

No special conditions were recommended.

V. Pharmacovigilance Findings**Risk Management Plan**

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

Safety Specification

The following is a summary of the Ongoing Safety Concerns as specified by the sponsor in the RMP:

| | |
|--|---|
| Important identified risks | Gastrointestinal-related AEs Infections |
| Important potential risks | Skin lesions (erosion, ulcer, necrosis) Lymphopenia Thrombocytopenia Localized edema Hypoglycemia Pancreatitis Bone fracture Severe hypersensitivity, including severe cutaneous adverse reaction |
| Important missing/limited information | Paediatric safety Renal Impairment Hepatic Impairment Cardiovascular disease including congestive heart failure Immunocompromised subjects Elderly population >75 year old Pregnancy and breast-feeding |

OPR reviewer comment:

The above summary of the Ongoing Safety Concerns was considered acceptable. The sponsor was asked to comment on the listing of 'Renal Impairment' under important missing/limited information in light of the proposed new use of saxagliptin in patients with renal impairment. The sponsor comments that 'Renal Impairment' was inadvertently not removed. The sponsor commits to providing an updated RMP post approval.

Pharmacovigilance Plan

Routine pharmacovigilance⁷ as proposed by the sponsor, including ongoing studies, is considered sufficient to monitor the Ongoing Safety Concerns associated with saxagliptin. The routine activities that the sponsor has outlined are consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices. Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)*.

Ongoing studies

Protocols of ongoing studies have not been reviewed as these are already in progress. However, the justification for assigning each ongoing study to its particular safety concerns is considered satisfactory. In addition, the additional outcomes measurements planned in the Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR) trial are considered appropriate to further elucidate the assigned Ongoing Safety Concerns. Results from ongoing studies will be monitored through regularly submitted PSURs.

The milestones for reporting results of the ongoing clinical trials were considered acceptable.

Risk Minimisation Activities

In the RMP it is stated:

Based on the following reasons, the sponsor considers the current planned actions are sufficient to monitor any emerging safety signal and manage potential risk and no additional (non-routine) risk minimisation activities are proposed:

Saxagliptin, at a daily dose of either 2.5 or 5 mg, demonstrated a clinical adverse reaction profile that was generally similar to placebo in the pooled placebo-controlled Phase III studies. The 10 mg dose was also generally safe and well tolerated, providing a margin of safety for subjects with increased exposures. The safety profile is similar to others in the same drug class but without some of the safety issues.

For the Important identified and Potential risks, the product labelling is sufficient to communicate safety information for healthcare professionals and patients. Routine pharmacovigilance with targeted questionnaires will be sufficient to monitor the potential risks. The need for additional risk minimisation measures will be re-assessed whenever the safety specification is updated.

OPR reviewer comment:

The sponsor's conclusion in regards to only requiring routine risk minimisation activities⁸ are considered sufficient to mitigate the ongoing safety concerns associated with saxagliptin.

⁷ Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

⁸ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

In regard to the proposed routine risk minimisation activities, the draft product information and consumer medicine documents are considered satisfactory.

Summary of Recommendations

The OPR provides the following recommendation in the context that the submitted RMP is supportive to the application:

The implementation of RMP Version 7 dated 23 December 2010, including the sponsor's response to the request for information/documents and any future updates be imposed as a condition of registration.

VI. Overall Conclusion and Risk/Benefit Assessment

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

Quality

As originally noted, the different strengths are not direct scales (that is, identical qualitative formulation; dose proportional only for the active ingredient);

"A direct bioequivalence comparison of the 2.5 and 5 mg tablets has not been undertaken. Both tablet strengths were used in pivotal clinical trials. Tablet dissolution of 2.5 and 5 mg tablets is similarly rapid at pH 1.2, 4.5 and 6.8. Registration of the 2.5 mg tablets (with respect to biopharmaceutic aspects) is recommended on the basis of these data."

Minor differences exist between the clinical trial and "for marketing" formulations, "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. Dissolution data are very similar."

A two year shelf life has been assigned in blister packs; chemistry and quality control issues have not been fully resolved as the evaluator seeks an end of shelf-life dissolution specification.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator mentions the previously evaluated pharmacokinetic findings in various degrees of renal impairment. Essentially, moderate to severe renal impairment have significant effects on the exposure to the unchanged drug and to its active metabolite, BMS-510849,

"...with mild renal impairment (CrCl 50-80 mL/min), AUC of saxagliptin is increased by 16% and of BMS-510849 by 67% by comparison with values in healthy subjects. For moderate renal impairment (CrCl 30-50), these increases were 41% and 192% respectively, and in severe renal impairment (CrCl <30), 108% and 345%."

New pharmacokinetic data were generated in the pivotal efficacy/safety study D1680C00007 (Study 07) and the evaluator discusses these findings in the report. Small numbers enable only an impression that similar trends pertain at a dose of 2.5 mg. Based on cross-study comparisons, the evaluator suggests that regarding exposure to saxagliptin,

"The above data suggest a degree of increase in exposure of between 50 and 100% for the 2.5 mg dose with impaired renal function, similar to that reported for study CV181019 in

which a 10 mg dose was used, although without the progressive increase with degree of renal impairment” and that regarding the active metabolite, “The degree of accumulation is clearly progressive with increasing severity of renal impairment and consistent with the data previously documented for the 10 mg dose in study CV181019.” [That, is 2-3 times higher levels.] The evaluator concluded that this justifies the lower dose of 2.5 mg.

