20 September 2012
EMA/CHMP/508574/2012
Committee for Medicinal Products for Human Use (CHMP)

# Assessment report

## Trajenta

linagliptin

**Procedure No.:** EMEA/H/C/002110/II/0004/G

## Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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# List of abbreviations

| | |
|---|---|
| BMI | Body mass index |
| CHMP | Committee for Medicinal Products for Human Use |
| EFF | Efficacy study grouping |
| eGFR | Estimated glomerular filtration rate |
| FAS | Full analysis set |
| FPG | Fasting plasma glucose |
| gMean | overall geometric mean |
| $HbA_{1c}$ | Glycated hemoglobin |
| IU | International Units |
| MAA | Marketing Authorisation Application |
| MDRD | Modification of Diet in Renal Disease |
| MMRM | Mixed model repeated measurements |
| MTT | Meal Tolerance Test |
| PV | Protocol Violation |
| SAF | Safety study grouping |
| SU | Sulfonylurea |
| T2DM | Type 2 diabetes mellitus |

# 1. Background information on the procedure

## *1.1. Requested Type II Group of variations*

Pursuant to Article 7.2(b) of Commission Regulation (EC) No 1234/2008, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 14 March 2012 an application for a group of variations.

This application concerns the following medicinal product:

| Medicinal product: | International non-proprietary name: | Presentations: |
|---|---|---|
| Trajenta | linagliptin | See Annex A |

The following variations were requested in the group:

| **Variations requested** | | **Type** |
|---|---|---|
| C.I.6.a | Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | II |
| C.I.4 | Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | II |

The MAH proposed the update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to extend the indication for the treatment of type 2 diabetes in combination with insulin (with or without other oral antidiabetic medications, metformin, pioglitazone, sulphonylurea) when this regimen alone, with diet and exercise, does not provide adequate glycaemic control. Sections 1 and 4 of the Package Leaflet were proposed to be updated in accordance.

The MAH also proposed the update of sections 4.2, 4.8 and 5.1 of the SmPC to include the results of study 1218.63, a study conducted in elderly patients.

In addition, the MAH took the opportunity to include the Marketing Authorisation numbers in the SmPC and Labelling and to make linguistic corrections in the Spanish Annexes.

Furthermore, the PI is being brought in line with the latest QRD template version 8.

The requested group of variations proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.

Rapporteur: Pieter de Graeff

Co-Rapporteur: Martina Weise

# 2. Scientific discussion

## 2.1. Introduction

### About the product and this procedure

Linagliptin is a selective, orally administered, xanthine-based inhibitor of dipeptidylpeptidase-4 (DPP-4). The approved therapeutic dose of linagliptin is 5 mg once daily. Like other DPP-4 inhibitors, linagliptin lowers blood glucose by extending the half-life of glucagon-like peptide 1 (GLP-1), which is secreted in response to a meal. GLP-1 lowers blood glucose by augmenting the glucose-stimulated insulin release and limiting glucagon secretion to slow gastric emptying and to induce satiety. Therefore, linagliptin predominately affects postprandial glycaemic excursions. The advantages of DPP-4 inhibitors over other established antidiabetic medications include the low risk of hypoglycaemia and lack of weight gain.

Trajenta was approved throughout the European Union on the 24th of August 2011.

With regard to the present submission, results from 3 Phase III studies that include data on the efficacy and safety of linagliptin 5 mg once daily added to a background of insulin therapy with or without oral antidiabetic drugs in adult patients with T2DM are submitted by the MAH. The results from these 3 studies are supported by updated analyses of the safety profile of linagliptin based on pooled data from all linagliptin studies in patients with T2DM and from all placebo-controlled studies with linagliptin 5 mg.

The principal proof of the efficacy of linagliptin added to ongoing insulin therapy is derived from the new pivotal, double-blind, placebo-controlled Phase III study 1218.36. The efficacy of linagliptin as add-on therapy to insulin in patients with severe chronic renal impairment was evaluated in the subgroup EFF-2, which comprised a subset of patients from study 1218.43. Study 1218.43 was already submitted during the evaluation of Trajenta initial MAA. The efficacy of linagliptin as add-on therapy to basal insulin in elderly patients is shown based on EFF-3. For this grouping, data from patients from study 1218.36 who were aged 70 years and above were pooled with data from patients who were taking basal insulin as background therapy from study 1218.63.

Study 1218.63 is a 24-week study that investigated the efficacy and safety of linagliptin 5 mg versus placebo in elderly patients (aged 70 years or older) with T2DM and insufficient glycaemic control despite treatment with metformin and/or SU and/or insulin. Study 1218.63 has already been submitted for review by the CHMP as Trajenta MEA 009.

### GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH. 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.

### Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) N° 1901/2006 as amended, the application included an EMA decision (P/114/209) for the following condition(s):

- Type 2 diabetes mellitus

on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

## *2.2. Non-clinical aspects*

**Ecotoxicity/environmental risk assessment**

A full environmental risk assessment was provided with the Trajenta initial MAA. No environmental risk was identified for the active ingredient linagliptin. No increase of the environmental burden is expected by the MAH with this grouping application including an extension of indication. Since the maximum daily dose of the medicinal product would not change, no change to the outcome of the ERA is anticipated. This justification was considered acceptable by the CHMP.

## *2.3. Clinical aspects*

### 2.3.1. Clinical efficacy

To support the extension of indication as add-on to insulin, the MAH submitted a new Phase III study, study 1218.36 in which linagliptin was added to a background of insulin therapy with or without oral antidiabetic drugs in adult patients with T2DM. In addition, the MAH submitted two studies, study 1218.43 and study 1218.63 which included small subgroups of patients treated with linagliptin in combination with insulin therapy. These two additional studies have already been submitted to the CHMP as part of the initial MAA for Trajenta and as part of Trajenta MEA 009 respectively. These three studies (1218.36, 1218.43 and 1218.63) have been arranged into relevant efficacy groupings (EFF-1 to EFF-3) to only include those patients who were treated with insulin as background therapy.

To support the update of the SmPC regarding use of linagliptin in elderly patients, the MAH submitted study 1218.63, a Phase III efficacy and safety study conducted in patients ≥ 70 years of age treated with linagliptin 5 mg daily over 24 weeks.

**Add-on to insulin extension of indication**

#### *Methods for study 1218.36*

Study 1218.36 was a Phase III randomised, double-blind, placebo-controlled, parallel group efficacy and safety study of linagliptin (5 mg), administered orally once daily for at least 52 weeks in type 2 diabetic patients in combination with basal insulin therapy.

#### Study Participants

The study was performed in 167 centers in the following countries: Argentina, Belgium, Brazil, Canada, Czech Republic, Finland, Germany, Greece, Italy, Korea, Mexico, the Netherlands, Norway, Peru, Russia, Slovakia, Spain, Taiwan, the United States.

Main inclusion criteria:

- Diagnosis of T2DM prior to informed consent. This had to be confirmed by a measurable C-peptide level at screening (Visit 1).

- Male and female patients pre-treated with basal insulin alone or basal insulin in combination with metformin and/or pioglitazone. Acceptable basal insulins could be insulin glargine, insulin detemir or NPH insulin with a duration of action up to 24 h. According to the original protocol, the antidiabetic therapy had to remain unchanged for at least 12 weeks prior to Visit 3 (randomisation). According to protocol amendment no. 1 (dated 27 April 2010), the total prescribed insulin dose was not to change by more than 10% of the baseline value within the 12 weeks prior to randomisation. The oral antidiabetic therapy had to be unchanged for at least 12 weeks prior to randomization.
- HbA1c at screening (Visit 1): ≥7.0% to ≤10.0%
- Age at screening (Visit 1): ≥18 years
- BMI (Body Mass Index) at screening (Visit 1): ≤45 kg/m2
- Signed and dated written informed consent had to be obtained by date of Visit 1 in accordance with GCP and local legislation.

**Main exclusion criteria:**

- Uncontrolled fasting hyperglycaemia with a glucose level >240 mg/dl (>13.3 mmol/L) after a fast of at least 6 hours during placebo run-in, as confirmed by a second measurement on a following day
- Myocardial infarction, stroke, or transient ischaemic attack within 6 months prior to the date of informed consent
- Impaired hepatic function, defined as serum levels of either alanine transaminase (ALT/SGPT), aspartate transaminase (AST/SGOT), or alkaline phosphatase(ALP) above 3 x the upper limit of normal (ULN) as determined at Visit 1
- Gastric bypass surgery
- Medical history of cancer (except for basal cell carcinoma) with respective treatment in the last 5 years prior to screening
- Treatment with rosiglitazone, sulfonylurea, GLP-1 analogues or DPP-IV inhibitors within 3 months prior to informed consent
- Treatment with anti-obesity drugs (e.g. sibutramine, orlistat, rimonabant) 3 months prior to informed consent.

This randomised, double-blind, parallel group trial was performed to compare the efficacy, safety, and tolerability of 5 mg linagliptin (administered orally, once daily, for at least 52 weeks) with placebo in patients with T2DM and insufficient glycaemic control who were receiving background basal insulin therapy.

According to current guidelines (American Diabetes Association, European Association for the Study of Diabetes), insulin therapy should be initiated immediately in patients newly diagnosed with T2DM with an HbA1c >8.5% or as a second step in patients with insufficient glycaemic control despite treatment with oral antidiabetic agents. Therefore, patients treated with basal insulin therapy alone or combined with metformin or pioglitazone represent an important proportion of the patient population with T2DM.

In the first 24 weeks of the treatment period, the doses of background insulin therapy were to remain stable to allow the assessment of efficacy of linagliptin in this patient population. In the following treatment period of at least 28 weeks, the insulin dose could be adjusted according to the judgment of

the investigator. This treatment period was to provide additional safety and tolerability data for linagliptin in patients receiving background insulin therapy. In addition, this study included patients with mild to moderate renal impairment to obtain information on efficacy and safety of linagliptin in this patient population.

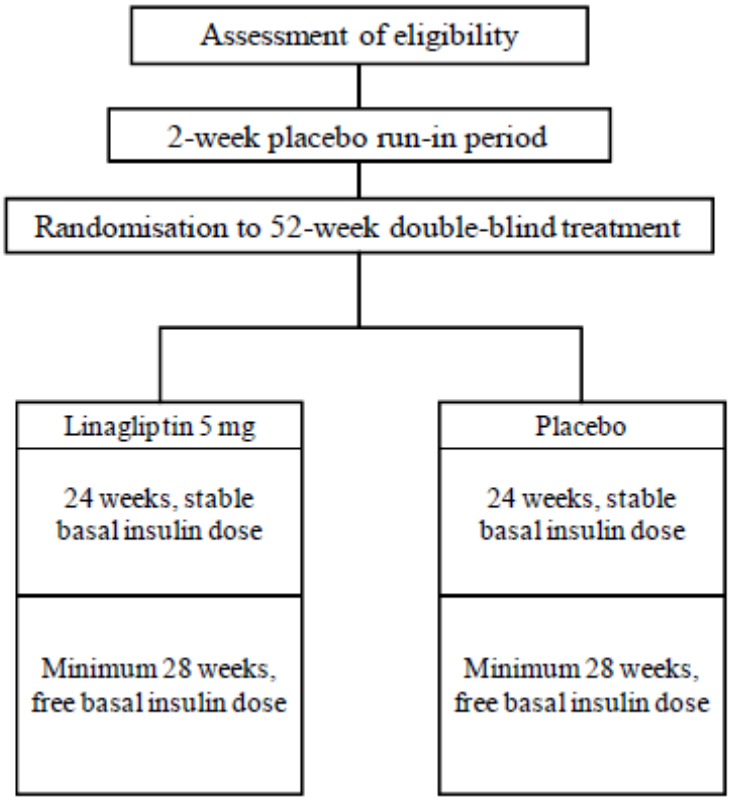
## Treatments

Patients were to continue with their standard basal insulin therapy with or without concomitant metformin or/and pioglitazone therapy throughout the entire study.

All patients took placebo (1 tablet, once daily) during the 2-week open-label run-in period. During the double-blind treatment period, each patient took 1 tablet daily: those in the linagliptin group took one tablet of 5 mg linagliptin; those in the placebo group took one placebo tablet that had the same appearance as the linagliptin 5 mg tablet. The dose of prescribed basal insulin was to remain stable during the first 24-week period of randomized treatment

After the first 24 weeks of randomised treatment (from Visit 7 onwards), the dose of prescribed basal insulin could be adjusted according to the clinical judgment of the investigator with a treatment target for FPG of 110 mg/dL. The background medication of metformin or pioglitazone was to remain unchanged throughout the study. Patients could take their background medication as they were used to, though it was suggested that basal insulin was always administered in the evening. Morning doses of metformin or pioglitazone could be taken before the visits, but it was to be emphasised that the patients should have the same habits of dosing before the visit throughout the trial (i.e. either to always take the dose in the morning before the visit or to always come to the visit without having yet taken any dose of metformin or pioglitazone).

**Figure 1. Trial design**



## Objectives

The objective of this study was to investigate efficacy and safety of linagliptin 5 mg versus placebo administered for at least 52 weeks in combination with basal insulin to patients with T2DM and insufficient glycaemic control. Efficacy was to be evaluated as a primary endpoint after 24 weeks of randomised treatment, while safety and tolerability were planned to be followed up during long-term treatment.

A secondary objective of this study was to evaluate efficacy, safety, and tolerability of linagliptin in patients with mild to moderate renal impairment.

## Outcomes/endpoints

Primary endpoint:

- Change from baseline in HbA1c after 24 weeks of treatment. Throughout this CTR, the term 'baseline' refers to the last observation prior to the start of randomised study treatment.

Secondary endpoints:

- Occurrence of a treat-to-target efficacy response, i.e. HbA1c on treatment <7.0% after 24 weeks and 52 weeks of treatment
- Occurrence of a treat-to-target efficacy response, i.e. HbA1c on treatment <6.5% after 24 weeks and 52 weeks of treatment
- Occurrence of relative efficacy response, i.e. HbA1c lowering by at least 0.5% after 24 weeks and 52 weeks of treatment
- Change from baseline in HbA1c by visit over time
- Change from baseline in FPG after 52 weeks of treatment
- Change from baseline in FPG by visit over time
- Change from baseline in mean basal insulin dose after 52 weeks of treatment
- Change from baseline in weighted Mean Daily Glucose using the 8-point blood glucose profile after 52 weeks of treatment
- Change from baseline in incremental PPG (iPPG) at 24 weeks

## Sample size

Based on a standard deviation of 1.2% for a change in HbA1c from baseline to 24 weeks, a total of 284 patients per treatment group would be sufficient to achieve a power of 93% to detect a 0.35% difference in HbA1c change from baseline between the treatment groups. The sample size in this trial with 600 patients in each treatment group was chosen to fulfill the regulatory requirements of the whole program to detect AEs in treated patients across trials.

