EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Assessment report

for

ONGLYZA

International nonproprietary name:

saxagliptin

Procedure No. EMEA/H/C/001039/X/0004

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

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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Background information on the procedure

1.1. Submission of the dossier

The Applicant Bristol-Myers Squibb / AstraZeneca EEIG submitted on 01 March 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Onglyza, through the centralised procedure, pursuant to Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I point 2 (c).

This is an extension of marketing authorisation, as described in Annex I to the Commission Regulation (EC) 1234/2008 (variation regulation).

The changes requiring an extension application pertinent to this application are according to point 2 (c):

2. Changes to strength, pharmaceutical form and route of administration

(c) change or addition of a new strength/potency

Information on Paediatric requirements

Not applicable

Information relating to Orphan Market Exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Licensing status

Onglyza 5 mg film-coated tablets has been given a Marketing Authorisation in the EU on 1 October 2009.

Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Prof. Pieter de Graeff.

- The application was received by the EMA on 1 March 2010.
- The procedure started on 24 March 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 June 2010 .
- During the meeting on 22 July 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 22 July 2010
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 September 2010.
- The Rapporteurs circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 October 2010
- During the CHMP meeting on 15-18 November, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 24 November 2010.
- The Rapporteurs circulated the Assessment Report on the applicant's responses to the consolidated List of Outstanding Issues to all CHMP members on 3 December 2010
- During the meeting in December 2010 the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Onglyza 2,5 mg film-coated tablets on 16 December 2010. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 15 December 2010

2. Scientific discussion

2.1. Introduction

Diabetic nephropathy is the leading cause of chronic kidney disease in patients starting renal replacement therapy and is associated with increased cardiovascular mortality. The incidence of diabetes has reached epidemic proportions throughout the world, with an expected doubling in the number of patients with type 2 diabetes in the next 25 years. This, in turn, will lead to a further increased incidence of diabetic nephropathy, of which approximately 30% progress to end-stage renal disease.
Metformin is contraindicated in diabetic patients with impaired renal function. Therefore, there is a need for safe and effective oral antidiabetic agents (OADs) in patients with moderate, severe, and end-stage renal impairment.
Renal impairment affects the PK of saxagliptin by reducing renal clearance, thereby increasing systemic exposure. The approved dose is 5 mg for subjects with normal renal function. A dose of 2.5 mg of saxagliptin in these subjects will result in systemic exposures to BMS-510849 near or below the exposures typically achieved from a 10 mg dose of saxagliptin in subjects with normal renal function.

This is an extension application, introducing a new product strength: Onglyza 2.5 mg film-coated tablet intended for use in renal impaired patients.
The existing product is: Onglyza 5 mg film-coated tablet; this was recently approved (October 2009; EMEA/H/C/001039). Both product strengths are indicated for treatment of type 2 diabetes mellitus.
A type II variation II/08 has also been submitted to update the Product Information of the 5 mg tablet strength with the the dosing recommendations in patients with moderate and severe renal impairment.

2.2. Quality aspects

2.2.1. Introduction

This is a line extension application for marketing authorisation, introducing a new strength, Onglyza 2.5 mg film-coated tablet. The existing product is Onglyza 5 mg film-coated tablet.
Onglyza contains saxagliptin as active substance which is a highly potent, selective, reversible, and competitive dipeptidyl peptidase 4 (DPP4) inhibitor. DPP4 is the enzyme responsible for the inactivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).
Incretin hormones are gastrointestinal hormones that increase insulin secretion in response to enteral stimulation. In humans, incretins such as GLP-1, regulate blood glucose via multiple mechanisms; these include stimulation of glucose-dependent insulin secretion, delaying of gastric emptying, and inhibition of hepatic glucose production. However, incretins such as GLP-1 are rapidly inactivated by DPP4. Therefore, DPP4 inhibitors should extend the effects of incretins.
Onglyza 2.5 mg is an immediate release, film-coated tablet. The tablets contain 2.5 mg saxagliptin and are commercially supplied in Alu/Alu blister packaging.

2.2.2. Active Substance

The active substance has been previously assessed for the existing 5 mg film coated tablets. There are no changes or new information in relation to manufacture, control or stability of the drug substance in the context of this submission.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The immediate release tablet consists of a tablet core without drug substance, covered by a number of film-coat layers. The drug substance saxagliptin is embedded within the middle layer, as a – in situ formed- hydrochloride (HCl) salt. The product contains 2.5 mg saxagliptin.
Saxagliptin is prone to undergo an intra-molecular cyclisation reaction in solution and solid states to form a cyclic amidine. To minimise this phenomenon the proposed tablet formulation was developed. The design of the 2.5 mg tablets is the same as the existing strength.
Quality by design concepts have been used in the manufacturing process development for this strength as well as for the registered one. These are outlined in the dossier and the design space is presented for several manufacturing conditions. Nevertheless the drug product is routinely tested at release regarding most quality aspects, and batch analysis as well as stability data have been submitted.

Adventitious agents

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

Manufacture of the product

The manufacturing process is identical to the one for the registered 5 mg strength. The manufacturing process for Onglyza tablets involves active coating of saxagliptin onto an inert core tablet, followed by standard unit operations such as film-coating and printing.
The process validation was performed in a conventional manner, according to the NfG on process validation. At least three production batches were validated, and results were well within the criteria.