Comment: It is perhaps easier to draw this conclusion in moderate renal impairment from the small numbers in end stage renal disease and the lack of a direct comparison involving those with normal renal function.

There was also a study, Study CV 181059, involving metabolic interactions with rifampicin, an inducer of CYP CYP3A4/5. The study was conducted in healthy males, most of whom were African-Americans. Thirteen completed both phases of the study. Each received a single 5 mg oral dose of saxagliptin on Day 1 and then 600 mg once daily oral doses of rifampicin from Days 2 to 6 inclusive. A second 5 mg oral dose of saxagliptin was then given on Day 7 together with a 600 mg dose of rifampicin. As reported by the evaluator;

“Overall, rifampicin had a much more marked effect on the PK of saxagliptin than on that of BMS-510849. For saxagliptin, C_{max} was reduced by 53%, $AUC_{(inf)}$ by 76% and $AUC_{(0-T)}$ by 80%, whereas for BMS-510849 C_{max} was increased by 39% but $AUC_{(inf)}$ and $AUC_{(0-T)}$ by only 3% and 4%, respectively. For BMS-510849, comparison of the population means for the 2 treatments showed the 90% CI to be contained well within the 80-125% no-effect interval for $AUC_{(inf)}$ and $AUC_{(0-T)}$ but outside these limits for C_{max} and for all the saxagliptin parameters.”

This result (the modest effect on the principal metabolite) was unexpected. No definitive reason was elucidated. As shown in the report, there is suggestion of a shortened time to wearing off of DPP-4 inhibition when rifampicin is taken together with saxagliptin.

Study CV181067 was an interaction study in 20 women that examined the pharmacokinetics of saxagliptin with and without a combined oral contraceptive. Unfortunately, the progestogenic component was norgestimate but the oestrogen used was ethinyloestradiol. The evaluator concluded that no significant interaction was shown.

Efficacy

There was one study. As mentioned above, Study 07 (D1680C00007) had a Short-term Phase that ran for 12 weeks in a multicentre, randomised, parallel group, double blind, placebo controlled design. Saxagliptin 2.5 mg was compared with placebo in the treatment of adult patients with Type II Diabetes in the presence of moderate, severe and end-stage renal impairment⁹. "End-stage" comprised patients on haemodialysis. Efficacy endpoints were HbA1c and fasting plasma glucose. The Long-term Phase of Study 07 consisted of an additional 40 week randomised, parallel group, double blind, placebo controlled observation period. An additional endpoint was the examination of changes to concomitant antidiabetic therapy.

Subjects enrolled in the study were allowed to receive insulin.

Five hundred and seventy-two adult subjects were enrolled of which 561 entered the lead-in period which involved the information giving and consent process and the initial screening investigations. This reduced the study population to 170¹⁰. The patient

⁹ Mild renal impairment: CrCl 50-80 mL/min. Moderate renal impairment: CrCl 30-50. Severe renal impairment: CrCl <30.

¹⁰ The high attrition rate has been explained subsequently by the applicant in terms of “these subjects were correctly enrolled according to the study plan but were subsequently found to be ineligible for randomisation (that is, did not

disposition throughout the study was described in the report. The power calculations required 168 patients to be randomised and treated in order to yield 80% power to detect a 0.45% difference in HbA1c between the two randomised treatment groups in change from baseline to Week 12 in HbA1c at $p=0.05$, assuming a standard deviation of change from baseline in HbA1c of 1.0%. The evaluator considered that this limited the capacity to make comparisons between subgroups. In fact, 61 saxagliptin group patients completed Week 12 whereas 68 placebo group subjects completed 12 weeks. The corresponding 12 month figures are 42 and 50. The evaluation report describes the subcategories at various time points.

Efficacy at Week 12, the primary endpoint is shown in Table 5 above.

The evaluator considers that this is a “modest but statistically significant treatment effect of saxagliptin 2.5 mg”. In subcategories, no treatment effect was seen in the end-stage renal impairment group. No clear reason was apparent to the evaluator; insulin use was very common but not restricted to this subgroup.

The evaluator is of the view that efficacy persisted to 52 weeks, as shown in the sponsor’s Figure 8 above.

Evaluator’s Conclusions Regarding Efficacy

As stated in the evaluation report,

“The availability to the physician of an oral agent which is effective and does not promote weight gain and fluid retention or compromise renal function, will be beneficial for the patient. Excluding off-label use, this benefit will be somewhat restricted as the conditions for registration as applied for do not permit monotherapy or use with insulin. Less than 30% of the patients who participated in pivotal Study 07 would qualify for the approved indications.”