## Randomisation

Patients who met the trial eligibility criteria at the end of the 2-week placebo run-in period were randomly assigned to one of the 2 treatment groups (linagliptin 5 mg or placebo) in a balanced ratio.

## Blinding (masking)

The placebo run-in period of this trial was performed open-label, i.e. both the investigator and the patient knew that the patient received placebo during the run-in period. The randomised period of this trial was performed double-blind, i.e. after randomisation at Visit 3, neither the patient nor the investigator was aware of the identity of a patient's study treatment.

## Statistical methods

The primary analysis was performed on the full analysis set (FAS). The FAS comprised all randomised patients who were treated with at least one dose of study medication, had a baseline HbA1c measurement, and had at least one on-treatment HbA1c measurement within the first 24 weeks of double-blind treatment.

A per-protocol set (PPS) consisting of patients following the CTP in essential criteria was created for sensitivity analyses. Patients included in the FAS who had important PVs were excluded from the PPS. The FAS-completers comprised all patients in the FAS who completed 149 days of treatment and had an HbA1c measurement after 24 weeks of treatment. The treated set for safety evaluation included all patients who were treated with at least one dose of study medication in the randomised period of the trial.

Primary endpoint: Testing of superiority hypothesis versus placebo with an analysis of covariance (ANCOVA) with treatment, concomitant oral antidiabetics, and baseline renal function impairment category as fixed classification effects, and baseline HbA1c as covariate

Secondary and other endpoints: ANCOVA (exploratory); for use of rescue medication logistic regression and Kaplan-Meier analysis

Safety endpoints: Descriptive statistics; for hypoglycaemic events logistic regression and Kaplan-Meier analysis

For this interim analysis, data were analysed for visits that occurred on or before the cut-off date of 12 February 2011.

**Use of linagliptin in elderly patients**

### *Methods for study 1218.63*

Study 1218.63 was a Phase III multi-national, randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of linagliptin (5 mg), administered orally once daily over 24 weeks in type 2 diabetic (T2DM) patients, age ≥70 years, with insufficient glycaemic control (HbA1c ≥7.0%) despite metformin and/or sulphonylurea (SU) and/or insulin therapy.

## Study Participants

This study was performed in 33 centres in 5 countries (Australia, Canada, Denmark, Netherlands, and Sweden).

Main inclusion criteria:

- Male and female patients with a diagnosis of T2DM and stable treatment with metformin and/or a SU and/or basal insulin (taken up to 2 times daily) prior to informed consent (amendment 3, dated

07 Sep 2010). Treatment with metformin and/or SU had to be unchanged for 8 weeks prior to informed consent; the insulin dose should not have changed within the 8 weeks prior to informed consent by more than 20% from the baseline value at randomization.

- HbA1c ≥7.0 % at Visit 1
- Age ≥70 years at Visit 1
- Signed and dated written informed consent by date of Visit 1 in accordance with GCP and local legislation.

Main exclusion criteria included Fasting plasma glucose level (FPG) >240 mg/dL (>13.3 mmol/L) during placebo run-in; History of MI, stroke, or transient ischaemic attack within last 3 months; Impaired hepatic function [serum levels of either alanine transaminase, aspartate transaminase, or alkaline phosphatase above 3x the upper limit of normal]; Treatment with glitazones, α-glucosidase inhibitors, glinides, GLP-1 analogues, or DPP-4 inhibitors; Treatment with rapid acting or pre-mixed insulins; or treatment with anti-obesity drugs.

## Treatments

Patients who met the trial eligibility criteria at the end of the 2-week placebo run-in period were randomly assigned to one of the 2 treatment groups (linagliptin 5 mg or placebo) in a 2:1 ratio (linagliptin 5 mg:placebo).

All patients received placebo during the 2-week open-label run-in period. The timing and dosing schedule of the run-in period (1 tablet, once daily in the morning) mirrored the dosing schedule of the randomised period.

Patients continued their current metformin and/or SU and/or insulin therapy during the study. During the double-blind treatment period, each patient took 1 tablet daily: those in the linagliptin group took 1 tablet of linagliptin 5 mg, those in the placebo group took one placebo tablet having the same appearance as the linagliptin 5 mg tablets. During screening and run-in and in the first 12 weeks (Visits 3 to 5) no dose adjustments were allowed unless required for safety reasons such as hypoglycaemic episodes as defined in the CTP or hyperglycaemia as defined in the CTP. Any insulin adjustment of less than 20% was not considered as a rescue. Patients could have some (minor) changes in insulin over time (amendment 2, dated 19 Mar 2010). The final decision on dose adjustments was left to the discretion of the investigator. There was no limitation for dose adjustments throughout the remainder of the study.

After the screening period and a 2-week open-label placebo run-in period, patients were randomised to linagliptin 5 mg or placebo. Randomisation was stratified by HbA1c (<8.5% versus ≥8.5%) and background insulin use (yes/no). Doses of background diabetes medications were kept stable during screening, run-in and the first 12 weeks of randomised treatment, after which adjustments were permitted. Treatment duration was 24 weeks followed by 1 week follow-up.

Rescue therapy in the case of hyperglycaemia (when occurred in minimum of 2 occasions) was initiated during the randomised period, if:

- FPG level >13.3 mmol/L (Week 1-12) or >11.1 mmol/L (Week 12-24)

- Random Glucose level >22.2 mmol/L (Week 1-24)

During Week 12-24 adjustments in background glucose-lowering medications were permitted, therefore only introduction of new glucose-lowering therapy was regarded as rescue therapy during Week 12 to Week 24.

## Objectives

The objective of this study was to investigate the efficacy and safety of linagliptin 5 mg versus placebo administered for 24 weeks as add-on to stable background therapy to elderly patients with T2DM and insufficient glycaemic control.

## Outcomes/endpoints

Primary endpoint:

- Change from baseline in HbA1c after 24 weeks of treatment. Throughout this CTR, the term 'baseline' refers to the last observation prior to the start of randomised study treatment.

Secondary endpoints:

- Occurrence of a treat-to-target efficacy response, i.e. HbA1c on treatment <7.0% after 24 weeks of treatment
- Occurrence of relative efficacy response, i.e. HbA1c lowering by at least 0.5% after 24 weeks of treatment
- Change from baseline in HbA1c by visit over time
- Change from baseline in FPG after 24 weeks of treatment
- Change from baseline in FPG by visit over time
- Use of rescue therapy.

## Sample size

A number of 77 evaluable patients in the placebo group and 154 in the linagliptin group were required to achieve a power of 90% to detect a 0.5% difference in HbA1c change from baseline using a 2-sided test with $\alpha$=0.05. To account for potential drop-outs 5% were to be added to each treatment group, resulting in a total sample size of 243 randomised patients.

## Randomisation

Patients who met the trial eligibility criteria at the end of the 2-week placebo run-in period were randomly assigned to one of the 2 treatment groups (linagliptin 5 mg or placebo) in a 2:1 ratio (linagliptin 5 mg:placebo).

Randomisation was performed at Visit 3, if the patients were still considered eligible after the placebo run-in period, stratified by HbA1c (<8.5% versus ≥8.5%) as determined from the blood sample taken at the beginning of the placebo run-in period (Visit 2), and also by insulin use (yes or no).

## Blinding (masking)

The placebo run-in period of this trial was performed open-label, i.e. both the investigator and the patient knew that the patient received placebo during the run-in period. The randomised period of this trial was performed double-blind, i.e. after randomisation at Visit 3 neither the patient nor the investigator were aware of the identity of a patient's treatment.

## Statistical methods

The primary analysis was performed on the full analysis set (FAS). The FAS consisted of all randomised patients who were treated with at least one dose of study drug, had a baseline, and at least 1 on-treatment HbA1c measurement.

A per protocol set (PPS) of patients following the trial protocol in essential criteria was created for sensitivity analyses. Patients included in the FAS who had important PVs were excluded from the PPS. A PV was considered important if a distorting influence on the assessment of the primary endpoint was to be expected.

The FAS-completers set of patients was defined as all patients in the FAS who completed at least 21 weeks of treatment and had an HbA1c measurement after at least 21 weeks of treatment.

The PPS-completers set of patients was defined as all patients in the PPS who completed 21 weeks of treatment and had an HbA1c measurement after 21 weeks of treatment.

All patients treated with at least one dose of study drug (Treated Set) were included in the safety evaluation.

Primary endpoint: Testing of superiority hypothesis of linagliptin 5 mg over placebo with an analysis of covariance (ANCOVA) with treatment and prior use of insulin as fixed classification effects and baseline HbA1c as linear covariate.

Secondary and other endpoints: ANCOVA (exploratory), descriptive statistics, for use of rescue medication logistic regression and Kaplan-Meier analysis. Safety endpoints: Descriptive statistics; for hypoglycaemic events logistic regression and Kaplan-Meier analysis.

**Add-on to insulin extension of indication**

## *Results of the relevant efficacy groupings (EFF-1 to EFF-3)*

As explained previously, the three studies 1218.36, 1218.43 and 1218.63 have been arranged into relevant efficacy groupings (EFF-1 to EFF-3) to only include those patients who were treated with insulin as background therapy.

The pivotal placebo-controlled study is study 1218.36 (EFF-1). All patients in study 1218.36 were treated with basal insulin as background therapy and are therefore included in EFF-1. As described above, the primary endpoint was $HbA_{1c}$ change from baseline after 24 weeks. The overall study duration was at least 52 weeks. Data obtained beyond 24 weeks up to the interim cut-off (cut-off date: 12 February 2011) was used to show persistence of efficacy over time. There was a particular emphasis on data up to 40 weeks, as more than 400 patients had reached that time point at the interim cut-off date.

Efficacy of linagliptin as add-on therapy to insulin in patients with severe chronic renal impairment was evaluated in EFF-2, which comprised a subset of patients from study 1218.43. Only those patients from study 1218.43 who were taking insulin as background therapy (with or without other antidiabetic drugs) were included in EFF-2. The primary endpoint, the change from baseline in $HbA_{1c}$, was analysed after 12 weeks of treatment, though the overall study duration was 52 weeks. Data over 52 weeks was used to investigate persistence of efficacy over time.

The efficacy of linagliptin as add-on therapy to basal insulin in elderly patients is investigated in EFF-3. For this grouping, data from patients included in study 1218.36 who were aged 70 years and above were pooled with data from the 24-week study 1218.63 (EFF-3). From study 1218.63, which was performed exclusively in patients aged 70 years or above, only those patients who were taking basal insulin as background therapy were included in EFF-3. For both studies contributing patients to EFF-3, the primary endpoint was the $HbA_{1c}$ change from baseline after 24 weeks.

A summary of the efficacy groupings is shown in the table below. In these 3 groupings, a total of 720 patients were treated with linagliptin 5 mg once daily and 700 patients received placebo. Note that patients aged 70 years or more from trial 1218.36 were included in both EFF-1 and EFF-3.

**Table 1. Summary of study groupings for the evaluation of efficacy**

| Characteristics (Study grouping) | Contributing studies | Treated patients included in the efficacy grouping, N (%) [1] | | |
|---|---|---|---|---|
| | | Placebo | Linagliptin | Total |
| Pivotal double-blind, placebo-controlled efficacy study (EFF-1) | 1218.36 | 630 (50.0) | 631 (50.0) | 1261 (100.0) |
| Supportive double-blind, placebo-controlled efficacy study in patients with severe chronic renal impairment (EFF-2) [2] | 1218.43 | 55 (41.4) | 54 (40.6) | 109 (82.0) |
| Supportive double-blind, placebo-controlled efficacy studies in elderly patients (EFF-3) [3] | 1218.36 | 106 (8.4) | 91 (7.2) | 197 (15.6) |
| | 1218.63 | 15 (6.2) | 35 (14.5) | 50 (20.7) |
| | EFF-3 total | 121 (8.1) | 126 (8.4) | 247 (16.4) |

1 Percentages refer to the overall number of patients treated within the respective trials
2 Includes only patients from 1218.43 taking insulin as background therapy
3 Includes only patients from 1218.36 aged 70 years or more and patients from 1218.63 taking basal insulin as background therapy

For each of the efficacy study groupings, the rate of premature discontinuations up to the time point of analysis of the primary endpoint was less than 10% and was lower in the patients treated with linagliptin than those receiving placebo. The most frequent reasons for early discontinuations in patients treated with linagliptin were the occurrence of adverse events and administrative reasons (i.e. loss to follow-up, refusal to continue medication, or non-compliance with the protocol). Overall disposition was additionally determined up to the interim cut-off date for the pivotal study 1218.36 (EFF-1) and over the entire 52-week study duration for the patients with severe chronic renal impairment (EFF-2). For the grouping of elderly patients (EFF-3), the overall disposition was based on data up to the interim cut-off date for study 1218.36 and the entire 24-week study duration for study 1218.63. Almost a quarter of patients in the grouping of patients with severe chronic renal impairment (EFF-2) discontinued prematurely, which is to be expected in this population of more vulnerable patients. The rate of premature discontinuations was maintained at less than 10% for patients treated with linagliptin in the pivotal study 1218.36 (EFF-1) and in the grouping of elderly patients (EFF-3) and was less than the percentage for patients receiving placebo. The most frequent reasons for early discontinuations in patients treated with linagliptin were the same as those described above for the period up to the analysis of the primary endpoint. Disposition in the efficacy study groupings is summarised in the table below.