Product Specification

The specifications of the drug product at release and shelf-life include tests for description (visual), identification (HPLC, UV), assay (HPLC), uniformity of dosage units (Ph.Eur.), impurities/ degradants (HPLC), dissolution (Ph.Eur. HPLC, not routinely), microbial limits (Ph. Eur.). Drug dissolution results have been presented for six commercial scale batches of drug product. All batches show fast dissolution: 86 % or more after 10 minutes. Moreover, saxagliptin can be classified as a BCS Class III (high solubility, low permeability) compound meaning the absorption rate is the rate limiting step in vivo. It is therefore justified not to test dissolution routinely. Instead, dissolution will be tested in the 10 first commercial batches and thereafter one batch per year. The periodical dissolution test is included in the product specification.
Batch analysis results have been provided for seven representative pivotal batches from the proposed manufacturing site.
Also three additional batches from another site have been submitted as supportive data. All results were well within specification.

Stability of the product

Stability data were presented for three representative batches. The tablets were made from different batches of drug substance manufactured by Process C. The data cover 36 months at 25°C/60%RH, 30°C/65%RH and 30°C/75%RH, and 6 months at 40°C/75%RH. The tablets were stable at all storage conditions tested, and statistical analysis was performed to support extrapolation of the data.
A matrix approach was applied to the long term conditions. For one batch the hold time of active suspension was the maximum proposed. The results for these batches were not significantly different from the results from the other batches.
After 36 months storage at 30°C/65%RH and 30°C/75%RH total aerobic microbial count and total combined yeast and mould count results were < 100 colony-forming units (CFU)/g and E. coli was absent.
For photo-stability studies in accordance with ICH Q1B, showed the product is not sensitive to light.
The 36 months results cover the approved shelf-life. The new results remain within the limits and thus confirm the approved shelf-life. There is also no need for shelf-life criteria for water content, based on the diagrams of water contents over time, impurities contents over time, and dissolution over time over 36 months, which show no specific upward or downward trend in water content over time, and no relationship between water content over time versus impurities levels and dissolution.
In conclusion the proposed shelf life and storage conditions are acceptable.
In accordance with EU GMP guidelines, any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

2.2.4. Discussion and Conclusions on chemical, pharmaceutical and biological aspects

The quality of Onglyza 2.5 film coated tablet is adequately established. Information on development, manufacture and control of the drug substance has been presented in a satisfactory manner. The quality of the active substance is considered sufficiently described and adequately supported by data. Sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the drug product has been presented. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.
Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

2.3. Non-clinical aspects

No new non-clinical data have been submitted what is considered acceptable.

2.4. Clinical aspects

2.4.1. Introduction

This is an extension application, introducing a new product strength: Onglyza 2.5 mg film-coated tablet intended for use in renal impaired patients. The existing product is: Onglyza 5 mg film-coated tablet;

this was approved in October 2009 (EMEA/H/C/001039). Both product strengths are indicated for treatment of type 2 diabetes mellitus.
With this application for the 2.5 mg strength the following pharmacokinetic documentation has been submitted: One phase III renal impairment study D1680C00007 (study 07).

It should be noted that the original procedure for saxagliptin started with both the 2.5 mg and the 5 mg strength and at the end, the 2.5 mg strength was withdrawn, for clinical reasons. When applicable to the current application reference is made to the previous assessment report.
Bio-equivalence of the lowest strength (2.5 mg) has not been evaluated. However, since the qualitative composition of the 2.5 mg strength is the same as the 5 mg strength and since the quantitative composition of both strengths (<5% saxagliptin) is very similar, and all other conditions hold true, a bio-waiver can be granted for the 2.5 mg dose strength on the basis of similarity of dissolution profiles.

In the original marketing authorisation application (MAA) renal impairment study CV181019 was submitted. In this study it was found that in mild renal impairment, saxagliptin's AUC (INF) values were less than 2-fold higher than the mean values in subjects with normal renal function. Therefore, no dosage adjustment has been recommended for patients with mild renal impairment. The mean AUC (INF) values for BMS-510849 were however ~3-fold higher in subjects with moderate renal impairment than in subjects with normal renal function. The MAH therefore proposed a dose of 2.5 mg in subjects with moderate renal impairment. In severe renal impairment, saxagliptin's and BMS-510849 AUC (INF) values were 2.1 and 4.5 folds higher than those observed in subjects with normal renal function. A dose of 2.5 mg in subjects with severe renal impairment is therefore proposed by the MAH. Since patients undergoing hemodialysis also have severe renal impairment, a dose of 2.5 mg was also proposed in these patients.
Based on the results of this study it was concluded that the proposed dose-recommendations for subjects with mild renal impairment are acceptable. However, the use of Onglyza in patients with moderate renal impairment was not recommended due to limited clinical study experience. Additionally, dose-recommendations in case of severe renal impairment were found not to be acceptable. The MAH proposed similar dose recommendations for moderate and severe renal impairment, whereas the AUC (INF) values in subjects with severe renal impairment were 1.6 fold higher than in subjects with moderate renal impairment (4.5 folds versus 2.9 fold higher exposure).

GCP

According to the MAH, the study submitted with this application was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) and applicable regulatory requirements and the AstraZeneca policy on Bioethics. Questions were raised on the design and conduct of the study, but the MAH could answer these questions sufficiently. Therefore a GCP inspection was not considered necessary.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

To further assess the PK of the 2.5 mg dosage in patients with renal impairment, plasma levels of saxagliptin and its major metabolite BMS-510849 were measured in some patients of the phase III renal impairment study D1680C00007 (study 07). This was a 12-week, international, multi-centre, randomised, parallel-group, double-blind, placebo-controlled study to evaluate the treatment effect and tolerability of saxagliptin 2.5 mg compared with placebo in adult subjects with type 2 diabetes and renal impairment (moderate, severe, and end-stage). After a 2-week single-blind placebo lead-in period, subjects underwent stratified randomisation to 52 weeks double-blind treatment with either saxagliptin or placebo, in a 1:1 ratio within each renal impairment category. Randomisation was stratified by renal impairment category at baseline. Data from the first 12 weeks are presented.