As stated in the evaluation report,

“Attention is drawn to the fact that approval of this application will effectively restrict the use of the 2.5 mg tablet to combination therapy with either a sulphonylurea or a thiazolidinedione, as use with metformin is contraindicated in all but mildly renally impaired patients, and there is no approval or evidence to support monotherapy or use with insulin.”

Adverse effects

The overall adverse event rates in the first 12 weeks were similarly distributed across both study arms but serious adverse events and discontinuations due to adverse events (for typical morbidities) were more frequent in the saxagliptin group;

“there were 10 AEs of nervous system disorders including dizziness or headache in the saxagliptin group versus 4 in the placebo group; and 3 episodes of hyperglycaemia in the saxagliptin group only”.

This imbalance was not a feature of the extension study.

The evaluator found that no new adverse effects that are specific to the population with renal impairment were identified in the submitted study.

satisfy inclusion and exclusion criteria when all information from the screening/enrolment visit was collated at Visit 2). ... most subjects who were enrolled but discontinued prior to randomisation were, in effect, screen failures.”

Recommendations of the clinical evaluator

The evaluator recommends that registration of the 2.5 mg tablet should proceed. Various changes to the product information document were suggested.

Response to the Clinical Evaluation Report

The response related to the questions asked by the clinical evaluator in relation to the product information document has been assessed. The sponsor has added some comments including,

“It should be noted that there are other potential additional glucose lowering mechanisms for DPP-4 inhibitors besides enhanced insulin secretion. Patients with Type II Diabetes have elevated glucagon levels, resulting in sustained endogenous hepatic glucose production. It has been shown in clinical studies previously reviewed by TGA that saxagliptin reduces glucagon levels, most likely via enhanced GLP-1 activity. This information is also included in the current Onglyza Product Information.”

This is considered to be not controversial from a clinical perspective.

Risk Management Plan

Some of the questions related to the Risk Management Plan were considered by Office of Product Review.

The evaluator states:

“Routine pharmacovigilance, including ongoing studies, is considered sufficient to monitor the ongoing safety concerns associated with saxagliptin. The routine activities that the sponsor has outlined are consistent with the activities outlined in *3.1.2 Routine pharmacovigilance practices. Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03)*.”

The registration of the new dosage regimen is accepted on the basis of the continued use of Version 7 of the Risk Management Plan, as revised from time to time. No change has occurred in the light of a response by the applicant to the evaluators' questions.

Risk-Benefit Analysis**Delegate Considerations****Comments**

The clinical evaluator concluded,

“Despite the limitations of the data, it is therefore concluded that efficacy of saxagliptin is maintained despite progressive impairment of renal function and that the 2.5 mg dosage is appropriate, particularly as:

- a) drug exposure with the 2.5 mg dosage was equivalent to that with the recommended 5 mg dosage in subjects with normal renal function; and
- b) there is no a priori reason to believe that diminishing renal function would in itself impair the action of saxagliptin.”

In regard to (a), this conclusion is questionable due to few data points in severe renal impairment or ESRD as conceded by the evaluator, for example inability to assign a gradation in saxagliptin levels to progressively more severe renal impairment.

In regard to (b) this biological plausibility may be persuasive but insulin was used frequently in the study. It is therefore arguable that the model of use does not reflect the

sub-population that would qualify for use of saxagliptin within the existing registration but would support the use of saxagliptin in patients with renal impairment and who require insulin. A general application to extend the use of saxagliptin to include use with insulin has not been made.

As noted by the ADEC at the time of the original application;

“Neither the dose response studies nor the sponsor’s pooled analysis showed convincing evidence of any dose-response to differentiate 2.5 mg/day from 5 mg/day.”

That is, the dose ranging was suboptimal. However, a dose of 2.5 mg per day is likely to be therapeutically equivalent to a dose of 5 mg in the same population if only because it is effective in persons with normal renal function.

How this dose might be useful in patients with renal impairment is a question that the ACPM might wish to consider.

In regard to renal insufficiency, pioglitazone’s PI states,

“Dose adjustment in patients with renal insufficiency is not recommended (see Pharmacology, Pharmacokinetics). No information is available for patients on dialysis therefore Actos should not be used in such patients.”

“**Oedema** As thiazolidinediones can cause fluid retention, Actos should be used with caution in patients with oedema. In placebo controlled clinical trials oedema was reported more frequently in patients treated with Actos than in placebo treated patients.”

Whereas glibenclamide is contraindicated in,

“Severe impairment of renal function.”

... and there is a precaution concerning hypoglycaemia,

“Debilitated, malnourished or geriatric patients and patients with mild disease or impaired hepatic or renal function should be carefully monitored and dosage of glibenclamide should be carefully adjusted in these patients, since they may be predisposed to developing hypoglycaemia. Renal or hepatic insufficiency may cause increased serum concentrations of glibenclamide and hepatic insufficiency may also diminish gluconeogenic capacity, both of which increase the risk of severe hypoglycaemic reactions.”

It is notable that the original registration package used *glibenclamide* as the sulfonylurea.

As noted by the evaluator, insulin was used in a number of patients in the study but this usage with saxagliptin is not approved. To be effective, saxagliptin would have to be used in patients with significant pancreatic function. This would leave a niche amongst patients who might respond to monotherapy with saxagliptin (also not approved). The Committee was asked to suggest whether the submitted study defines a role for saxagliptin. Any other comments or suggestions are welcomed.