**Table 2. Summary of disposition of randomised patients in the efficacy study groupings – FAS**

| | EFF-1 | | EFF-2 | | EFF-3 | |
|---|---|---|---|---|---|---|
| | Placebo (N=617) | Linagliptin (N=618) | Placebo (N=52) | Linagliptin (N=52) | Placebo (N=118) | Linagliptin (N=126) |
| Proportion of patients, (%) | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 | 100.0 |
| **Disposition up to primary endpoint** [1] | | | | | | |
| Not prematurely discontinued | 93.5 | 96.3 | 90.4 | 94.2 | 90.7 | 96.0 |
| Prematurely discontinued | 6.5 | 3.7 | 9.6 | 5.8 | 9.3 | 4.0 |
| Adverse events | 1.8 | 1.3 | 5.8 | 3.8 | 1.7 | 3.2 |
| Lack of efficacy [2] | 1.0 | 0 | 1.9 | 0 | 0.8 | 0 |
| Administrative reasons [3] | 2.3 | 1.6 | 1.9 | 1.9 | 5.1 | 0.8 |
| Other reasons | 1.5 | 0.8 | 0 | 0 | 1.7 | 0 |
| **Overall disposition** [4] | | | | | | |
| Not prematurely discontinued | 89.5 | 93.2 | 76.9 | 76.9 | 88.1 | 92.9 |
| Prematurely discontinued | 10.5 | 6.8 | 23.1 | 23.1 | 11.9 | 7.1 |
| Adverse events | 3.2 | 2.6 | 15.4 | 11.5 | 2.5 | 4.0 |
| Lack of efficacy [2] | 1.5 | 0.2 | 1.9 | 1.9 | 0.8 | 0 |
| Administrative reasons [3] | 3.9 | 2.9 | 5.8 | 7.7 | 5.9 | 3.2 |
| Other reasons | 1.9 | 1.1 | 0 | 1.9 | 2.5 | 0 |

1 Data up to 24 weeks for EFF-1 and EFF-3; data up to 12 weeks for EFF-2
2 Includes patients who discontinued due to hyperglycaemia
3 Non-compliance to study protocol, lost to follow-up, or refusal to continue study medication
4 Data up to the interim cut-off date for EFF-1; data up to the end of study (52 weeks) for EFF-2; data up to the interim cut-off for 1218.36 and end of study (24 weeks) for 1218.63 for studies comprising EFF-3

## Demographics and baseline characteristics

Age and body mass index (BMI) were comparable between treatment groups for each of the efficacy study groupings, though the percentage of patients who were male was notably higher for the linagliptin groups than the placebo groups in EFF-2 and EFF-3. The linagliptin and placebo groups were generally balanced with regard to the geographical region and race of the patients. Selected demographic data in the efficacy study groupings are summarised in the table below.

**Table 3. Summary of selected demographic data in the efficacy study groupings – FAS**

| | EFF-1 | | EFF-2 | | EFF-3 | |
|---|---|---|---|---|---|---|
| | Placebo | Linagliptin | Placebo | Linagliptin | Placebo | Linagliptin |
| Number of patients, N (%) | 617 (100.0) | 618 (100.0) | 52 (100.0) | 52 (100.0) | 118 (100.0) | 126 (100.0) |
| Age, mean (SD) [years] | 60.5 (9.9) | 59.8 (9.9) | 64.3 (9.8) | 65.5 (8.5) | 74.3 (4.1) | 74.3 (3.8) |
| BMI, mean (SD) [kg/m$^2$] | 31.2 (5.0) | 30.8 (5.4) | 32.3 (6.0) | 32.3 (5.9) | 30.3 (4.4) | 30.3 (5.2) |
| Male gender, (%) | 51.7 | 52.3 | 57.7 | 69.2 | 45.8 | 55.6 |
| Geographic region, (%) | | | | | | |
| Asia | 11.2 | 11.2 | 44.2 | 32.7 | 4.2 | 4.0 |
| Europe | 45.4 | 44.8 | 7.7 | 3.8 | 66.1 | 62.7 |
| North America [1] | 16.9 | 18.3 | 48.1 | 63.5 | 16.1 | 21.4 |
| South America [2] | 26.6 | 25.7 | 0 | 0 | 13.6 | 11.9 |
| Race, (%) | | | | | | |
| White | 80.2 | 79.9 | 69.2 | 78.8 | 92.4 | 92.1 |
| Black [3] | 6.3 | 6.3 | 11.5 | 5.8 | 2.5 | 1.6 |
| Asian | 13.5 | 13.8 | 19.2 | 15.4 | 5.1 | 6.3 |

1 Including New Zealand and Australia
2 Including Mexico
3 Or African American

The mean $HbA_{1c}$ at baseline was similar across efficacy groupings and between treatment groups. With respect to baseline FPG, there was a notable difference between treatment groups in patients with severe chronic renal impairment (EFF-2); the mean FPG at baseline was 147.9 mg/dL in the linagliptin group and 164.1 mg/dL in the placebo group. This baseline difference between the groups may have had an influence on the FPG results for the patients with severe chronic renal impairment. In the other two efficacy groupings, EFF-1 and EFF-3, the mean FPG at baseline was similar between treatment groups. The vast majority of patients in each of the efficacy groupings had been diagnosed with diabetes for more than 5 years. As would be expected for patients with severe chronic renal impairment, the EFF-2 grouping had the highest incidences of microvascular disease and macrovascular disease. Almost all patients with severe chronic renal impairment were treated with antihypertensive drugs. The overall baseline characteristics were generally comparable between treatment groups for each of the efficacy study groupings, with the exception of the baseline FPG in EFF-2 as described above. Selected baseline characteristics are summarised in the table below.

**Table 4. Summary of selected baseline characteristics in the efficacy study groupings – FAS**

| | EFF-1 | | EFF-2 | | EFF-3 | |
|---|---|---|---|---|---|---|
| | Placebo | Linagliptin | Placebo | Linagliptin | Placebo | Linagliptin |
| Number of patients, N (%) | 617 (100) | 618 (100) | 52 (100.0) | 52 (100.0) | 118 (100.0) | 126 (100.0) |
| Baseline $HbA_{1c}$, mean (SD) [%] | 8.3 (0.9) | 8.3 (0.9) | 8.3 (0.9) | 8.3 (1.0) | 8.2 (0.8) | 8.2 (0.8) |
| Baseline FPG, mean (SD) [mg/dL] | 151.3 (46.4) | 147.2 (46.0) | 164.1 (69.7) | 147.9 (68.3) | 153.0 (48.1) | 150.5 (42.9) |
| Diabetes for >5 years, (%) | 87.4 | 83.8 | 94.2 | 96.2 | 96.6 | 94.4 |
| Microvascular disease, (%) [1] | 46.7 | 46.4 | 98.1 | 96.2 | 44.1 | 52.4 |
| Macrovascular disease, (%) | | | | | | |
| Coronary artery disease | 17.7 | 17.6 | 44.2 | 42.3 | 31.4 | 23.8 |
| Peripheral artery occlusive disease | 5.3 | 4.9 | 17.3 | 21.2 | 11.0 | 5.6 |
| Cerebrovascular disease | 4.4 | 4.2 | 15.4 | 21.2 | 5.1 | 6.3 |
| Concomitant therapies at screening, (%) | | | | | | |
| Antihypertensives | 76.8 | 79.8 | 100.0 | 98.1 | 84.7 | 88.1 |
| Lipid-lowering drugs | 59.6 | 54.9 | 78.8 | 84.6 | 66.1 | 58.7 |
| Concomitant diagnoses at screening, (%) | | | | | | |
| At least 1 concomitant diagnosis | 95.1 | 95.0 | 100.0 | 100.0 | 98.3 | 96.0 |
| Vascular disorders | 44.4 | 46.3 | 51.9 | 46.2 | 47.5 | 54.0 |
| Cardiac disorders | 25.0 | 25.6 | 36.5 | 48.1 | 41.5 | 35.7 |

1 Retinopathy, nephropathy, and neuropathy.

## Concomitant antidiabetic drugs

In addition to insulin, most patients in the pivotal study 1218.36 (EFF-1) were taking concomitant oral antidiabetic drugs at screening. The majority were taking metformin, either as monotherapy (75.1% of all patients in EFF-1) or in combination with pioglitazone (7.3%). Overall, 16% of the patients were taking neither metformin nor pioglitazone at screening. Metformin is contraindicated in patients with severe renal impairment. Therefore, most patients in EFF-2 (76.9%) were not taking any concomitant oral antidiabetic drugs at screening. A sulphonylurea was taken by 12.5% of patients in EFF-2 at screening, while pioglitazone was taken by 3.8%. Most patients in the grouping of elderly patients (EFF-3) were taking concomitant oral antidiabetic drugs at screening, the majority of whom were taking metformin, either as monotherapy (65.6% of all patients in EFF-3) or in combination with pioglitazone (5.3%) or sulphonylurea (4.1%).

## Background insulin

All patients included in the efficacy study groupings for this submission were, by definition, treated with insulin as background therapy. A prerequisite for participation in study 1218.36 (EFF-1) was that patients were treated with basal insulin. Almost half of the patients in EFF-1 (47.3%) were taking insulin glargine as their basal insulin therapy, whereas 34.7% were taking Neutral Protamine Hagedorn (NPH) insulin and 17.9% were taking insulin detemir. Different types of insulin were permitted in study 1218.43, which contributed patients to EFF-2. Most patients in EFF-2 (74.0%) were taking basal insulin, whereas 41.3% were taking fast/rapid acting insulin, and 21.2% were taking an insulin mixture. Patients in EFF-2 could have been taking more than one type of insulin. All patients in EFF-3 were taking basal insulin as specified by the protocols of the two trials that contributed patients to this grouping of elderly patients; most were taking insulin glargine (47.1%) or NPH insulin (41.0%), and only 11.9% were taking insulin detemir.

Insulin dose at screening and throughout the treatment duration was recorded during each of the trials and expressed in International Units (IU). The mean dose of daily basal insulin at screening was lower for patients in EFF-3 (35.8 IU) than for patients in EFF-1 (40.9 IU) and EFF-2 (40.8 IU). Note, however, that the type of insulin permitted in EFF-2 was not restricted to basal insulin; patients in study 1218.43 could also take fast/rapid acting insulin and insulin mixture. Thus, the overall mean insulin dose at screening in EFF-2 was 64.9 IU, which was considerably higher than the mean dose in the other efficacy study groupings.

## HbA1c

For each of the trials contributing to the evaluation of efficacy in this new indication in combination with insulin, the primary analysis was based on the change from baseline in $HbA_{1c.}$ In trials 1218.36 and 1218.63 the primary endpoint was analysed at 24 weeks; in trial 1218.43 the primary endpoint was analysed at 12 weeks. Therefore, in the current submission, the primary analysis of efficacy is based on 24-week data for EFF-1 and EFF-3 and on 12-week data for EFF-2.

**Change from baseline in $HbA_{1c}$ in the pivotal study 1218.36 (EFF-1)**

After 24 weeks of treatment there was a reduction in the adjusted mean $HbA_{1c}$ of -0.55% in patients treated with linagliptin but an increase of 0.10% in the patients receiving placebo. The adjusted mean treatment difference was -0.65 % (95% CI -0.74, -0.55; p<0.0001) (see table below). This result was corroborated by sensitivity analyses. Thus, in patients with T2DM taking basal insulin as background therapy with or without oral antidiabetic drugs, treatment with linagliptin provided a statistically significant and clinically meaningful reduction in $HbA_{1c}$.

**Table 5. Change from baseline in $HbA_{1c}$ [%] after 24 weeks in the pivotal placebo-controlled trial (EFF-1) - FAS (LOCF)**

| Efficacy grouping/ treatment group | Number of patients | Baseline $HbA_{1c,}$ mean (SD) | Change from baseline in $HbA_{1c}$ | | Difference from placebo | | |
|---|---|---|---|---|---|---|---|
| | | | Mean (SD) | Adjusted mean (SE) | Adjusted mean (SE) | 95% CI | p-value |
| EFF-1[1] | | | | | | | |
| Placebo | 617 | 8.29 (0.85) | 0.04 (0.92) | 0.10 (0.04) | | | |
| Linagliptin | 618 | 8.31 (0.85) | -0.62 (0.87) | -0.55 (0.04) | -0.65 (0.05) | (-0.74, -0.55) | <0.0001 |

1 Model includes continuous baseline $HbA_{1c}$, renal function impairment category, treatment, and concomitant oral antidiabetic drugs

A comparison can be made with study 1218.17 from the initial linagliptin clinical development programme. In study 1218.17, in which the efficacy of linagliptin was investigated in patients treated with a background of metformin therapy, the adjusted mean treatment difference was -0.64%, which is almost identical to the value of -0.65% for EFF-1 observed here (with most patients on a background of insulin plus metformin). Thus, there appears to be a clinically comparable efficacy on a background therapy with basal insulin. The treatment effect of linagliptin observed in EFF-1 is also consistent with the effect of linagliptin in patients in whom diet and exercise alone did not achieve sufficient glycaemic control (-0.69%; study 1218.16) or when added to a background of metformin and a sulphonylurea (-0.62%; study 1218.18).

**Change from baseline in $HbA_{1c}$ in patients with severe chronic renal impairment (EFF-2)**

After 12 weeks of treatment with linagliptin, there was a statistically significant treatment difference from placebo in $HbA_{1c}$ change from baseline of -0.43%. This treatment effect, in the subset of patients from study 1218.43 who were treated with insulin as background therapy, was numerically smaller than the value of -0.59% reported for the overall study population in study 1218.43. The change in $HbA_{1c}$ from baseline was sustained for up to 52 weeks. The total number of patients in EFF-2 was considerably smaller than in the pivotal study 1218.36 (EFF-1).

**Table 6. Change from baseline in $HbA_{1c}$ [%] after 12 weeks in patients with severe chronic renal impairment (EFF-2) - FAS (LOCF)**

| Efficacy grouping/ treatment group | Number of patients | Baseline $HbA_{1c}$, mean (SD) | Change from baseline in $HbA_{1c}$ | | Difference from placebo | | |
|---|---|---|---|---|---|---|---|
| | | | Mean (SD) | Adjusted mean (SE) | Adjusted mean (SE) | 95% CI | p-value |
| EFF-2/[1] | | | | | | | |
| Placebo | 52 | 8.32 (0.88) | 0.04 (0.83) | -0.01 (0.13) | | | |
| Linagliptin | 52 | 8.26 (0.95) | -0.42 (0.81) | -0.44 (0.12) | -0.43 (0.16) | (-0.75, -0.11) | 0.0084 |

1 Model includes continuous baseline $HbA_{1c}$, continuous baseline creatinine clearance, treatment, and concomitant oral antidiabetic drugs

**Change from baseline in $HbA_{1c}$ in elderly patients aged at least 70 years (EFF-3)**

The adjusted mean treatment difference in $HbA_{1c}$ reduction from placebo in the grouping of elderly patients (EFF-3) was -0.77% and was statistically significant (see table below). This value is numerically greater than the overall treatment effect of -0.64% in trial 1218.63 in which the efficacy of linagliptin was studied in patients aged at least 70 years with or without basal insulin background. A subgroup analysis by background therapy that was performed in trial 1218.63 revealed no evidence that the treatment effect of linagliptin was influenced by a background of insulin therapy. Thus, linagliptin is at least as efficacious in elderly patients taking background basal insulin therapy as in elderly patients not taking background insulin. Furthermore, based on the comparison with the treatment difference in EFF-1 (-0.65%), the $HbA_{1c}$-lowering effect of linagliptin appears not to be diminished in older patients.