Results were as follows. It should be noted that among end-stage subjects, blood samples for PK analysis were taken in the morning before scheduled dialysis. The peak mean plasma concentrations of BMS-510849 were observed at the last nominal sampling time point of 4 hours post-dose in all groups.

Table pk2: Mean (SD) steady state plasma concentrations (ng/mL) of saxagliptin and BMS 10849

	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)

Data derived from Table 8.14aST, Section 11.3.9.
Abbreviations: FAS: Full analysis set; n: Number of subjects with available data; SD: Standard deviation.

The mean saxagliptin plasma steady-state concentrations at the nominal collection times of pre-dose, 1, 2, and 4 hours post-dose were generally similar across all of the renal impairment categories studied. Based on mean pre-dose plasma concentrations of saxagliptin, a small amount of saxagliptin accumulation was observed in all categories of the renal impairment studied, but there was no clear pattern to the extent of accumulation associated with renal impairment category. Based on mean pre-dose concentrations of BMS-510849, accumulation of BMS-510849 was observed in all categories of renal impairment studied with higher plasma levels with increasing severity of renal impairment (max 1.9 –fold increase), similar to study CV181019.
This raised the question whether a lower dose than 2.5 mg should have been chosen for the patients with severe and end-stage renal disease. BMS-510849 is the major metabolite of saxagliptin, being also a selective, reversible, competitive DPP-4 inhibitor, half as potent as saxagliptin. In the clinical study no complete pharmacokinetic evaluation was performed and only measurements were made up to 4 hours post-dose so that no definitive conclusions could be made with regard to differences in total exposure. Peak plasma concentrations in patients with severe renal impairment following the 2.5 dose did not exceed more than twice the peak plasma concentrations found for subjects without renal impairment after the 5 mg dose.
The steady-state concentrations of BMS-510849 obtained in Study 07 were compared to the maximum concentrations of BMS-510849 observed following a single 5- and 10-mg saxagliptin dose in healthy subjects. The mean 4-hour concentration (the approximate time of Cmax) ranged from ~30 ng/mL in moderate renal impairment to ~58 ng/mL in subjects with end-stage renal impairment. In comparison, in healthy subjects given a 5-mg or 10-mg saxagliptin dose, the Cmax of BMS-510849 was 50 ng/mL and 100 ng/mL, respectively. Thus, the plasma concentrations of BMS-510849 in subjects with renal impairment given a 2.5-mg saxagliptin dose in Study 07 compare favourably to the concentrations of BMS-510849 in subjects given 5 mg (the approved dose) or 10 mg (a dose shown to be safe in phase 3 studies). It is unlikely that the imbalance in observed AEs is related to active metabolite concentrations, but is more likely due to underlying diabetes mellitus and its complications in this difficult-to-treat population. This can be verified by adding the concentration data from this study to the population PK analysis of saxagliptin. In this analysis the systemic exposures of both saxagliptin

and 5-hydroxy saxagliptin were found to be higher with lower creatinine clearance. The results of this new analysis do not change the opinion that the clinical relevance of the higher exposure in severe renal impaired patients and patients with ESRD is difficult to predict in a quantitative way and therefore saxagliptin should be used with care in patients with severe renal impairment and should not be used in patients with ESRD. At least no excessive exposure to the active moyeties appears likely when dose is adapted to 2.5 mg daily in patients whose creatinine clearance has declined to 10 ml/min.

2.5. Clinical efficacy

2.5.1. Main study

As mentioned before with this application for the Onglyza 2.5mg strength the phase III renal impairment study D1680C00007 (study 07) has been submitted.

Methodology
Study 07 included subjects with type 2 diabetes, inadequate glycaemic control (HbA1c ≥7.0% to ≤11%) and moderate, severe, or end-stage renal impairment. The categorisation of renal impairment was determined by estimated Creatinine clearance (CrCl) from the Cockcroft-Gault equation using central laboratory measurements of Serum creatinine (SCr) collected at study entry.
According to the MAH the database design did not allow partitioning of all of the short-term and long-term data. Thus, it was not possible to ensure that there were no changes made retrospectively to the short-term data post-lock (eg. to concomitant medication or AE data). However, all tables, figures and listings were based on the locked ST database, and thus efficacy and safety results of the ST-period were not changed. Furthermore, most changes were only minor and did not affect the efficacy and safety results.

A comprehensive statistical analysis plan (SAP) was prepared before unblinding of the week 12 data.

Numbers of patients
Of a total of 572 patients were enrolled, 170 were randomised. Incorrect enrolment was the main reason for not entering the study. In effect, most subjects were screen failures. Screening and enrolment were performed at the same visit, and not all laboratory variables were available at the time of medical record review. These arguments are considered plausible reasons for the large number of subjects not fulfilling all inclusion and exclusion criteria. One hundred and twenty nine (129, 75.9%) subjects completed the 12-week treatment period and entered the long-term treatment period. More patients in the saxagliptin group (24/85, 28.2%) vs placebo group (17/85, 20%) did not complete the 12 weeks period, mainly because subjects withdrew consent (13 vs 7 subjects) or did no longer meet study criteria (5 subjects in each group).
Long-term data consisted of extension data to 52-weeks. Of the 129 subjects who entered the LT treatment period, 92 (54.1% of randomised subjects) completed the study (52 weeks), 42 in the saxagliptin group and 50 in the placebo group.