If this application was to be approved, therapy would have to be limited to dual therapy with either pioglitazone or a sulfonylurea. Moreover, the PI document would need to specify that saxagliptin may be used with pioglitazone in patients with moderate renal impairment but not severe renal impairment (sulfonylureas can be used in moderate renal impairment) or in those who require dialysis (pioglitazone is contraindicated in this group). It would also be necessary to emphasise that saxagliptin is not approved for use in patients who require insulin and that the sulfonylurea used in the pivotal clinical trials, glibenclamide, is not suitable for use in severe renal impairment.

The Delegate acknowledged that there is practical problem that arises for clinicians from this lack of data.

The figure below is taken from the most recent Australasian guideline that the Delegate could find.¹¹ The authors suggest that sulfonylurea be used in patients with eGFR <30mL/min or that acarbose could be used (acarbose is contraindicated in Australia in severe renal impairment and saxagliptin is not approved for use with acarbose).

The guideline points to the possibility of using GLP-1 agonists or DPP-IV inhibitors with insulin. Indeed the study submitted with this submission points to some treatment effect when insulin is used. It is likely that saxagliptin would be of benefit when used with a long acting basal insulin and that this benefit would not be limited to the renally impaired. However, no such specific Phase III study has been done.

This application would have been more realistically made after registration on concomitant use of saxagliptin with insulin in patients with mild renal impairment or normal renal function.

Proposed Actions

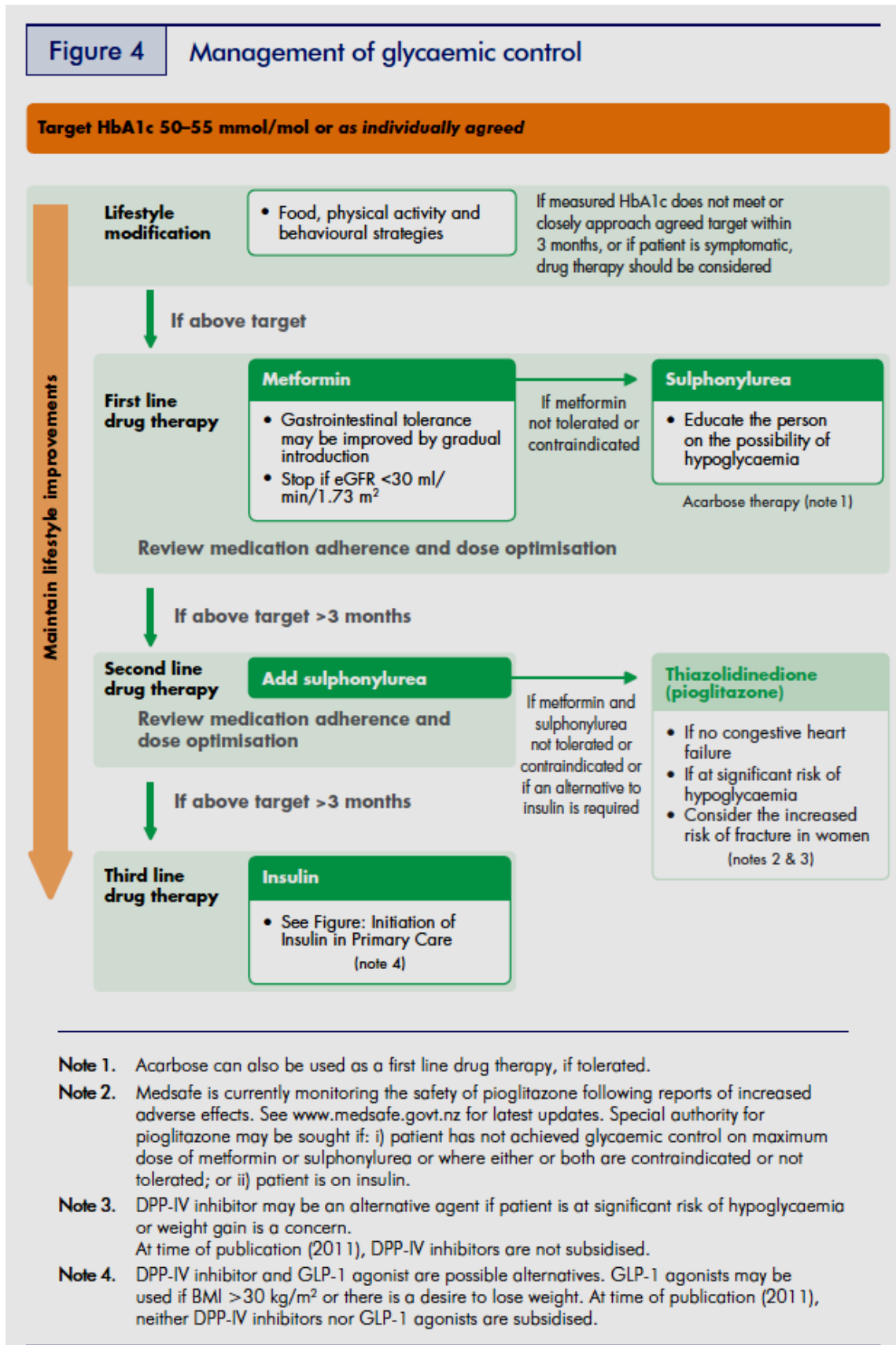
The application by Bristol-Myers Squibb Australia Pty Ltd to register Onglyza film coated tablets containing 2.5 mg of saxagliptin (as saxagliptin hydrochloride) to be used in patients with moderate or severe renal impairment or end-stage renal disease requiring haemodialysis should be rejected due to inadequate pharmacokinetic data in severe and end stage renal impairment and due to a lack of efficacy and safety data to define a therapeutic role in this patient group.