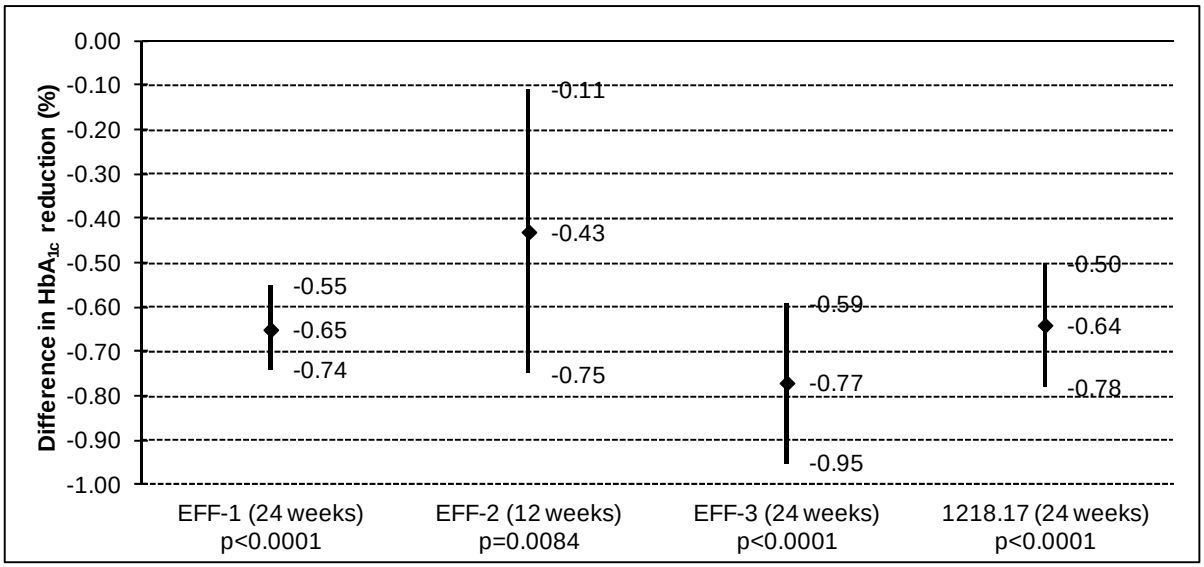
**Table 7. Change from baseline in $HbA_{1c}$ [%] after 24 weeks in elderly patients aged at least 70 years (EFF-3) - FAS (LOCF)**

| Efficacy grouping/ treatment group | Number of patients | Baseline $HbA_{1c}$, mean (SD) | Change from baseline in $HbA_{1c}$ | | Difference from placebo | | |
|---|---|---|---|---|---|---|---|
| | | | Mean (SD) | Adjusted mean (SE) | Adjusted mean (SE) | 95% CI | p-value |
| EFF-3/[1] | | | | | | | |
| Placebo | 118 | 8.20 (0.84) | 0.06 (0.78) | 0.09 (0.08) | | | |
| Linagliptin | 126 | 8.19 (0.83) | -0.71 (0.70) | -0.68 (0.08) | -0.77 (0.09) | (-0.95, -0.59) | <0.0001 |

1 Model includes continuous baseline $HbA_{1c}$, treatment, study, and concomitant oral antidiabetic drugs

A comparison of the treatment effects of linagliptin between the 3 efficacy groupings in the current submission and the pivotal study 1218.17, in which linagliptin was investigated in patients treated with a background of metformin therapy, is shown in the following figure below. The primary endpoint for EFF-2, comprising the patients with severe chronic renal impairment, was assessed after 12 weeks of treatment, before the maximal treatment effect had been reached.

**Figure 4. Adjusted mean difference between linagliptin and placebo in $HbA_{1c}$ with p-values and 95% confidence intervals in the efficacy groupings with insulin background and trial 1218.17 without insulin background**



**HbA1c Goals**

The proportion of patients who reached target $HbA_{1c}$ values of <7.0% was analysed for each of the efficacy groupings, with a higher proportion of patients treated with linagliptin than receiving placebo achieving this target. For the pivotal study 1218.36 ( EFF-1), 19.5% of patients treated with linagliptin who had a baseline $HbA_{1c}$ value of at least 7.0% reached the $HbA_{1c}$ target of <7.0%, compared with 8.1% of those who received placebo. For the patients with severe chronic renal impairment (EFF-2), 16.0% of patients who had a baseline $HbA_{1c}$ value of at least 7.0% and were treated with linagliptin reached the target, compared with 11.5% of those who received placebo. For the grouping of elderly patients (EFF-3), 25.4% of patients who had a baseline $HbA_{1c}$ value of at least 7.0% and were treated with linagliptin reached the target, compared with 5.3% of those who received placebo.

**Efficacy in subgroups**

Since the principal proof of efficacy was derived from the pivotal placebo-controlled study 1218.36, the data from this study (EFF-1) were used to evaluate the efficacy of linagliptin in relevant subgroups.

For most subgroups investigated, the treatment effect was consistent and the achieved changes from baseline in $HbA_{1c}$ were comparable across all subcategories (see table below).

**Table 8. Summary of the analyses of change in $HbA_{1c}$ in subgroups of EFF-1**

| Subgroup name | Subcategories analysed | Differential treatment effect of linagliptin across subcategories [1] |
|---|---|---|
| Age | ≤50 years vs. 51 to 64 years vs. 65 to 74 years vs. ≥75 years | yes |
| Gender | male vs. female | no |
| Race | White vs. Black/African American vs. Asian | no |
| Ethnicity | Hispanic/Latino vs. not Hispanic/Latino | no |
| Geographical region | Europe vs. North America [2] vs. South America [3] vs. Asia | yes |
| Baseline BMI | <30 $kg/m^2$ vs. ≥30 $kg/m^2$ | no |
| Baseline $HbA_{1c}$ | <7.0% vs. 7.0% to <8.0% vs. 8.0% to <9.0% vs. ≥9.0% | no |
| Time since diagnosis of diabetes | ≤1 year vs. >1 to 5 years vs. >5 years | yes |
| Concomitant oral antidiabetic drugs | none vs. metformin vs. pioglitazone vs. metformin and pioglitazone | no |
| Type of basal insulin | glargine vs. detemir vs. NPH | no |
| Presence of metabolic syndrome at baseline | yes vs. no | no |
| Use of rescue medication | yes vs. no | no [4] |
| Renal impairment (MDRD) [5] | none (≥90 mL/min) vs. mild (60 to <90 mL/min) vs. moderate (30 to <60 mL/min) vs. severe or end stage (<30 mL/min) | no |
| Renal impairment (Cockcroft-Gault) [6] | none (≥80 mL/min) vs. mild (50 to <80 mL/min) vs. moderate (30 to <50 mL/min) vs. severe or end stage (<30 mL/min) | no |

1 Indicated by a p-value for the interaction term of <0.1
2 Including New Zealand and Australia
3 Including Mexico
4 No inferential analysis; descriptive statistics showed a numerically greater reduction in $HbA_{1c}$ for patients (in both treatment groups) that did not take rescue medication compared with patients that required rescue medication.
5 Based on eGFR, as calculated using the MDRD formula
6 Based on eCcr, as calculated using the Cockcroft-Gault formula

In addition, for each of the 4 geographical regions included in the study, linagliptin provided statistically significant and clinically meaningful reductions in $HbA_{1c}$. There were, however, differences between regions with regard to the magnitude of the treatment effect; the adjusted mean treatment differences were -1.01% for Asia, -0.65% for South America, -0.61% for Europe, and -0.49% for North America (all $p<0.0001$). The p-value for the treatment-by-geographical region interaction term was 0.0456. Patients from the region Asia had, on average, the highest $HbA_{1c}$ values at baseline.

With regard to age, linagliptin provided statistically significant and clinically relevant reductions in mean $HbA_{1c}$ for all 4 age categories of EFF-1. The p-value for the treatment-by-age interaction was 0.0826. However, no overall trend with increasing age was observed; the treatment effect was -0.51% in patients aged up to 50 years, -0.72% in patients aged 51 to 64 years, -0.51% in patients aged 65 to 74 years, and -0.92% in patients aged 75 years and older.

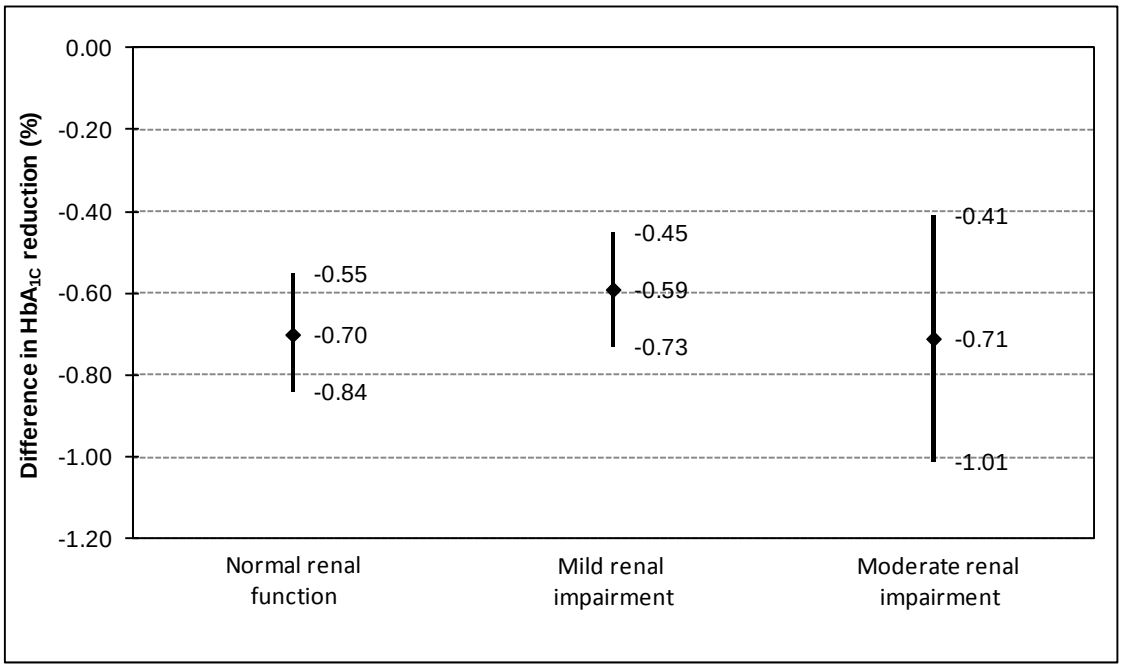
For the time since diagnosis of diabetes, a significant treatment-by-subgroup interaction was noted (p=0.0084). As would be expected for patients requiring insulin, the vast majority of patients (85.6%) had been diagnosed for 5 years or longer. In this subcategory, the treatment effect of linagliptin versus placebo was -0.70%. For the much smaller subgroups of patients not as advanced in the duration of their diabetes, lesser treatment effects were found: -0.31% for patients diagnosed for between 1 and 5 years, and -0.11% for patients diagnosed for up to a year. This was primarily due to a strong placebo response in patients diagnosed for between >1 and 5 years (-0.16% adjusted mean change from baseline) and for up to a year (-0.40%), compared with patients diagnosed for more than 5 years (0.14%). The adjusted mean change in $HbA_{1c}$ from baseline after treatment with linagliptin was similar across the subgroup categories.

In EFF-1, a subgroup analysis was performed by additional concomitant oral antidiabetic drugs on insulin background. This showed that, for patients taking metformin only, the treatment difference was -0.66%. Linagliptin also provided clinically meaningful $HbA_{1c}$ reductions for patients treated with pioglitazone, either alone (treatment difference: -0.74%) or in combination with metformin (treatment difference: -0.71%). However, the treatment effect for patients taking pioglitazone only as an oral antidiabetic drug did not reach statistical significance due to the small number of patients in this category. For patients taking insulin alone without oral antidiabetic drugs, there was also a clinically relevant reduction in $HbA_{1c}$ after treatment with linagliptin, with a treatment difference of -0.52%. The p-value of 0.7306 for the treatment-by-subgroup interaction also indicates that the efficacy of linagliptin is not influenced by the category of concomitant oral antidiabetic drugs.

With regard to the type of basal insulin, the treatment effect was consistent and the achieved changes from baseline in $HbA_{1c}$ were comparable across all 3 types of basal insulin. Based on the large p-value of 0.8955 for the treatment-by-subgroup interaction, the type of basal insulin does not appear to influence the efficacy of linagliptin.

The analysis by renal impairment category is of major clinical importance, since patients requiring insulin therapy generally have more advanced diabetes and are therefore more likely to present with the co-morbidities of diabetes, including renal impairment. Treatment with linagliptin provided clinically meaningful and statistically significant reductions in $HbA_{1c}$ in patients with normal renal function, mild renal impairment, and moderate renal impairment (categories based on eGFR estimated by the MDRD formula). In EFF-1, too few patients (N=7) had severe or end-stage renal impairment to allow for a meaningful interpretation of efficacy in this category. The treatment difference was similar for patients with normal renal function (-0.70%) and moderate renal impairment (-0.71%), but numerically smaller for patients with mild renal impairment (-0.59%). The large p-value for the treatment-by-renal impairment interaction term (0.5672) indicated that the treatment effect of linagliptin was not influenced by the degree of renal impairment.