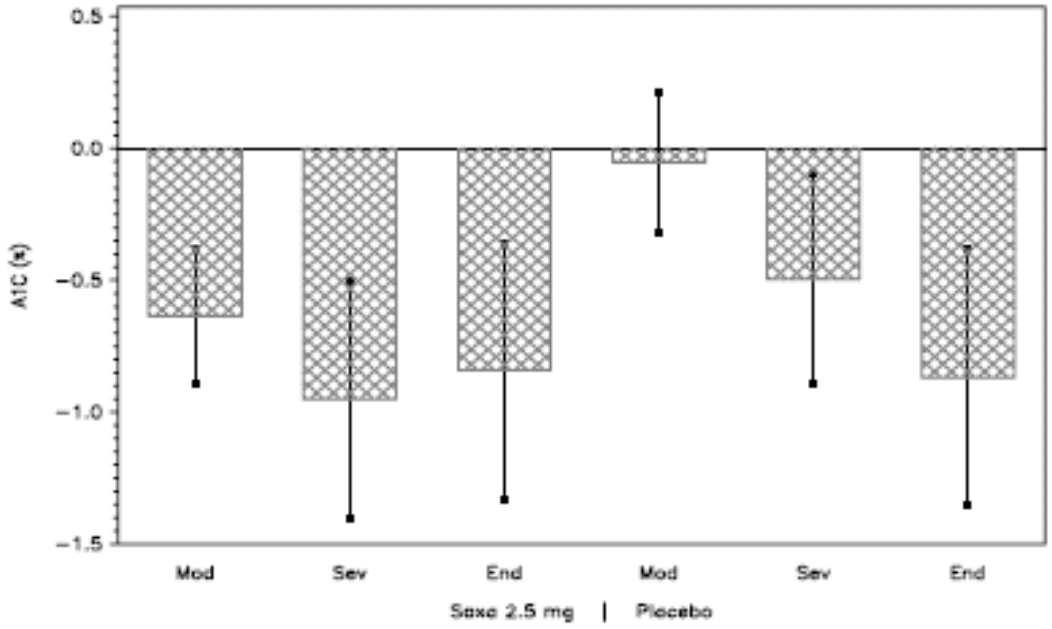
Baseline characteristics
Baseline characteristics were largely comparable between treatment groups. There were no significant differences in age, gender, weight, BMI, duration of diabetes (mean 17 years). HbA1c at baseline was slightly higher in the saxagliptin group (8.5% vs 8.1%). Baseline HbA1c range was 6.6-11.3% in the saxagliptin group, 5.0-11.1% in the placebo group. However, there were differences in renal impairment and in insulin use at baseline. Of the randomised subjects, 90 subjects (52.9%) had moderate renal impairment at baseline, 41 subjects (24.1%) had severe renal impairment, and 39 subjects (22.9%) had end-stage renal disease. There were more moderate subjects in the saxagliptin group (48 [56.6%] versus 42 [49.4%] subjects) and more severe subjects in the placebo group (23 [27.1%] vs 18 [21.2%] subjects) compared with the corresponding treatment group. This was due to incorrect assignment by the investigator of 7 subjects in the saxagliptin group and 7 in the placebo group. One possible explanation for the initial incorrect assignment could be that the investigator by mistake entered the estimated glomerular filtration rate (eGFR) assessment instead of CrCl which yielded lower values. This could have been the case for 5 of the patients in the saxagliptin group and 4 of the patients in the placebo group. The corrected category was used for the analysis of all study data. Although the misclassifications resulted in an imbalance of subjects in the moderate and severe impairment categories by treatment group, this is not considered to affect the interpretation of the

results. If there was any effect on HbA1c results, it is expected that the placebo group had a larger reduction because of the more severe renally impaired patients included in this group.
The majority of subjects were using other antihyperglycaemic medications, including insulin and oral blood glucose lowering drugs. Number of patients using insulin was 70/85 subjects (82.4%) in the saxa group versus 55/85 subjects (64.7%) in the placebo group. Mean insulin dose was 50.73 IU in the saxagliptin group and 41.68 IU in the placebo group. Percentage of patients using oral blood glucose lowering drugs was 27.1 in the saxagliptin group and 36.5 in the placebo group.

Protocol deviations
According to the MAH, 29 (17.1%) subjects had significant protocol deviations: 13 (15.3%) in the saxagliptin group and 16 (18.8%) in the placebo group. The most common significant protocol deviations were changes in dose and/or type of allowed OAD or insulin regimen except for safety reasons (14, 8.2% subjects overall), and medication compliance <80% or > 120% (12, 7.1% subjects overall). Other protocol violations were reported for 22 (12.9%) subjects overall. The most common reason was compliance with study medication during lead-in. Although the proportion of subjects who discontinued from the study or had protocol deviations was higher than seen in other saxagliptin studies, difficulties in subject retention and strict adherence to the protocol was expected within this study population with multiple concomitant diseases. The result of the PP analysis for change from baseline in HbA1c at Week 12, which excluded data in subjects with significant protocol deviations, was consistent with the primary HbA1c analysis, providing additional support for the validity of the trial and the reliability of the data.

HbA1c
HbA1c was reduced from baseline to week 12 in both treatment groups. Mean change was -0.82± 0.114 in the saxagliptin group and -0.29± 0.122 in the placebo group. The difference was statistically significant. Mean difference (SE) was -0.42± (95% CI -0.71 to -0.12); p-value 0.007.
Analysis by renal impairment revealed that the treatment-by-baseline renal impairment interaction was not statistically significant. Numerically larger adjusted mean reductions from baseline to Week 12 in HbA1c were observed with saxagliptin compared with placebo in subjects with moderate renal impairment (adjusted mean [SE] change from baseline -0.64% [0.134%] for the saxagliptin group and -0.05% [0.139%] for the placebo group) and in subjects with severe renal impairment (adjusted mean [SE] change from baseline -0.95% [0.228%] for the saxagliptin group and -0.50% [0.201%] for the placebo group). In subjects with end-stage renal impairment, the adjusted mean (SE) change from baseline to Week 12 in HbA1c was -0.84% (0.243%) in the saxagliptin group and -0.87% (0.243%) in the placebo group (Figure 1).