The applicant is encouraged to undertake appropriate studies, including the use of concomitant therapies that mirror clinical practice.

The application was submitted to ACPM for advice.

¹¹ New Zealand Guidelines Group. *Guidance on the Management of Type II Diabetes 2011*, Wellington: New Zealand Guidelines Group; 2011.

Figure 10. Management of Glycaemic control.



Response from Sponsor

Introduction

The Sponsor acknowledges the recommendations of the clinical evaluator to approve the sponsor's application to register 2.5 mg saxagliptin for use in patients with Type II Diabetes mellitus (T2DM) with renal impairment and the endorsement of the Office of Product Review for a satisfactory Risk Management Plan submitted with this application. The sponsor also acknowledges the issues raised by the Delegate and wishes to address these as part of this pre-ACPM response.

The sponsor believes the evidence from a study in subjects with renal impairment, D1680C00007, (hereafter referred to as Study 07) supports a positive benefit:risk profile of saxagliptin in individuals with renal impairment based on a statistically and clinically significant treatment effect at 12 weeks that was durable over 52 weeks, and a safety profile similar to individuals with normal renal function that is relevant to this difficult-to-treat patient population.

Study 07 is relevant to clinical practice because treatment options are limited for individuals with renal insufficiency. While insulin is often an early choice in this population, patients not managed with insulin represent a difficult-to-treat patient group. It is in this context that the evidence from Study 07 supports the use of a 2.5 mg saxagliptin dose.

The sequencing of treatment in this study, as well as in clinical practice, means that initial treatment with a sulfonylurea (SU) or a thiazolidinedione (TZD) would be prescribed according to their registered indications and precautions, consequently the addition of saxagliptin would be implemented consistent with the proposed Onglyza PI. As a result, amendments to the Onglyza PI to describe the precautions or patient groups suited to previously initiated therapy are not required.

The addition of a therapy that effectively improves glycaemia and does not promote weight gain, fluid retention or compromise renal function will be a useful tool for clinicians managing their patients with renal insufficiency.

This response addresses issues raised by the Delegate in the following areas:

- Justification of the optimal dose of saxagliptin in T2DM patients with renal impairment.
- Pharmacokinetics of saxagliptin in patients with T2DM and renal impairment.
- Overview of the efficacy and safety findings from Study 07 in the context of the Delegate's proposed actions, particularly with respect to insulin administration.
- The therapeutic role of saxagliptin in this patient population.

Dose Considerations for Saxagliptin

The Delegate suggests that the dose-response relationship for different doses of saxagliptin has not been appropriately established to justify the use of a 2.5 mg dose in patients with renal impairment. The Phase II and III development program for saxagliptin employed a broad range of doses, mainly 2.5 mg, 5 mg and 10 mg saxagliptin. Clinically relevant and statistically significant improvements in glycaemic parameters were observed with saxagliptin in every Phase III study with the 5 mg dose, which is the approved clinical dose. Based on evaluation of pharmacokinetic data from individuals with renal impairment, 2.5 mg was chosen as the dose for the safety and efficacy assessment in

Study 07, as it approximates the exposures achieved by the 5 mg dose in individuals with normal renal function or mild renal impairment.

Safety evaluations have not demonstrated any dose-dependent adverse effects when comparing the 2.5 and 5 mg doses. In addition, the 10 mg dose provides a safety margin with respect to levels of exposure of the recommended 2.5 mg dose of saxagliptin in patients with renal impairment.

Pharmacokinetics

The sponsor thoroughly evaluated the pharmacokinetics (PK) of saxagliptin and its active metabolite, 5-hydroxy saxagliptin, in patients with renal impairment in Study CV181019. The sponsor also evaluated the PK of saxagliptin and 5-hydroxy saxagliptin in patients with T2DM in Study 07. Steady-state exposures of saxagliptin, 5-hydroxy saxagliptin, and the total active moieties (TAM, in nM.h, defined as saxagliptin exposure + 5-hydroxy saxagliptin exposure multiplied by 0.5 to account for the difference in potency of 5-hydroxy saxagliptin compared to saxagliptin) in T2DM patients with normal, mild, moderate, severe or ESRD are presented in Table 8.