**Figure 5. Adjusted mean treatment difference in the $HbA_{1c}$ change from baseline after 24 weeks with p-values and 95% confidence intervals by renal impairment subcategories in EFF-1**




## Change in baseline FPG

The change from baseline in FPG was a secondary endpoint in all trials included in the analysis of efficacy for this new indication in combination with insulin. For patients in the pivotal study 1218.36 (EFF-1) and the grouping of elderly patients (EFF-3), treatment with linagliptin led to substantial reductions in FPG from baseline to 24 weeks compared with placebo. For patients with severe chronic renal impairment (EFF-2), however, the treatment effect with regard to FPG was negligible, in contrast to the $HbA_{1c}$ results for this efficacy grouping.

In EFF-1 (the placebo-controlled pivotal study 1218.36), the adjusted mean difference between linagliptin and placebo with regard to the FPG change from baseline was -11.2 mg/dL ($p<0.0001$), which is smaller than the treatment effect observed in the metformin add-on study 1218.17 (-21.1 mg/dL). In contrast to study 1218.17, patients in EFF-1 did not wash out previous antidiabetic drugs, which may have contributed to the smaller treatment difference in EFF-1 compared with study 1218.17. The smaller reduction in FPG in EFF-1 compared with study 1218.17 might also be explained by linagliptin exerting its glucose-lowering effect primarily on postprandial glucose levels in patients treated with basal insulin.

For patients with severe chronic renal impairment (EFF-2), there was an increase in adjusted mean FPG from baseline to 12 weeks for patients treated with linagliptin (11.9 mg/dL) and for patients receiving placebo (13.6 mg/dL). The treatment difference of -1.8 mg/dL was not statistically significant (p=0.8982). These results diverge from the mean $HbA_{1c}$ change from baseline in the same efficacy grouping, where linagliptin provided a reduction in mean $HbA_{1c}$ from baseline and a clinically relevant treatment difference between linagliptin and placebo was noted. They are, however, in line with the overall changes in FPG observed after 12 weeks in study 1218.43 (adjusted mean treatment difference of 0.39 mg/dL), from which a subset of patients comprised EFF-2 for this submission. Note that for patients in EFF-2 (i.e. the subset of patients from study 1218.43 who were treated with insulin as background therapy), the FPG at baseline was considerably lower in the linagliptin group (148.2 mg/dL) than in the placebo group (159.4 mg/dL). Moreover, the inconsistency between changes in $HbA_{1c}$ and FPG after DPP-4 inhibition in patients with severe chronic renal impairment is not restricted to linagliptin. For other DPP-4 inhibitors, similar findings have been reported in patients with severe chronic renal impairment, i.e. lowering of $HbA_{1c}$ compared with placebo but no significant treatment difference for FPG.

For the grouping of elderly patients (EFF-3), treatment with linagliptin provided a statistically significant reduction in FPG from baseline, with an adjusted mean treatment difference of -19.4 mg/dL (p=0.0011). This treatment effect is numerically greater than that observed in the pivotal trial (EFF-1) and is consistent with the results for $HbA_{1c}$.

## Use of rescue medication and insulin dose

As an additional measure for the efficacy of treatment with linagliptin, it was analysed how many patients in each efficacy grouping required rescue medication. Due to their study designs, there were slight differences in the definitions of rescue medication in each of the trials contributing patients to the efficacy analysis. In study 1218.36, the first choice of rescue medication was the adjustment of basal insulin therapy; any increase in prescribed insulin dose of more than 10% of the baseline dose was regarded as rescue medication. In very rare cases, background therapy could be adjusted or another oral antidiabetic medication could be added as rescue medication. In study 1218.43, any additional antidiabetic drug or increase in the dose of background therapy during the first 12 weeks of treatment was regarded as rescue medication. In study 1218.63, rescue medication was considered as any addition of an antidiabetic drug or increase in the dose of background medication for more than 7 days.

For each of the efficacy groupings, the use of rescue medication was lower for patients treated with linagliptin than for patients receiving placebo. In the pivotal study 1218.36 (EFF-1), 13.1% of patients treated with linagliptin required rescue medication, compared with 20.9% of patients who received placebo. Of the patients with severe chronic renal impairment (EFF-2), 11.5% of those treated with linagliptin required rescue medication, compared with 17.3% of patients who received placebo. Of the grouping of elderly patients (EFF-3), 8.7% of those treated with linagliptin required rescue medication after 12 weeks, compared with 19.5% of patients who received placebo.

According to the trial protocols, the background insulin dose was to have been maintained at a stable level up to 24 weeks for study 1218.36 and 12 weeks for studies 1218.43 and 1218.63. Analysis of the mean changes in insulin dose in the efficacy groupings showed that mean insulin doses were stable up to the time points of the primary analysis (less than 2% change from baseline for both treatment groups in each of the efficacy groupings). For each of the efficacy groupings a smaller proportion of patients treated with linagliptin than patients receiving placebo had insulin dose increases of more than 10% during the period up to the primary endpoint. These results are consistent with the results for use of rescue medication as described above.

## Body weight

In each of the efficacy groupings, there were only minor effects on body weight in both treatment groups (less than ±0.5 kg change in adjusted mean weight from baseline) at the timepoint of the primary analysis. These results, observed while the background insulin dose was stable, confirm that treatment with linagliptin is weight neutral.

## Long term effects

In the current submission, the persistence of efficacy of linagliptin as add-on therapy to insulin was investigated using data from beyond the timepoint of the primary analysis for EFF-1 and EFF-2. For EFF-1, which is based on the pivotal placebo-controlled study 1218.36, data over time up to the cut-off date for the interim report were analysed using the "observed cases" approach (FAS OC), excluding measurements taken after the start of rescue medication. Data for up to 64 weeks were available; however, for the period beyond 40 weeks, the numbers of patients were not considered to be large enough to draw meaningful conclusions. For EFF-2 (based on study 1218.43), in which efficacy was investigated in patients with severe chronic renal impairment, data over the entire study duration of 52 weeks were analysed, also based on the FAS OC. In studies 1218.36 and 1218.43, investigators were free to adjust the background insulin dose after the timepoint for analysis of the primary endpoint had been reached. Therefore, analysis of the changes in insulin dose over time is highly relevant in interpreting the persistence of the efficacy of linagliptin for both study groupings.

**Persistence of efficacy in the pivotal placebo-controlled trial (EFF-1)**

There was no evidence for a diminution over time of the efficacy of linagliptin given as add-on therapy to a background of basal insulin with or without oral antidiabetic drugs. In patients treated with linagliptin, a clinically relevant change in mean $HbA_{1c}$ from baseline of -0.67% was observed after 24 weeks, increasing to -0.76% after 40 weeks of treatment. For patients receiving placebo, a slight reduction from baseline in $HbA_{1c}$ over time (-0.12% at Week 40) was noted (see figure below).

**Figure 6. Mean change in $HbA_{1c}$ (%) and SE from baseline to 40 weeks of treatment in EFF-1 – FAS (OC)**

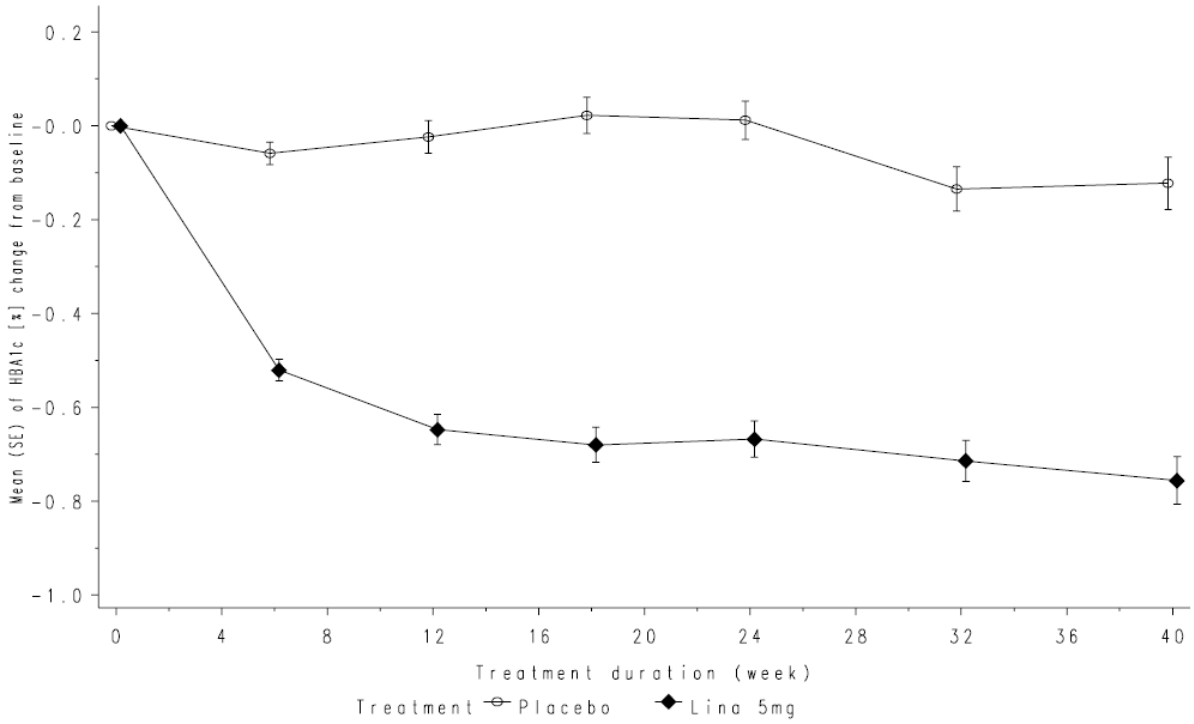



Figure includes data up to the interim cut-off date. There were 1013 patients with data at 24 weeks, 720 patients at 32 weeks, and 484 patients at 40 weeks. Beyond this, there were insufficient patients to allow a meaningful interpretation of efficacy.

The average change in insulin dose from baseline to 40 weeks in patients receiving placebo was only about a 6% increase from the baseline value (increase of 2.5 IU from a baseline dose of 40.1 IU). This was despite most patients having $HbA_{1c}$ values that remained above the recommended treatment goal of 7% and the freedom of investigators to adjust the insulin dose according to their medical judgment. Thus, investigators may have been reluctant to try to improve glycaemic control by increasing the insulin dose, possibly due to the risk of hypoglycaemia and weight gain associated with insulin. For patients treated with linagliptin, the initial improvements in glycaemic control were sustained over time with an even smaller increase in mean insulin dose of about 3% (increase of 1.3 IU from a baseline dose of 41.6 IU).

With regard to use of rescue medication and changes in body weight, both these endpoints were evaluated in study 1218.36 along with the primary endpoint at 24 weeks.

**Persistence of efficacy in the patients with severe chronic renal impairment (EFF-2)**

The adjusted mean treatment difference, based on the FAS (LOCF), in the change in mean $HbA_{1c}$ from baseline at 52 weeks was -0.55% (95% CI -0.90, -0.20; p=0.0024). In patients treated with linagliptin, a change in mean $HbA_{1c}$ from baseline of -0.42% was observed after 12 weeks, which was maintained until the end of the study at 52 weeks (-0.37%). In contrast, patients receiving placebo had an increase in their mean $HbA_{1c}$ from baseline to 12 weeks (0.04%) and to the end of the study at 52 weeks (0.20%).

As permitted by the protocol, investigators were free to change the insulin dose beyond 12 weeks of treatment. By 52 weeks, patients treated with linagliptin had a numerically greater reduction in their adjusted mean insulin dose from baseline compared with patients receiving placebo. The reduction in adjusted mean insulin dose for patients treated with linagliptin, based on the FAS (OC-ROC), was about 16% (change of -10.1 IU from a baseline dose of 63.5 IU) up to 52 weeks. Patients receiving placebo had a reduction in their adjusted mean insulin dose of about 12% (change of -7.1 IU from a baseline dose of 57.1 IU).

Taken together, these results show that linagliptin treatment up to 52 weeks was associated with improvements in glycaemic control for patients with severe chronic renal impairment, permitting a reduction in the insulin dose.

**Table 9. Patients with changes in maximum insulin dose up to 52 weeks in EFF-2 – FAS (OC-ROC)**

| | Placebo | Linagliptin |
|---|---|---|
| Patients with stable insulin dose, N (%) | 25 (48.1) | 24 (46.2) |
| Patients with insulin dose increase, N (%) | | |
| >10% | 17 (32.7) | 11 (21.2) |
| >20% | 10 (19.2) | 7 (13.5) |
| Patients with insulin dose decrease, N (%) | | |
| >10% | 10 (19.2) | 21 (40.4) |
| >20% | 7 (13.5) | 16 (30.8) |

Patients could be assigned to more than 1 category

The analysis of the numbers of patients who achieved $HbA_{1c}$ levels of less than 7.0% after 52 weeks were in line with the mean changes in $HbA_{1c}$ described above. A higher proportion of patients who had a baseline $HbA_{1c}$ value of at least 7.0% and who were treated with linagliptin (14.0%) attained $HbA_{1c}$ values of less than 7.0% after 52 weeks of treatment than patients receiving placebo (9.6%).

With regard to the changes in FPG over time, the changes in FPG up to 52 weeks did not reflect the reduction in $HbA_{1c}$ over the same time period. By 52 weeks, the mean change in FPG from baseline, based on the FAS (LOCF), was 6.8 mg/dL in the linagliptin group and -8.1 mg/dL in the placebo group. Several factors may have contributed to this result, including the lower FPG at baseline in patients receiving linagliptin as well as the mechanism of action of linagliptin, which exerts its effects mainly on postprandial rather than fasting glucose levels. Furthermore, the raised FPG levels in patients treated with linagliptin may have been a consequence of the reduction in insulin dose that was observed.

There was a slight decrease in mean body weight from baseline to 52 weeks (-1.8 kg) in patients treated with linagliptin. Since linagliptin itself is considered weight neutral, this weight loss may have resulted from the reduction in insulin dose in the patients treated with linagliptin. For patients receiving placebo, the change in body weight from baseline was -0.1 kg.

Another efficacy endpoint analysed after 52 weeks was the use of rescue medication. For both treatment groups, the percentage of patients requiring rescue medication had more than doubled by 52 weeks when compared with the 12-week endpoint. As was the case at 12 weeks, a lower percentage of patients treated with linagliptin (28.8%) than with placebo (46.2%) required rescue medication during the 52-week duration of the study.