Figure 1: Adjusted mean change in HbA1c (%) from baseline at Week 12 by baseline renal impairment category. Displayed are means and 95% confidence intervals



The percentage of subjects achieving a therapeutic response at Week 12 (LOCF) (defined as HbA1c reduction from baseline ≥0.5%) was higher in the saxagliptin group than the placebo group. Secondary efficacy endpoints were in accordance with these results. On request, the MAH has presented the percentages of patients achieving HbA1c <7%. After 12 weeks these percentages were 33.3% in the saxagliptin group versus 24.1% in the placebo group.
Insulin dose had decreased slightly from baseline in the saxagliptin group but remained relatively constant in the placebo group: in the FAS, there were 66 subjects in the saxagliptin group and 53 subjects in the placebo group who were taking background insulin therapy during the lead-in and short-term treatment periods. At Week 12, the mean (SE) insulin dose had decreased slightly from baseline in the saxagliptin group but stayed relatively constant in the placebo group.
In both treatment groups, a larger reduction in mean FPG from baseline to Week 12 was seen in subjects who were receiving background insulin therapy compared with those who were not.
Long-term data up to 52-weeks indicate a sustained effect of saxagliptin. However, the (low) numbers and proportions of subjects with available data at time-points in the LT period of the study should be taken into consideration when interpreting the LT efficacy results. In subjects with moderate or severe renal impairment, larger unadjusted mean reductions from baseline were seen at all time-points for the saxagliptin group compared with the placebo group. However, in the severe group the placebo response was larger than that observed for subjects with moderate renal impairment.
Results were generally similar in the Full analysis set using observed values. Improvement in glycaemic control during treatment with saxagliptin in subjects with renal impairment was confirmed and sustained during LT treatment of up to 52 weeks.

The excess of withdrawals on the saxagliptin arm relative to placebo might however be an issue. LOCF is used for data imputation which is potentially reasonable given that improvement is expected over time. However, the MAH does not provide a report on the timing of withdrawals and the impact of the data imputation on the magnitude of effects observed. The values imputed for withdrawing patients should be listed and summarised. Some bias in favour of saxagliptin is likely in these circumstances, in particular if patients derive initial benefit from treatment (greater than those on placebo) but then withdraw from the trial - this "benefit" will be artificially maintained (through the extrapolation) to the Week 12 timepoint. There might also be the common problem with LOCF of the imputation increasing estimated precision, hence narrowing confidence intervals and simultaneously decreasing the p-value, all artificially (see revised CHMP guideline on missing data). The MAH is requested to provide and to discuss some sensitivity analyses; BOCF would be conservative (though is also likely to suffer from artificially increased precision), but potentially persuasive.
In his response the MAH presented data from 4 sensitivity analyses: LOCF, Repeated Measures analysis, Observed case and BOCF. In all analyses an effect of saxagliptin was seen, albeit that in the BOCF (baseline observation carried forward) the difference was not statistically significant anymore. However, all analyses point in the same direction, and the analyses suggest that the influence of withdrawals is not very large.

2.5.2. Discussion on clinical efficacy

HbA1c was reduced from baseline to week 12 in both treatment groups. The reduction was statistically significantly greater with saxagliptin 2.5 mg than with placebo. Secondary efficacy endpoints were in accordance with these results. Initially a number of questions were raised regarding the design and conduct of the study. However, the MAH was able to explain adequately the reasons for the discrepancy between the number of enrolled subjects (572) and subjects randomised (170), the incorrect initial assignment in severity of the renal disease in 14 patients, and the number of withdrawals and protocol violations.
Furthermore, the MAH demonstrated it was plausible that imbalances between treatment groups did not affect the results. Imbalance in severity of renal impairment (more severe in the saxagliptin group) would not be in favour of saxagliptin, as the placebo response in patients with severe renal impairment was larger than in patients with moderate disease. Imbalance in patients using background insulin was shown not to influence the results to a great extent. A post-hoc analysis of the reduction in HbA1c from baseline to Week 12 using the primary analysis model with baseline insulin use as a covariate revealed no influence of the insulin treatment.

Initially, the MAH had submitted 12-week data only. Long-term data were submitted at Day 120. Although the primary endpoint was decrease in HbA1c at week 12, and although the number of patients completing the full 52 weeks was small (42 in the saxagliptin group and 50 in the placebo group), results indicate a sustained effect of saxagliptin during this period.

Although the treatment-by-baseline renal impairment interaction was not statistically significant, numerically larger mean reductions from baseline to week 12 were observed with saxagliptin compared to placebo in subjects with moderate or severe renal impairment, but there was no difference between treatment groups in patients with end-stage renal disease. The MAH decided to withdraw the claim for end-stage renal disease. For patients with severe renal disease, long-term data were suggestive for a sustained effect of saxagliptin, although the number of patients in this group was limited.

The percentage of subjects achieving a therapeutic response at Week 12 (LOCF) (defined as HbA1c reduction from baseline ≥ 0.5%) was higher in the saxagliptin group than the placebo group. However, mean HbA1c at baseline was higher in the saxagliptin group compared with the placebo group (8.45% versus 8.09%, respectively). On request, the MAH has presented the percentages of patients achieving HbA1c <7%:33.3% in the saxagliptin group versus 24.1% in the placebo group.

Insulin dose decreased slightly from baseline in the saxagliptin group but remained relatively constant in the placebo group.