Table 8. Steady-state exposure of saxagliptin, 5-hydroxy saxagliptin, and total active moieties by renal function group

| Renal function category (number of subjects, dose) | Steady-state exposure ^a after once daily saxagliptin oral dosing (Median [min, max]) | | |
|--|--|------------------------------------|---------------------------------|
| | Saxagliptin (ng•h/mL) | 5-hydroxy saxagliptin (ng•h/mL) | Total active moieties (nM•h) |
| Normal/Mild (CV181011) (n=84, 5 mg) | 118 [72.1, 548] | 209 [110, 1493] | 721 [446, 3991] |
| Normal/Mild (CV181011) (n=74, 10 mg) | 235 [96.7, 443] | 482 [139, 1882] | 1479 [516, 3508] |
| Moderate (D1680C00007) (n=40, 2.5 mg) | 259 [68.7, 1111] | 547 [246, 1177] | 1755 [691, 5007] |
| Severe (D1680C00007) (n=15, 2.5 mg) | 148 [72.4, 347] | 803 [459, 1501] | 1965 [918, 2711] |
| End Stage (D1680C00007) (n=12, 2.5 mg) | 198 [77.2, 353] | 1182 [474, 3239] | 2648 [1694, 5321] |

Sources: ST+LT CSR for Study CV181011 and ST + LT CSR for Study D1680C00007.

^a Steady-state exposure given as AUC_{ss}.

Similar saxagliptin exposures were observed in patients with moderate, severe or ESRD versus those observed in healthy subjects or patients with mild renal impairment who received 10 mg of saxagliptin. Similar 5-hydroxy saxagliptin and TAM exposures were also observed in patients with moderate and severe renal impairment versus those observed in patients with normal or mild renal impairment who received the 10 mg saxagliptin once a day (qd) dose. However, the 5-hydroxy saxagliptin and TAM exposures were higher in T2DM patients with ESRD when compared with those observed in patients with normal renal function or mild renal impairment. Nevertheless, higher 5-hydroxy saxagliptin and TAM exposures were not associated with any safety concerns, and higher doses of

saxagliptin (40 mg once a day (QD) up to 12 weeks and 100 mg qd up to 6 weeks) have been shown to be safe and well tolerated in Phase II studies.

To further compare the exposures of saxagliptin, 5-hydroxy saxagliptin, and TAM in T2DM patients with moderate, severe or ESRD with a general patient population, simulations were conducted to predict the exposures of saxagliptin, 5-hydroxy saxagliptin and TAM in patients with creatinine clearances (CrCL) ranging from 10-130 mL/min (Table 9).

Table 9. Model-predicted steady-state exposures of saxagliptin, 5-hydroxy saxagliptin, and total active moieties in patients with a creatinine clearance from 10 to 130 mL/min

| Creatinine clearance (mL/min) ^b | Dose (mg) | Estimated steady-state exposure ^a after once daily saxagliptin oral dosing (Median [2.5 th percentile, 97.5 th percentile]) | | |
|--|-----------|--|---------------------------------|------------------------------|
| | | Saxagliptin (ng•h/mL) | 5-hydroxy saxagliptin (ng•h/mL) | Total active moieties (nM•h) |
| 10 | 2.5 | 79.2 [36.7, 157] | 1032 [633, 1695] | 1821 [1173, 2879] |
| 15 | 2.5 | 76.5 [38.2, 163] | 793 [468, 1289] | 1460 [934, 2241] |
| 20 | 2.5 | 76.2 [36.5, 154] | 635 [382, 1040] | 1215 [781, 1854] |
| 30 | 2.5 | 71.8 [36.0, 148] | 464 [284, 790] | 944 [633, 1478] |
| 40 | 2.5 | 71.1 [35.3, 140] | 365 [222, 613] | 785 [519, 1194] |
| 50 | 2.5 | 67.8 [32.6, 140] | 297 [176, 494] | 673 [453, 1046] |
| 60 | 5 | 132 [63.7, 261] | 503 [301, 811] | 1212 [798, 1771] |
| 70 | 5 | 132 [64.8, 282] | 437 [266, 744] | 1082 [702, 1703] |
| 80 | 5 | 124 [62.3, 270] | 387 [236, 612] | 995 [671, 1517] |
| 90 | 5 | 121 [59.3, 246] | 348 [218, 556] | 925 [620, 1387] |
| 100 | 5 | 119 [55.3, 251] | 312 [189, 518] | 867 [576, 1331] |
| 110 | 5 | 117 [57.2, 243] | 284 [170, 481] | 821 [536, 1277] |
| 120 | 5 | 112 [57.1, 237] | 260 [156, 426] | 757 [508, 1241] |
| 130 | 5 | 112 [52.9, 234] | 242 [142, 407] | 731 [468, 1177] |

Source: ST + LT CSR for Study 07.