**Use of linagliptin in elderly patients**

### *Results from study 1218.63*

## Participant flow

A total of 377 patients were enrolled in this study. Of the enrolled patients, 241 patients were randomised in a 2:1 ratio to receive treatment either with linagliptin 5 mg (162 patients) or placebo (79 patients). The most common reason for an enrolled patient not being randomised was not meeting the criterion of HbA1c ≥7.0% at Visit 1 (97 patients, 25.7%).

**Table 12. Disposition of randomised patients – Screened Set**

| | Placebo N (%) | Linagliptin N (%) | Total N (%) |
|---|---|---|---|
| Enrolled | | | 377 |
| Started placebo run-in | | | 253 |
| Randomised | 79 | 162 | 241 |
| Treated | 79 (100.0) | 162 (100.0) | 241 (100.0) |
| Not prematurely discontinued trial medication | 74 ( 93.7) | 146 ( 90.1) | 220 ( 91.3) |
| Prematurely discontinued trial medication | 5 ( 6.3) | 16 ( 9.9) | 21 ( 8.7) |
| Adverse events | 1 ( 1.3) | 8 ( 4.9) | 9 ( 3.7) |
| Other disease worsening | 0 ( 0.0) | 2 ( 1.2) | 2 ( 0.8) |
| Other adverse event | 1 ( 1.3) | 6 ( 3.7) | 7 ( 2.9) |
| Non-compliance with protocol | 3 ( 3.8) | 7 ( 4.3) | 10 ( 4.1) |
| Refused to continue trial medication | 1 ( 1.3) | 1 ( 0.6) | 2 ( 0.8) |

All of the 241 patients who were randomised received trial medication. Of these, 21 patients (8.7%) prematurely discontinued trial medication (5/79 [6.3%] placebo; 16/162 [9.9%] linagliptin), see table above. The higher proportion of patients prematurely discontinued from linagliptin compared with placebo was mostly due to AEs (1.3% placebo; 4.9% linagliptin), although the most frequent reason for premature discontinuation was non-compliance with the protocol (3.8% placebo; 4.3% linagliptin).

Analyses Sets

The table below shows the different analysis sets. The treated set was composed of all patients in the randomised set who received at least one dose of study medication (N=241).The Full analysis set (FAS) was a subset of the randomised set and included all patients who had a baseline and at least one on-treatment HbA1c measurement available (N=238). The FAS-completers was a subset of the FAS who completed the 24-week treatment period (N=218).

The per protocol set (PPS) including all patients who did not have an important Protocol Violation (PV) that impacted on efficacy (N=212). The PPS-completers set were patients from the PPS who completed the study (N=185).

**Table 13. Number of patients by analysis set**

| Included in set | | Placebo N (%) | Linagliptin N (%) | Total N (%) |
|---|---|---|---|---|
| Randomised set | N | 79 | 162 | 241 |
| Treated set | N (% of Randomised set) | 79 (100.0) | 162 (100.0) | 241 (100.0) |
| FAS | N (% of Randomised set) | 78 ( 98.7) | 160 ( 98.8) | 238 ( 98.8) |
| FAS-completers set[1] | N (% of FAS) | 73 ( 93.6) | 145 ( 90.6) | 218 ( 91.6) |
| PPS | N (% of FAS) | 69 ( 88.5) | 143 ( 89.4) | 212 ( 89.1) |
| PPS-completers set[1] | N (% of PPS) | 66 ( 95.7) | 130 ( 90.9) | 196 ( 92.5) |
| PPS–NR–completers | N (% of PPS) | 58 ( 84.1) | 127 ( 88.8) | 185 ( 87.3) |

FAS = full analysis set, PPS = per protocol set, PPS-NR = per protocol set not rescue completers

1 Completers were patients with a minimum treatment duration of 149 days who also had an $HbA_{1c}$ value within the Week 24 visit window.

## Recruitment

Study 1218.63 was conducted from the 10th of March 2012 until the 22nd of June 2011.

## Conduct of the study

There were 5 global amendments and no local amendments to the original CTP. These amendments are not expected to have clinically relevant impact on the overall trial result.

## Baseline data

At total of 114 patients (47.3%) were randomised in European countries. Most patients were White (96.7%). Mean age overall was 74.9 years; 44.4% of patients were 75 years of age or over. The majority of patients had either normal renal function (eGRF [MDRD staging] ≥90 mL/min/1.73m$^2$; 21.2%) or mild renal impairment (eGFR 60 to <90 mL/min/1.73m$^2$; 51.9%). Three (1.2%) patients had severe renal impairment (eGFR <30 mL/min/1.73m$^2$).

Randomisation was stratified by HbA1c and insulin use. Overall, the proportions of patients in each stratum were comparable between the treatment groups, see table below. There were 19.0% of patients in the placebo group and 21.0% of patients in the linagliptin group who had been previously treated with insulin. A total of 81.3% of patients (82.3% placebo; 80.9% linagliptin) had an HbA1c less than 8.5%.

**Table 14. Number of randomised patients by stratum –Randomised set**

| | Placebo N (%) | Linagliptin N (%) | Total N (%) |
|---|---|---|---|
| $HbA_{1c}$ at run-in (categorical) | | | |
| Total | | | |
| Prior use of insulin, [N (%)] | | | |
| Total | 79 (100.0) | 162 (100.0) | 241 (100.0) |
| Prior | 15 ( 19.0) | 34 ( 21.0) | 49 ( 20.3) |
| No prior | 64 ( 81.0) | 128 ( 79.0) | 192 ( 79.7) |
| <8.5% | | | |
| Prior use of insulin [N (%)] | | | |
| Total | 65 ( 82.3) | 131 ( 80.9) | 196 ( 81.3) |
| Prior | 11 ( 13.9) | 24 ( 14.8) | 35 ( 14.5) |
| No prior | 54 ( 68.4) | 107 ( 66.0) | 161 ( 66.8) |
| ≥8.5% | | | |
| Prior use of insulin [N (%)] | | | |
| Total | 14 ( 17.7) | 31 ( 19.1) | 45 ( 18.7) |
| Prior | 4 ( 5.1) | 10 ( 6.2) | 14 ( 5.8) |
| No prior | 10 ( 12.7) | 21 ( 13.0) | 31 ( 12.9) |

The $HbA_{1c}$ and prior use of insulin use strata displayed on this table are as implemented by the IVRS. Strata for analysis were however calculated directly from the antidiabetes medications and baseline $HbA_{1c}$ values.

Overall, the demographic profile was balanced between the treatment groups, see table 15. However, there were more male patients in the linagliptin group (71.6%) than in the placebo group (62.0%). Baseline mean HbA1c levels were 7.82% in the linagliptin group, versus 7.70% in the placebo group. Median HbA1c was 7.60% in both treatment groups. Table 16 shows baseline HbA1c per category. In general, HbA1c levels were comparable between the treatment groups. Table 17 shows the background glucose-lowering treatment at screening. Background glucose-lowering therapy with metformin was more common in the placebo group (88.5%) than in the linagliptin group (83.1%) whereas SU was more common in the linagliptin group (58.8%) than in the placebo group (55.1%). The daily dose of metformin was slightly higher in the linagliptin group (1764.29 mg versus 1748.55 mg.

**Table 15. Demographic data – Treated set**

| | Placebo | Linagliptin | Total |
|---|---|---|---|
| Number of patients, N (%) | 79 (100.0) | 162 (100.0) | 241 (100.0) |
| Gender, N (%) | | | |
| Male | 49 ( 62.0) | 116 ( 71.6) | 165 ( 68.5) |
| Female | 30 ( 38.0) | 46 ( 28.4) | 76 ( 31.5) |
| Race, N (%) | | | |
| Asian | 2 ( 2.5) | 3 ( 1.9) | 5 ( 2.1) |
| Black or African American | 1 ( 1.3) | 2 ( 1.2) | 3 ( 1.2) |
| White | 76 ( 96.2) | 157 ( 96.9) | 233 ( 96.7) |
| Ethnicity – Hispanic / Latino, N (%) | | | |
| Not Hispanic / Latino | 77 ( 97.5) | 159 ( 98.1) | 236 ( 97.9) |
| Hispanic / Latino | 1 ( 1.3) | 0 ( 0.0) | 1 ( 0.4) |
| Missing | 1 ( 1.3) | 3 ( 1.9) | 4 ( 1.7) |
| Age [years] | | | |
| Mean (SD) | 74.9 (4.2) | 74.9 (4.4) | 74.9 (4.3) |
| Age groups [years], N (%) | | | |
| <75 | 43 ( 54.4) | 91 ( 56.2) | 134 ( 55.6) |
| ≥75 | 36 ( 45.6) | 71 ( 43.8) | 107 ( 44.4) |
| Baseline weight [kg] | | | |
| Mean (SD) | 84.37 (15.28) | 86.34 (16.38) | 85.70 (16.02) |
| Baseline BMI [kg/m$^2$] | | | |
| Mean (SD) | 29.80 (4.54) | 29.60 (4.74) | 29.67 (4.67) |
| Baseline BMI, categorical [kg/m$^2$], N (%) | | | |
| <25 | 11 ( 13.9) | 24 ( 14.8) | 35 ( 14.5) |
| ≥25 to <30 | 32 ( 40.5) | 72 ( 44.4) | 104 ( 43.2) |
| ≥30 | 36 ( 45.6) | 66 ( 40.7) | 102 ( 42.3) |
| Baseline eGFR (MDRD staging)[1], N (%) | | | |
| Normal renal function | 15 ( 19.0) | 36 ( 22.2) | 51 ( 21.2) |
| Mild renal impairment | 42 ( 53.2) | 83 ( 51.2) | 125 ( 51.9) |
| Moderate renal impairment | 21 ( 26.6) | 41 ( 25.3) | 62 ( 25.7) |
| Severe renal impairment and beyond | 1 ( 1.3) | 2 ( 1.2) | 3 ( 1.2) |

BMI = body mass index, eCcr = estimated creatinine clearance rate, eGFR = estimated glomerular filtration rate, MDRD = modification of diet in renal disease, N = number of patients, SD = standard deviation

1 The degree of renal impairment based on eGFR was calculated by the MDRD formula: normal renal function ≥90 mL/min/1.73m$^2$, mild renal impairment 60 to <90 mL/min/1.73m$^2$, moderate renal impairment 30 to <60 mL/min/1.73m$^2$, and severe renal impairment, including end-stage renal disease <30 mL/min/1.73m$^2$

**Table 16. Baseline efficacy variables - FAS**

| | Placebo | Linagliptin | Total |
|---|---|---|---|
| Number of patients | 78 (100.0) | 160 (100.0) | 238 (100.0) |
| Baseline $HbA_{1c}$ [%] | | | |
| Mean (SD) | 7.70 (0.70) | 7.82 (0.78) | 7.78 (0.76) |
| Baseline $HbA_{1c}$, categorical, N (%) | | | |
| <7.0% | 6 (7.7) | 11 (6.9) | 17 (7.1) |
| 7.0% to <8.0% | 52 (66.7) | 91 (56.9) | 143 (60.1) |
| 8.0% to <9.0% | 15 (19.2) | 45 (28.1) | 60 (25.2) |
| ≥9.0% | 5 (6.4) | 13 (8.1) | 18 (7.6) |
| Baseline FPG [mg/dL] | | | |
| Mean (SD) | 144.1 (29.6) | 152.7 (28.7) | 149.9 (29.2) |

**Table 17. Glucose-lowering treatment at screening - FAS**

| | Placebo | Linagliptin | Total |
|---|---|---|---|
| Number of patients | 78 | 160 | 238 |
| Number of prior antidiabetes drugs, N (%) | | | |
| 1 | 29 (37.2) | 66 (41.3) | 95 (39.9) |
| 2 | 49 (62.8) | 84 (52.5) | 133 (55.9) |
| 3 | 0 (0.0) | 10 (6.3) | 10 (4.2) |
| Antidiabetes drugs at visit 1, N (%) | | | |
| Metformin, N (%) | 69 (88.5) | 133 (83.1) | 202 (84.9) |
| Sulphonylurea, N (%) | 43 (55.1) | 94 (58.8) | 137 (57.6) |
| Alpha–glucosidase inhibitor, N (%) | 0 (0.0) | 1 (0.6) | 1 (0.4) |
| Glinide, N (%) | 0 (0.0) | 1 (0.6) | 1 (0.4) |
| Insulin, N (%) | 15 (19.2) | 35 (21.9) | 50 (21.0) |
| Total daily dose of metformin [mg], mean (SD) | 1748.55 (628.61) | 1764.29 (647.39) | 1758.91 (639.51) |
| Total daily dose of metformin, categorical, N (%) | | | |
| <1500 | 14 (20.3) | 31 (23.3) | 45 (22.3) |
| =1500 | 19 (27.5) | 20 (15.0) | 39 (19.3) |
| >1500 to <2000 | 5 (7.2) | 13 (9.8) | 18 (8.9) |
| ≥2000 | 31 (44.9) | 69 (51.9) | 100 (49.5) |

Note that the table above shows glucose-lowering treatment at screening, not at randomisation.

The treatment groups were comparable in terms of the time since diagnosis of diabetes. More than half of the patients in both groups had been diagnosed with diabetes more than 10 years previously (53.8% placebo; 55.6% linagliptin). 1.9% of patients in the linagliptin group were diagnosed less than 1 year previously. The time since diagnosis of diabetes is summarised for the FAS in the table below.

**Table 18. Time since diagnosis of diabetes - FAS**

| | Placebo | Linagliptin | Total |
|---|---|---|---|
| Number of patients | 78 (100.0) | 160 (100.0) | 238 (100.0) |
| Time since diagnosis of diabetes, N (%) | | | |
| ≤ 1 year | 0 (0.0) | 3 (1.9) | 3 (1.3) |
| >1 to ≤5 years | 7 (9.0) | 20 (12.5) | 27 (11.3) |
| >5 to ≤ 10 years | 29 (37.2) | 48 (30.0) | 77 (32.4) |
| >10 years | 42 (53.8) | 89 (55.6) | 131 (55.0) |

Overall, more patients in the linagliptin group had microvascular disease (i.e., diabetic retinopathy, nephropathy, neuropathy) compared with the placebo group (25.3% placebo; 30.2% linagliptin); whereas more patients in the placebo group had macrovascular disease (coronary artery disease, peripheral artery occlusive disease, cerebrovascular disease and hypertension) compared with the linagliptin group (89.9% placebo; 85.8% linagliptin). Relevant concomitant diagnoses related to diabetes are summarised for the treated set in the table below.