The excess of withdrawals on the saxagliptin arm relative to placebo might however be an issue. The MAH was therefore requested to provide and to discuss some sensitivity analyses; BOCF would be conservative (though is also likely to suffer from artificially increased precision), but potentially persuasive. The MAH presented data from 4 sensitivity analyses. In all analyses an effect of saxagliptin was found. Data suggest that the influence of withdrawals was not very large.

2.5.3. Conclusions on the clinical efficacy

Saxagliptin 2.5 mg resulted in a clinically relevant decrease in HbA1c in patients with moderate or severe renal insufficiency. Therefore the use of saxagliptin in this population is approvable. However, as the number of patients in the group with severe renal insufficiency was small, the SmPC should reflect that the experience in this group is limited.
The MAH has withdrawn the claim for treatment in end-stage renal disease.

2.6. Clinical safety

Extent of exposure to study medication during short-term period is given in the next **Table 1**.

Table 1 Extent of exposure to study medication summary during short-term treatment period: safety set

Exposure (days)	Saxa 2.5 mg (N=85)		Placebo (N=85)	
	n	(%)	n	(%)
1-11	3	(3.5)	0	
12-25	5	(5.9)	3	(3.5)
26-39	2	(2.4)	1	(1.2)
40-60	5	(5.9)	3	(3.5)
61-81	10	(11.8)	8	(9.4)
82-88	51	(60.0)	62	(72.9)
88+	9	(10.6)	8	(9.4)
Summary statistics				
Mean (SD)	74.5 (23.94)		80.3 (16.88)	
Median	84.0		84.0	
Range	2.0-120.0		15.0-124.0	

The denominator of each percent is the number of subjects in the treatment group.
Exposure=last dosing date (short-term double-blind treatment)–first dosing date (short-term double-blind treatment)+1.

Mean exposure to randomised study medication was 74.5 days in the saxagliptin group and 80.3 days in the placebo group. The majority of subjects (60.0% and 72.9% of subjects, respectively) were exposed to treatment for 82 to 88 days (Table 1).

The number of subjects with any adverse event (AE) was similar between the treatment groups (57.6 vs 54.1% in the saxagliptin and placebo group, respectively). However, (Table 2) in the saxagliptin group more subjects had a SAE (12 [14.1%] vs 7 [8.2%]) and more subjects discontinued due to an (S)AE (8 [9.4%] vs 2 [2.4%] subjects).

Table 2 Overall summary of adverse events during the short-term treatment period: safety set

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)

Events of hypoglycaemia were included in all categories.

There was a higher incidence of AEs in severe and end-stage renal impairment as compared with moderate renal impairment (Table 3), and in these groups incidence of AEs was higher in the saxagliptin group than in the placebo group (severe: 72% vs 61%; end-stage 63% vs 55%).
In the saxagliptin group, the incidence of serious adverse events (SAEs) was similar in each baseline renal impairment category, whereas in the placebo group, the incidence of SAEs was higher in the moderate baseline renal impairment group compared with the severe and end-stage groups. Within each baseline renal impairment category, the incidence of SAEs was higher in the saxagliptin group compared with the placebo group. The incidence rates of SAEs for the saxagliptin and placebo groups were 11.1% (n=2) versus 4.3% (n=1), respectively, for subjects with severe renal impairment and

15.8% (n=3) versus 5.0% (n=1), respectively, for subjects with end-stage renal impairment. However, the differences represent only 1 to 2 subjects and the SAEs documented were more likely related to underlying diabetes mellitus and its complications rather than a drug effect with saxagliptin.
At Day 120 long-term data were presented. It should be remarked that the number of patients in the severe and end-stage renal impairment group was low. Incidence of AEs in the moderate impairment group was 58.3% [n=28] vs 59.5 [n=25] for the saxagliptin and placebo group respectively, in the severe impairment group 83.3% [n=15] vs 69.6 [n=16] for saxagliptin vs placebo, and in end-stage renal disease group 57.9% [n=11] vs 70.0 [n=14]. Thus, there is no clear relationship between renal impairment and the incidence of AEs. The most common AEs in saxagliptin-treated subjects included urinary tract infection, hypertension, dyspnoea and anaemia. The most common AEs in the placebo group included anaemia, oedema peripheral and hypertension. Overall, the incidence and type of SAEs, including deaths (saxagliptin: 23 [27.1%] subjects; placebo: 24 [28.2%] subjects) and SAEs leading to discontinuation were not unexpected for this subject population given the severity of renal disease. In general, AEs and SAEs were equally distributed across various system organ classes (SOCs) and preferred terms (PTs) without any major imbalances between treatment groups. There were 7 deaths during the study, 3 in the saxagliptin group (sudden death, cardiac arrest and cerebrovascular accident) and 4 in the placebo group (2 cases of sudden death, cardiac failure and sepsis). None of the deaths were considered by the investigator to be related to study medication.

Table 3 Overall summary of adverse events during the short-term treatment period by baseline renal impairment category: safety set

Category of AE	Saxa 2.5 mg (N=85)			Placebo (N=85)		
n (%)	Baseline renal impairment category			Baseline renal impairment category		
	Moderate (N=48)	Severe (N=18)	End-stage (N=19)	Moderate (N=42)	Severe (N=23)	End-stage (N=20)
At least 1 AE	24 (50.0)	13 (72.2)	12 (63.2)	21 (50.0)	14 (60.9)	11 (55.0)
At least 1 AE related to study medication	4 (8.3)	2 (11.1)	3 (15.8)	3 (7.1)	2 (8.7)	1 (5.0)
Deaths	0	0	0	0	0	0
At least 1 SAE	7 (14.6)	2 (11.1)	3 (15.8)	5 (11.9)	1 (4.3)	1 (5.0)
At least 1 SAE related to study medication	0	0	1 (5.3)	1 (2.4)	0	0
Discontinued study medication due to AE	2 (4.2)	1 (5.6)	2 (10.5)	1 (2.4)	0	0
Discontinued study medication due to SAE	1 (2.1)	0	2 (10.5)	1 (2.4)	0	0

Events of hypoglycaemia were included in all categories.