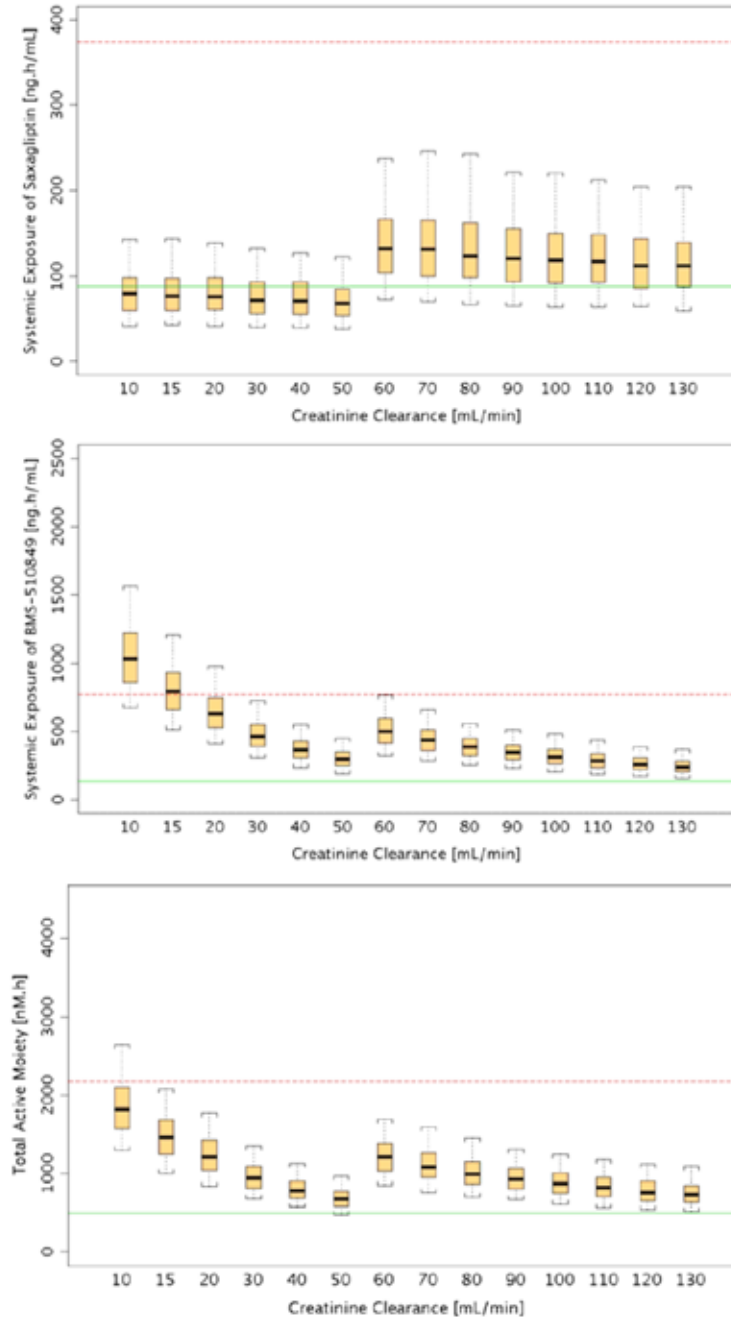
^a Steady-state exposure given as AUC₀₋₂₄.

^b n=1000 per group.

A safe and efficacious reference exposure range based on the tenth percentile of the approved 5 mg saxagliptin qd dose and the ninetieth percentile of 10 mg saxagliptin qd was established. Model-projected exposures across this range of creatinine clearance values showed that a saxagliptin regimen of 2.5 mg qd in patients with moderate or severe renal impairment or ESRD will produce saxagliptin exposures slightly below the reference exposure range, whereas the active metabolite exposures (5-hydroxy saxagliptin) will be slightly higher. Accordingly, model-projected TAM exposures are expected to be mostly within the safe and efficacious reference exposure range when patients with moderate, severe or ESRD receive a 2.5 mg qd saxagliptin regimen (Figure 11).

Figure 11.

re 1 **Model-predicted steady-state exposures of saxagliptin, 5-hydroxy saxagliptin, and total active moieties in patients with a creatinine clearance from 10 to 130 mL/min**



Solid line: 10th percentile of AUCs for 5 mg QD regimen (CV181011) saxagliptin, 88 ng·h/mL; 5-hydroxy saxagliptin: 135 ng·h/mL; TAM: 498 nM·h.

Dashed line: 90th percentile of AUCs for 10 mg QD regimens (CV181011) saxagliptin, 374 ng·h/mL; 5-hydroxy saxagliptin: 772 ng·h/mL; TAM: 2170 nM·h.

Bar plot: Median [2.5th percentile, 97.5th percentile].

Based on the saxagliptin, 5-hydroxy saxagliptin and TAM exposures observed in the clinical development program, and projected steady-state exposures, the sponsor considered that a dose adjustment to 2.5 mg saxagliptin qd is appropriate for T2DM

patients with moderate or severe renal impairment or ESRD. This is additionally confirmed by the safety and efficacy data provided by Study 07.