**Table 19. Relevant medical history – Treated set**

| | Placebo | Linagliptin | Total |
|---|---|---|---|
| Number of patients, N (%) | 79 (100.0) | 162 (100.0) | 241 (100.0) |
| Patients with | | | |
| Diabetic retinopathy, N (%) | 7 (8.9) | 17 (10.5) | 24 (10.0) |
| Diabetic nephropathy, N (%) | 4 (5.1) | 13 (8.0) | 17 (7.1) |
| Diabetic neuropathy, N (%) | 13 (16.5) | 32 (19.8) | 45 (18.7) |
| Diabetic foot, N (%) | 1 (1.3) | 8 (4.9) | 9 (3.7) |
| Coronary artery disease, N (%) | 23 (29.1) | 36 (22.2) | 59 (24.5) |
| Peripheral artery occlusive disease, N (%) | 5 (6.3) | 14 (8.6) | 19 (7.9) |
| Cerebrovascular disease, N (%) | 6 (7.6) | 11 (6.8) | 17 (7.1) |
| Hypertension, N (%) | 71 (89.9) | 134 (82.7) | 205 (85.1) |
| Microvascular disease[1], N (%) | 20 (25.3) | 49 (30.2) | 69 (28.6) |
| Macrovascular disease[2], N (%) | 71 (89.9) | 139 (85.8) | 210 (87.1) |

Note that a patient could have more than one concomitant diagnosis related to diabetes at baseline.
1 Microvascular disease includes diabetic retinopathy, nephropathy, neuropathy.
2 Macrovascular disease includes coronary artery disease, peripheral artery occlusive disease, cerebrovascular disease and hypertension.

Mean health survey data were similar in the two treatment groups as baseline.

## Outcomes and estimation

Primary endpoint

The primary endpoint was the change from baseline in HbA1c after 24 weeks of treatment. The change in HbA1c from baseline in both groups over time is shown in the figure below. As shown in the table below the estimated treatment difference between linagliptin (n=160) and placebo (n=78), calculated as the adjusted mean change from baseline in HbA1c at Week 24, was -0.64% (95% CI [-0.81; -0.48], p<0.0001), demonstrating superiority of linagliptin over placebo in the reduction of HbA1c. Sensitivity analyses on the PPS last observation carried forward (LOCF) analysis set confirmed these results.

**Figure 7. Unadjusted HbA1c mean change from baseline over time – FAS (LOCF)**

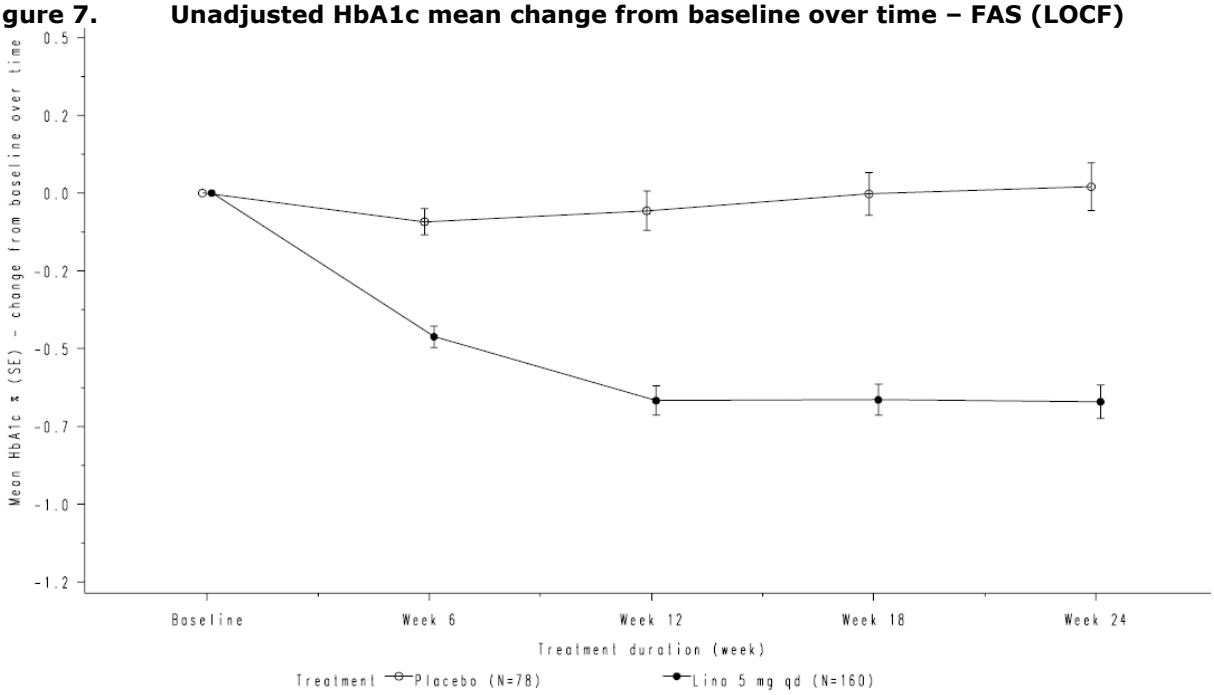



**Table 20. Change in HbA1c (%) from baseline at Week 24 – FAS (LOCF)**

| | Placebo | Linagliptin |
|---|---|---|
| Number of patients | 78 | 160 |
| Number of patients analysed | 78 | 160 |
| Baseline | | |
| Mean (SE) | 7.70 (0.08) | 7.82 (0.06) |
| Change from baseline | | |
| Mean (SE) | 0.02 (0.08) | −0.67 (0.05) |
| Adjusted[1] mean (SE) | 0.04 (0.07) | −0.61 (0.06) |
| Comparison vs. placebo (difference linagliptin – placebo) | | |
| Adjusted[1] mean (SE) | | −0.64 (0.08) |
| 95% confidence interval | | ( −0.81, −0.48) |
| p-value | | <0.0001 |

[1] Model includes continuous baseline $HbA_{1c}$, prior use of insulin, and treatment
SE = Standard error

Secondary endpoints

The differences in treatment groups in adjusted mean changes from baseline were -0.35% 95% CI [-0.45; -0.24] at Week 6 and -0.57% 95% CI [-0.71; -0.43] at Week 12. The difference between the treatment groups in mean change in HbA1c was sustained beyond 12 weeks, even though dose adjustment in background therapy was allowed after this time. The differences between the placebo and linagliptin groups in adjusted mean (±SE) change from baseline in HbA1c was for patients aged <75 years -0.58 (±0.11) and for patients aged ≥75 years -0.73 (±0.12).

There was a statistically significant difference between the linagliptin and placebo group in reduction in FPG. The estimated difference in the adjusted mean change from baseline to Week 24 in FPG between linagliptin and placebo was -20.7 mg/dL 95% CI= [-30.2; -11.2] (p<0.0001). The difference between the groups was sustained up to 24 weeks, even though changes in background therapy were permitted after Week 12. Sensitivity analyses confirmed the observed results.

Significantly more patients with baseline HbA1c ≥7% on linagliptin achieved the target treatment outcome of HbA1c <7.0% after 24 weeks of treatment (6/72 [8.3%] in placebo group; versus 58/149 [38.9%] in linagliptin group; p<0.0001). The proportion of patients with an HbA1c reduction of at least 0.5% at Week 24 was 12.8% of patients on placebo and 54.4% of patients on linagliptin. The table below provides an overview of the number of patients with categorical response after 24 weeks of treatment (FAS, non-completers considered failure (NCF).

**Table 21. Number of patients with categorical response at Week 24 – FAS (NCF)**

| | Placebo | | | Linagliptin | | |
|---|---|---|---|---|---|---|
| | n[1] | (%) | N[2] | n[1] | (%) | N[2] |
| Response criterion | | | | | | |
| $HbA_{1c}$<7.0% | 9 | (11.5) | 78 | 67 | (41.9) | 160 |
| Among patients with baseline $HbA_{1c}$ ≥7.0% | 6 | (8.3) | 72 | 58 | (38.9) | 149 |
| $HbA_{1c}$ reduction from baseline ≥0.5% | 10 | (12.8) | 78 | 87 | (54.4) | 160 |

[1] Number of patients with a response
[2] Number of patients analysed

Other endpoints

The proportion of patients requiring rescue therapy was greater for the placebo group compared with the linagliptin group (14.1% placebo; 4.4% linagliptin). The odds ratio of requiring rescue therapy overall was 0.214 (95% CI [0.073; 0.625], p= 0.0048). Similarly, a higher proportion of patients in the placebo group (13.5%) had at least one change in background glucose-lowering therapy between Week 12 and Week 24 compared with patients in the linagliptin group (5.8%).

The change in body weight during the study was small in both groups. The mean reduction in body weight in the linagliptin group was 0.2 kg. In the placebo group the reduction was slightly higher with 0.6 kg after 24 Weeks, see table below.

**Table 22. Descriptive statistics of body weight (kg) over time – TS (OC)**

| | Placebo (N=78) | | | | | | Lina 5 mg qd (N=160) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | N | Mean | SD | Min | Median | Max | N | Mean | SD | Min | Median | Max |
| OC | | | | | | | | | | | | |
| Baseline | 78 | 84.3 | 15.4 | 51 | 82.6 | 119 | 160 | 86.3 | 16.5 | 53 | 83.2 | 145 |
| Week 24 | 63 | 83.5 | 15.1 | 52 | 82.0 | 116 | 146 | 85.2 | 16.1 | 54 | 81.5 | 145 |
| Change from baseline at week 24 | 63 | -0.6 | 2.2 | -6 | -0.1 | 4 | 146 | -0.2 | 2.3 | -8 | 0.0 | 7 |

## Discussion on clinical efficacy

**Add-on to insulin extension of indication**

Three studies are supporting this extension of indication in combination with insulin. Study 1218.36 is a new pivotal Phase III study. Studies 1218.43 and 1218.63 have been assessed as part of the initial MAA for Trajenta and as part of Trajenta MEA 009 respectively.

In addition to insulin, most patients in the pivotal trial 1218.36 were taking metformin monotherapy (75.1% of all patients in EFF-1). The number of patients using other antidiabetic drugs was very low. Only 1.0% of patients were taking pioglitazone but not metformin, while 7.3% were taking both metformin and pioglitazone. Overall, 16% of the patients were taking neither metformin nor pioglitazone at screening. No patients were using SU. There were no notable differences among the groups. The MAH proposed initially the following new indication: "in combination with insulin (with or without other antidiabetic medications, metformin, pioglitazone, sulphonylurea) when this regimen alone, with diet and exercise, does not provide adequate glycaemic control". However linagliptin is not currently approved for use in combination with pioglitazone or SU. The safety and efficacy of linagliptin in combination with pioglitazone and SU cannot consequently be assessed appropriately in study 1218.36. The applicant recognized that the numbers of patients taking metformin and pioglitazone (92: 7.3%) and (13:1.0%), and taking pioglitazone without metformin included in study 1218.36 were limited. Consequently the MAH did reconsider the new indication wording initially proposed within this procedure and proposed a revised new indication now limited to the combination with insulin with or without metformin only. This was considered acceptable by the CHMP.

Efficacy was similar is most subgroups, however, there was a treatment by subgroup interaction for diabetes duration. In individuals with diabetes duration less than 1 year, the treatment effect of linagliptin was small. The CHMP agreed that the relative contribution of patients with diabetes duration of less than 1 year is relatively limited making up only 2% of the patient pool from EFF-1. This limits the precision of the point estimate. Nevertheless, patients with diabetes duration less than one year but already on insulin might differ from subjects with longer diabetes duration. In clinical practice, most patients who will be treated with a combination of linagliptin and insulin will have a longer diabetes duration.

For patients with renal impairment, the effect of linagliptin on fasting plasma glucose was small. However the decrease in HbA1c was clinically relevant.

**Use of linagliptin in elderly patients**

For the SmPC update with regard to the use in the elderly population, study 1218.63 was pivotal. The demographic characteristics of the study population were generally well balanced between the treatment groups and considered to be representative for elderly European T2DM patients. Mean age of participants was 74.9 years old (range 70 - 91 years). There was no increased percentage of discontinuations with linagliptin.

The analysis of the primary endpoint showed superiority of linagliptin versus placebo with an adjusted mean treatment difference of −0.64% 95% CI [-0.81; -0.48], ($p<0.0001$) for change in HbA1c from baseline to 24 weeks. The results in study 1218.63 are consistent with the results in earlier studies with linagliptin in younger patients (mean ages ranging from 55.7 to 58.1 years) with adjusted mean treatment differences in the change from baseline HbA1c ranging between -0.51% and -0.69%. This demonstrates that the efficacy in the elderly population is similar to that in the general population with T2DM.

## Conclusion on clinical efficacy

**Add-on to insulin extension of indication**

The design of the main study, study 1218.36, was considered acceptable by the CHMP. Study 1218.43 and study 1218.63 had been assessed as part of Trajenta initial MAA and as part of Trajenta MEA 009 respectively.

There was no increased percentage of discontinuations with linagliptin. The treatment effect was similar in men and women, as well as in Asians and Whites.

The efficacy of linagliptin as add-on to insulin was modest but statistically significant and clinically relevant. As most patients who will be treated with linagliptin in combination with insulin will have diabetes duration of more than one year, the observed smaller reduction of HbA1c in the subgroup of patients with diabetes duration of less than one year is not of concern in clinical practice.

For patients with renal impairment, the effect of linagliptin on fasting plasma glucose was small; nevertheless, the decrease in HbA1c was clinically relevant.

**Use of linagliptin in elderly patients**

Study 1218.63 demonstrated the beneficial blood glucose lowering effects of linagliptin in the elderly population. The benefit/risk balance in this elderly study population group was comparable to the younger T2DM age groups. The CHMP did not agree to delete the following statement from section 4.4 of the SmPC: "Clinical experience with patients > 75 years of age is limited" but instead recommended to amend it as follows: "Clinical experience with patients > 80 years of age is limited and caution should be exercised when treating this population."