Also in subjects receiving insulin as background treatment incidence of AEs, and SAEs was higher than in patients not treated with insulin. In these groups too, incidence in the saxagliptin group was higher as compared to the placebo group.
The most common AEs were infections and infestations (11%) in both the saxagliptin and the placebo group. The most common infections were urinary tract infection and nasopharyngitis (4.7 and 1.2% in the saxagliptin group, vs 2.4 each in the placebo group). (see Table 4)
There were no notable differences in incidence and type of AEs between the treatment groups and type of AEs within the 3 baseline renal impairment categories.

Table 4 Most common adverse events (incidence ≥2%) by system organ class and preferred term during the short-term treatment period: safety set

System organ class Preferred term	Saxa 2.5 mg (N=85)		Placebo (N=85)	
	n	(%)	n	(%)
Total number of subjects with an AE	**41**	**(48.2)**	**36**	**(42.4)**
Infections and infestations	9	(10.6)	10	(11.8)
Urinary tract infection	4	(4.7)	2	(2.4)
Nasopharyngitis	1	(1.2)	2	(2.4)
Gastrointestinal disorders	6	(7.1)	7	(8.2)
Diarrhoea	3	(3.5)	0	
Nausea	2	(2.4)	1	(1.2)
Vomiting	2	(2.4)	0	
Dyspepsia	0		3	(3.5)
Investigations	6	(7.1)	4	(4.7)
Blood pressure increased	2	(2.4)	0	
Nervous system disorders	6	(7.1)	3	(3.5)
Dizziness	2	(2.4)	0	
Headache	2	(2.4)	1	(1.2)
Vascular disorders	6	(7.1)	8	(9.4)
Hypertension	3	(3.5)	4	(4.7)
Hypertensive crisis	0		2	(2.4)
Injury, poisoning and procedural complications	4	(4.7)	3	(3.5)
Metabolism and nutrition disorders	4	(4.7)	2	(2.4)
Hyperglycaemia	3	(3.5)	0	
Cardiac disorders	3	(3.5)	4	(4.7)
General disorders and administration site conditions	3	(3.5)	4	(4.7)
Oedema peripheral	1	(1.2)	2	(2.4)
Musculoskeletal and connective tissue disorders	3	(3.5)	2	(2.4)
Respiratory, thoracic and mediastinal disorders	3	(3.5)	1	(1.2)
Dyspnoea	2	(2.4)	0	
Renal and urinary disorders	2	(2.4)	1	(1.2)
Skin and subcutaneous tissue disorders	2	(2.4)	2	(2.4)
Hyperhidrosis	2	(2.4)	1	(1.2)
Blood and lymphatic system disorders	1	(1.2)	4	(4.7)
Anaemia	1	(1.2)	4	(4.7)

Hypoglycaemia terms based upon the saxagliptin defined list of events are excluded.

SAEs occurred in 12 (14.7%) and 7 (8.2%) subjects of the saxagliptin and placebo group respectively. Two subjects reported hypoglycaemia as SAEs, both of whom were in the placebo group.
SAEs were reported across various SOCs, with no single SOC predominating.
Discontinuation due to AEs was higher in the saxagliptin group compared to the placebo group (5 subjects vs 1 subject, 5.9% vs 1.2%). There was no clear pattern in the incidence of AEs leading to discontinuation.

Hypoglycaemia occurred more or less similarly in both treatment groups. Major hypoglycaemia was seen in 1 subject in each treatment group; minor hypoglycaemic events were observed in 13 subjects (15.3%) with 44 events in the saxagliptin group and in 11 subjects (12.9%) with 26 events in the placebo group.
There were no clinically relevant changes in laboratory values and vital signs.

2.6.1. Discussion on clinical safety

The overall number of subjects with any AE was similar between the treatment groups. There was a higher incidence of (S)AEs in severe and end-stage renal impairment as compared with moderate baseline impairment with a larger difference compared to placebo. However, the differences represent only 1 to 2 subjects and the SAEs documented were more likely related to underlying diabetes mellitus and its complications rather than a drug effect with saxagliptin.
The question was raised whether this is related to the relative higher plasma levels of the active metabolite, as discussed under Pharmacokinetics. However, the plasma concentrations of BMS-510849 in subjects with renal impairment given a 2.5-mg saxagliptin dose in Study 07 compare favourably to the concentrations of BMS-510849 in subjects given 5 mg (the approved dose) or 10 mg (a dose shown to be safe in phase 3 studies). It is unlikely that the imbalance in observed AEs is related to active metabolite concentrations, but is more likely due to underlying diabetes mellitus and its complications in this difficult-to-treat population (see also Pharmacokinetics).
A higher percentage in the saxagliptin group discontinued due to (S)AEs as compared with placebo but the numbers were small (4 vs. 1). No AEs were found for lymphopenia, thrombocytopenia, skin disorders, localised oedema, hypersensitivity, and pancreatitis. Hypoglycaemic events occurred more or less similarly between treatment groups. There were no clinically relevant changes from baseline in vital signs, ECGs, body weight, BMI, or waist circumference in either treatment group.