Efficacy and Safety Findings for Saxagliptin in Study 07

In Study 07, the primary analysis was absolute change from baseline to Week 12 (last observation carried forward) in HbA1c in the full analysis set. The findings in this study demonstrated that saxagliptin improved glycaemic control in the renal-impaired patients overall, leading to a clinically relevant and statistically significantly greater adjusted mean reduction in HbA1c from baseline to Week 12 in saxagliptin-treated patients compared with placebo-treated patients (mean [standard error (SE)] treatment difference: -0.42 [0.151]; 95% CI: -0.71 to -0.12; p=0.007). These results were supported by the sensitivity analyses based on observed values, the per-protocol analysis set, and using the repeated measures analysis. Analysis by renal impairment category demonstrated that treatment-by-baseline HbA1c and treatment-by-baseline renal impairment interactions were not significant (p=0.9888 and p=0.3467, respectively). In patients with moderate or severe renal impairment, saxagliptin improved glycaemic control compared with placebo with numerically larger adjusted mean reductions in HbA1c from baseline (mean [SE] treatment difference: -0.54 [0.205]; 95% CI: -0.95 to -0.14 for the moderate group and -0.50 [0.300]; 95% CI: -1.10 to 0.09 for the severe group). However, while the mean reduction from baseline HbA1c for patients with end-stage renal failure on dialysis receiving saxagliptin was similar to that for patients with moderate and severe disease, the magnitude of the placebo response was greater.

Because treatment options are limited for individuals with renal insufficiency, insulin is often an early choice in this patient population. Study 07 is relevant in that it was conducted under conditions similar to clinical practice. Insulin therapy was to be stable for at least 4 weeks prior to study enrolment and subjects were not allowed to change insulin dose during the short term period reducing the potential influence of varying doses of concomitant medication. Importantly, a test for interaction based on insulin therapy was performed and was not significant (p=0.58). Therefore, findings from the overall study are relevant for individuals not taking insulin.

Safety data in the trial were also summarised by background insulin use. The incidences of AEs, SAEs, and AEs assessed by the investigator to be related to study medication were higher in subjects receiving background insulin therapy compared with subjects not receiving insulin in both treatment groups. Within each insulin use category, the incidence of AEs was similar in the 2 treatment groups. Since AEs were generally more frequent in subjects receiving background insulin therapy (regardless of treatment group), the fact that more subjects in the saxagliptin group than in the placebo group received background insulin could have resulted in more AEs being reported in the saxagliptin group overall.

Nevertheless, the clinical evaluator and the Delegate both identified no safety issues specific to patients with impaired renal function in their evaluations.

Medical Rationale

Patients with T2DM are often older and may either present with or develop renal impairment. Agent selection and dosing adjustments are critically important in these patients. Failure to select appropriately and dose optimally may increase the risk of hypoglycemia and other adverse events, such as oedema. In both older patients and in those with renal impairment, incretin-based pharmacotherapeutics may have an advantage in that their glucose-dependent mechanism of action reduces the risk of hypoglycaemia.

Saxagliptin effectively improves glycaemia and does not promote weight gain, fluid retention or compromise renal function as add on therapy in T2DM patients with renal impairment. In clinical situations where there is poor patient acceptability of insulin, the addition of saxagliptin represents an important and well tolerated option to assist management of renally impaired patients with T2DM. In this respect, the overall size of the patient population, although limited, does not diminish the value of this therapeutic option as evidenced by the approval of another agent in the DPP4 class with similar indications.

Conclusion

In summary, the sponsor believed the benefit:risk profile for saxagliptin in individuals with renal impairment is strongly positive based on study findings demonstrating a clinically relevant and statistically significant treatment effect at 12 weeks that was durable over 52 weeks and a safety profile similar to individuals with normal renal function. In addition, saxagliptin exposures in patients with creatinine clearance values ranging from 10 to 59 mL/min given a 2.5 mg qd dose are similar to saxagliptin exposures in patients with creatinine clearance values \geq 60 mL/min given a 5 mg qd dose. Given the difficulties inherent in treating individuals with T2DM and renal insufficiency, saxagliptin will be a useful tool for clinicians managing their patients with renal insufficiency.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM considered this product to have a negative benefit-risk profile for the proposed changes to the current ARTG listing, for the following reasons:

- The studies did not produce sufficient data to support the proposed change in dosage regimen and indication. Study 007 was confounded by the use of insulin. Moreover, glycosylated haemoglobin is a suboptimal endpoint in this population. While there is marginal evidence that does support the use of this product in patients with renal impairment who require insulin, the ACPM noted that this indication is not the subject of this submission. Overall, the studies have not been designed to clearly determine the benefit of concomitant therapies that match clinical practice for an appropriately defined population group. The registered indications of saxagliptin do not include monotherapy or use with insulin, leaving no role for saxagliptin in severe renal impairment.
- More pharmacokinetic data in patients with moderate to severe renal impairment should be submitted.
- The rationale for investigating the safety profile for use in severe and end-stage renal impairment has not been well considered, and again has not resulted in sufficient evidence to support safe concomitant use.

Outcome

The majority of this application was withdrawn by the sponsor prior to a decision being made by the TGA. The approval was limited to a minor change to the PI, the discussion of which is beyond the scope of this AusPAR.

Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published.
For the current Product Information please refer to the TGA website at www.tga.gov.au.

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www.tga.gov.au

Reference/Publication #