Long-term data were presented, but the number of patients completing 52 weeks was limited, especially in the severe and end-stage renal disease group. However, data did not reveal a consistent pattern in incidence of AEs related to renal insufficiency.
The MAH withdrew the claim for end-stage renal disease. It is emphasized in the SmPC that saxagliptin is not recommended for patients with end-stage renal disease requiring haemodialysis.
The use of saxagliptin in severe renal patients is acceptable. But it is reflected in the SmPC that the experience in patients with severe renal impairment is very limited and that saxagliptin should be used with caution in this population
More data will be needed to investigate safety in this category of patients with severe renal insufficiency. This can be done post-marketing when assessing the periodic safety update reports.

2.6.2. Conclusions on the clinical safety

Saxagliptin 2.5 mg once daily in general was well tolerated. However, more data will be needed to investigate safety in renal insufficiency, in particular in severe renal insufficiency. This can be done post-marketing when assessing the periodic safety update reports.

2.7. Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the current approved Pharmacovigilance system fulfils the legislative requirements and that no additional information is necessary for this extension application.

Risk Management Plan

The MAH claims that the information provided in the current approved version of the Risk Management Plan for Onglyza 5 mg is valid for Onglyza 2.5 mg as well. No new information was considered needed by the MAH.

The CHMP is of the opinion that no additional risk minimisation activities beyond those included in the product information are required for the extension of the Marketing Authorisation and agrees that the current version of the RMP is in principle valid. However for the next RMP update, awaited together with next PSUR, the applicant should include the recent already submitted and assessed data from study 07 in the section "safety specification". The MAH should also plan and perform a specific sub-population analysis within the ongoing phase IV database studies (CV181-P66/67/68/69/75) of the RMP.

User consultation

The MAH submitted a justification that the readability test performed and submitted for the initial MAA for Onglyza is relevant for this line extension application.
This is considered acceptable for the CHMP.

2.8. Benefit-Risk Balance

Benefits

Beneficial effects

The quality of Onglyza 2.5 film coated tablet is adequately established.

A 12-week study was performed in patients with different grades of renal insufficiency. Additionally data were presented from a 40 week extension of this trial. Treatment with saxagliptin resulted in a statistically significant greater reduction in HbA1c than placebo. Mean change was -0.82± 0.114 in the saxagliptin group and -0.29± 0.122 in the placebo group. Secondary efficacy endpoints were in accordance with these results.
Numerically larger adjusted mean reductions from baseline to Week 12 in HbA1c were observed with saxagliptin compared with placebo in subjects with moderate renal impairment (adjusted mean [SE] change from baseline -0.64% [0.134%] for the saxagliptin group and -0.05% [0.139%] for the placebo group) and in subjects with severe renal impairment (adjusted mean [SE] change from baseline -0.95% [0.228%] for the saxagliptin group and -0.50% [0.201%] for the placebo group). For the end-stage renal disease group, no difference with placebo was seen, but a large placebo response was noted.
Although the number of patients completing the full 52 weeks was small (42 in the saxagliptin group and 50 in the placebo group), results indicate a sustained effect of saxagliptin during this period.

Uncertainty in the knowledge about the beneficial effects

The number of patients completing 52 weeks of the study was limited: 42 in the saxagliptin group and 50 in the placebo group, with small numbers in the severe and end-stage renal disease groups.
The MAH withdrew the claim for use of saxagliptin in end-stage renal disease. It is emphasized in the SmPC that saxagliptin is not recommended for patients with end-stage renal disease requiring haemodialysis.
The use of saxagliptin in severe renal patients is acceptable. But it is reflected in the SmPC that the experience in patients with severe renal impairment is very limited and that saxagliptin should be used with caution in this population. More data in this category will be obtained through PSURs.

Risks

Unfavourable effects

The number of subjects with any AE was similar between the treatment groups (57.6 vs 54.1% in the saxa and placebo group, respectively). A higher percentage in the saxagliptin group discontinued due to (S)AEs as compared with placebo but the numbers were small (4 vs. 1). No AEs were found for lymphopenia, thrombocytopenia, skin disorders, localised oedema, hypersensitivity, and pancreatitis. Hypoglycaemic events occurred more or less similarly between treatment groups.
There was a higher incidence of (S)AEs in severe and end-stage renal impairment as compared with moderate baseline impairment with a larger difference compared to placebo. However, the differences represent only 1 to 2 subjects and the SAEs documented were more likely related to underlying diabetes mellitus and its complications rather than a drug effect with saxagliptin. There were no notable differences in type of AEs between the treatment groups.
There were no clinically relevant changes in laboratory values and vital signs. Long-term data did not reveal unexpected issues.

Uncertainty in the knowledge about the unfavourable effects

As noted above, the number of patients, especially in the severe and end-stage renal impairment groups was limited. Therefore, no definitive conclusions can be drawn on the safety of saxagliptin in this subgroups. The MAH withdrew the claim for use of saxagliptin in end-stage renal disease. It is emphasized in the SmPC that saxagliptin is not recommended for patients with end-stage renal disease requiring haemodialysis.
The use of saxagliptin in severe renal patients is acceptable. But it is reflected in the SmPC that the experience in patients with severe renal impairment is very limited and that saxagliptin should be used with caution in this population. More data in this category will be obtained through PSURs.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Saxagliptin resulted in a clinically relevant decrease in HbA1c in patients with moderate or severe renal impairment. Safety data, although limited in number of patients for the long-term treatment, is reassuring.

Benefit-risk balance

The overall Benefit/Risk balance of Onglyza (saxagliptin) 2.5 mg film-coated tablets intended for use in adult subjects with type 2 diabetes mellitus with moderate to severe renal impairment is positive.

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by concensus that the risk-benefit balance of Onglyza 2.5 mg film-coated tablets in the treatment of type 2 diabetes mellitus was favourable and therefore recommended the granting of the marketing authorisation.