## 2.3.2. Clinical safety aspects

**Add-on to insulin extension of indication**

This extension of indication is supported by safety data from 22 studies performed in patients with T2DM, including 14 Phase III trials, 5 Phase II trials, and 3 Phase I studies. Not included into this application are the data of the 22 Phase I trials that had been part of the initial linagliptin submission subsuming 20 trials performed in healthy volunteers, 1 study in non-diabetic and diabetic patients with renal impairment, and 1 study in non-diabetic patients with hepatic impairment.

To permit a structured analysis of safety data, the trials were categorised into 6 study groupings, SAF-1 to SAF-6, with the aim of grouping trials of similar designs, durations, and patient populations. Analyses of pooled data from several studies were performed in SAF-1, SAF-2, SAF-3, and SAF-6. The other 2 safety groupings SAF-4 and SAF-5 comprise data of 1 study each. SAF-3 to SAF-6 include the patients with insulin background therapy and are thus the important safety groupings for this submission. SAF-1 and SAF-2 present clinical safety data for linagliptin independent of the background medication; these 2 safety groupings have been updated from the initial linagliptin submission.

SAF-3 is the most pertinent set for this extension of indication; it comprises all patients who had received insulin background treatment, i.e. all patients from study 1218.36 and the subsets of insulin-treated patients from studies 1218.43 and 1218.63. SAF-4 represents the pivotal safety data and includes all patients that participated in trial 1218.36. SAF-5 comprises only those renally impaired patients in study 1218.43 that had received insulin and concomitantly linagliptin or placebo, representing 82% of the treated participants in that study. SAF-6 includes all patients who were 70 years of age or older and who received insulin and concomitantly linagliptin or placebo in trials 1218.63 and 1218.36. As such, SAF-6 comprises 21% of the patients treated in study 1218.63 and 16% of the patients treated in the pivotal study 1218.36.

SAF-1 (all studies in patients with T2DM) and SAF-2 (placebo-controlled studies with linagliptin 5 mg) represent updated safety groupings from the initial linagliptin MAA. SAF-1 comprises all patients who received linagliptin in clinical trials (n=6602); among them, 5955 patients received linagliptin 5 mg. Thereby, SAF-1 comprises 1915 patients more (all on linagliptin 5 mg) than the respective study grouping in the initial linagliptin submission. SAF-2, the grouping of the placebo-controlled trials, profiles linagliptin 5 mg against placebo. This grouping entails 4302 patients having received treatment with linagliptin 5 mg and therefore 1736 linagliptin-treated patients more than the same safety grouping in the initial linagliptin submission. Whereas SAF-2 includes patients from the placebo groups, patients from the various comparator groups are not displayed for SAF-1. As the largest set, SAF-1 was used to determine the frequency of events of special interest and to identify rare adverse events.

Since SAF-3 is the largest and most comprehensive placebo-controlled grouping for the analysis of patients receiving insulin and linagliptin concomitantly, subgroup analyses were based on this set. Furthermore, in addition to the subgroups analysed for efficacy, the influence of the concomitant use of P-gp inhibitors, CYP-3A4 inhibitors, and ACE inhibitors was analysed for SAF-2. Long-term safety data over 52 weeks of treatment are available from SAF-3 based on the 52-week data of studies 1218.36 and 1218.43.

The safety groupings overlap substantially in regard to patients who received linagliptin 5 mg: SAF-2 (placebo-controlled studies) comprises 72% of the patients in SAF-1 (all studies in patients with T2DM). SAF-3 (placebo-controlled studies with insulin background) is a subset of SAF-2 (17% of SAF-2). In turn, SAF-4 (pivotal trial with basal insulin) is a subset of SAF-3 comprising 88% of the patients included in SAF-3. Also SAF-5 and SAF-6 are subsets of SAF-3.

SAFs 4, 5, and 6 correspond to the 3 efficacy groupings EFF-1, EFF-2, and EFF-3, respectively, allowing a direct comparison of efficacy and safety results for each of these groupings. The different study groupings are summarized below.

**Table 23. Grouping of studies for the analysis of safety - TS**

| Shorthand | Characteristics of grouping (categories of analysis) | Treatment durations | Studies (without preceding '1218' ) | Number of patients treated |
|---|---|---|---|---|
| SAF-1 | All trials with linagliptin in patients with T2DM (linagliptin 5 mg vs. linagliptin all doses) | 12 days to 104 weeks | .2, .3, .5, .6, .12, .15, .16, .17, .18, .20, .23, .35, .36, .37, .40, .43, .46 .50, .52, .55, .62. ,63 (pooled analysis) | Lina 5 mg: 5955 Lina total: 6602 |
| SAF-2 | Placebo-controlled trials with linagliptin 5 mg in patients (placebo vs. linagliptin 5 mg) | 12 days to 52 weeks | .2, .3, .5, .6, .15, .16, .17, .18, .23, .35, .36, .37, .43, .46, .50, .52, .62, .63 (pooled analysis) | Placebo: 2364 Lina: 4302 |
| SAF-3 | Patients from placebo-controlled trials with insulin background (placebo vs. linagliptin 5 mg) | 24 weeks to 52 weeks | .36, .43, .63 (pooled analysis) | Placebo: 700 Lina: 720 |
| SAF-4 | Pivotal placebo-controlled trial with basal insulin in patients (placebo vs. linagliptin 5 mg) | 52 weeks | .36 (by-study analysis) | Placebo: 630 Lina: 631 |
| SAF-5 | Patients with severe renal impairment and insulin background (placebo vs. linagliptin 5 mg) | 52 weeks | .43 (subset of study population) | Placebo: 55 Lina: 54 |
| SAF-6 | Elderly patients with insulin background (placebo vs. linagliptin 5 mg) | 24 weeks | .63, .36, patients ≥70 years (pooled analysis) | Placebo: 121 Lina: 126 |

The treated set (TS) was used for the analysis of safety and comprised all patients who received at least one dose of study medication. Concomitant therapies were coded using the World Health Organization (WHO) Drug Dictionary, version 11.MAR. Concomitant diagnoses and adverse events were coded using the Medical Dictionary of Regulatory Affairs (MedDRA) version 14.0, with system organ class (SOC) and preferred term (PT).

### *Patient exposure*

The largest set, SAF-1, comprised 5955 patients that had been treated with linagliptin 5 mg/day with a median treatment duration of 430 days; of these, 1848 patients were treated for at least 102 weeks. In the set of placebo-controlled trials (SAF-2), exposure was similar in both treatment groups and a sizeable proportion of patients (placebo 5.2%, linagliptin 5.4%) were exposed for at least 78 weeks. In SAF-3 (all patients who received insulin background), a considerable proportion of patients (placebo 31.1%, linagliptin 31.8%) had been treated with linagliptin 5 mg for at least one year. The majority of these patients are from the pivotal study 1218.36 (SAF-4). The table below summarises the exposure data for SAFs 1 to 3.

**Table 24. Exposure (treatment duration) to study medication for SAF-1, SAF-2, and SAF-3 - TS**

| | SAF-1 | SAF-2 | | SAF-3 | |
|---|---|---|---|---|---|
| | Linagliptin 5 mg | Placebo | Linagliptin 5 mg | Placebo | Linagliptin 5 mg |
| Patients, N (%) | 5955 (100.0) | 2364 (100.0) | 4302 (100.0) | 700 (100.0) | 720 (100.0) |
| Exposure categories, N (%) | | | | | |
| ≥24 weeks | 4686 (78.7) | 1623 (68.7) | 2799 (65.1) | 631 (90.1) | 664 (92.2) |
| ≥52 weeks | 3446 (57.9) | 382 (16.2) | 525 (12.2) | 218 (31.1) | 229 (31.8) |
| ≥78 weeks | 2645 (44.4) | 122 (5.2) | 231 (5.4) | 0 | 0 |
| ≥102 weeks | 1848 (31.0) | 0 | 0 | 0 | 0 |
| Duration of treatment exposure [days] | | | | | |
| Mean (±SD) | 427 (257.3) | 209 (135.8) | 194 (126.8) | 292 (116.5) | 297 (111.8) |
| Median (min, max) | 430 (1, 794) | 171 (1, 580) | 169 (1, 582) | 295 (1, 531) | 298 (3, 531) |
| Patient years | 6965.9 | 1355.9 | 2284.0 | 559.0 | 585.1 |

For SAF-4 (pivotal study with basal insulin), the majority of patients had been exposed for at least 24 weeks, about a third of patients were treated for at least 52 weeks. The median exposure in SAF-5, the set of patients with severe renal impairment and insulin background, was about 1 year. The median exposure in the set of elderly patients with insulin background therapy (SAF-6) was longer in the placebo group (293 days) than in the linagliptin group (244 days). The exposure data for SAFs 4 to 6 are summarised in the table below.

**Table 25. Exposure (treatment duration) to study medication for SAF-4, SAF-5, and SAF-6 - TS**

| | SAF-4 | | SAF-5 | | SAF-6 | |
|---|---|---|---|---|---|---|
| | Placebo | Linagliptin 5 mg | Placebo | Linagliptin 5 mg | Placebo | Linagliptin 5 mg |
| Patients, N (%) | 630 (100.0) | 631 (100.0) | 55 (100.0) | 54 (100.0) | 121 (100.0) | 126 (100.0) |
| Exposure categories, N (%) | | | | | | |
| ≥24 weeks | 580 (92.1) | 598 (94.8) | 42 (76.4) | 47 (87.0) | 103 (85.1) | 109 (86.5) |
| ≥52 weeks | 186 (29.5) | 197 (31.2) | 32 (58.2) | 32 (59.3) | 34 (28.1) | 26 (20.6) |
| Duration of treatment exposure [days] | | | | | | |
| Mean (±SD) | 295 (114.5) | 303 (110.0) | 290 (132.6) | 315 (103.9) | 283 (122.0) | 265 (107.5) |
| Median (min, max) | 292 (4, 531) | 304 (3, 531) | 364 (1, 384) | 364 (29, 396) | 293 (4, 527) | 244 (11, 531) |
| Patient years | 508.8 | 523.6 | 43.6 | 46.6 | 93.8 | 91.3 |

**Disposition – premature discontinuation**

For the key safety set SAF-3 (patients with insulin background), the rates of premature discontinuations were higher in the placebo group (13.4%) than in the linagliptin group (10.1%) as was the rate of premature discontinuations due to adverse events (4.7% vs. 3.9%). This was corroborated by the analysis of disposition in SAF-2 (placebo-controlled studies) with premature discontinuation rates of 13.7% (placebo) and 9.5% (linagliptin) including 3.8% (placebo) and 3.2% (linagliptin) of premature discontinuations due to adverse events.

Higher discontinuation rates in the placebo groups were consistently seen across all subgroups in SAF-3. This applies to the age categories (≤50, 51 to <65, 65 to <75, ≥75 years of age), gender subgroups (male, female), the different geographic regions (Europe, North America, South America, Asia), BMI categories (<30, ≥30 kg/$m^2$), and the renal function subgroups (≥90 mL/min, 60 to <90 mL/min, 30 to <60 mL/min, and <30 mL/min). The only exception was in the small subgroup of Black patients (in total n=90) where the frequency of premature discontinuation was lower with placebo (10.9%) than with linagliptin (15.9%), however, the frequency of discontinuations due to adverse events was nevertheless higher in the placebo group (6.5% vs. 4.5%). The main reason for the overall disparity in Black patients was a difference in the proportion of patients who refused to continue with study medication (0% vs. 4.5%, i.e. 2 patients). A particularly high discontinuation rate in both treatment groups was observed in the geographic region of North America where 24.6% (placebo) and 20.0% (linagliptin) of patients discontinued prematurely.

For patients with severe renal impairment and insulin background (SAF-5), the frequencies of premature discontinuations were more than twice as high as for the population of patients without renal insufficiency (SAF-3) with 27.3% in the placebo group and 25.9% in the linagliptin group. The most frequent reason was the occurrence of adverse events (placebo 16.4%, linagliptin 13.0%). Differences between treatments were also seen in the frequency of patients that were lost to follow-up (placebo 5.5%, linagliptin 1.9%) and for the proportions of patients refusing to continue with study medication (placebo 1.8%, linagliptin 7.4%).

Also for elderly patients (≥70 years) with insulin background therapy (SAF-6), the frequencies of premature discontinuations were higher in the placebo group than in the linagliptin group (14.0% vs. 7.1%). The most frequent reasons were the occurrence of an adverse event (placebo 3.3%, linagliptin 4.0%) and the refusal to continue with trial medication (placebo 5.0%, linagliptin 1.6%).

### *Adverse events*

This section concentrates on the analysis of SAF-3 (patients with insulin background) as this is the safety grouping most relevant for this application. The analyses for SAF-3 are complemented and contrasted where relevant with the data of the other safety groupings.

Overall, the frequencies of patients reporting an adverse event were comparable between treatment groups: about 75% of patients in both treatment groups reported an adverse event. Also the proportions of patients with adverse events of severe intensity, of non-serious significant adverse events (pre-specified in the study protocols), and of serious adverse events were similar in both treatment groups. The frequencies of adverse events that were considered drug-related by the investigators and of adverse events leading to discontinuation of trial drug were slightly higher in the placebo group than in the linagliptin group (see table below).

**Table 26. Adverse event overall summary for SAF-3 (placebo-controlled studies with insulin background) - TS**

| | Placebo<br><br>N (%) | Linagliptin 5 mg<br>N (%) |
|---|---|---|
| Patient years of exposure | 559.0 | 585.1 |
| Number of patients | 700 (100.0) | 720 (100.0) |
| Patients with any AE | 523 (74.7) | 533 (74.0) |
| Patients with AEs of severe intensity | 54 (7.7) | 55 (7.6) |
| Patients with investigator-defined drug-related AEs | 142 (20.3) | 134 (18.6) |
| Patients with AEs leading to discontinuation of study drug | 30 (4.3) | 26 (3.6) |
| Patients with significant AEs (pre-specified)[1] | 15 (2.1) | 18 (2.5) |
| Patients with serious AEs | 82 (11.7) | 78 (10.8) |

[1] Pre-specified events (in the study protocols): i.e. hypersensitivity reactions, renal events, and hepatic events (based on investigator reporting). Only non-serious adverse events are included in this summary of significant adverse events.

When the set of patients who received insulin (SAF-3) is compared with the overall set of patients from placebo-controlled studies (SAF-2), it becomes apparent that the overall incidence of adverse events was higher in patients taking insulin (SAF-3) than in SAF-2 (placebo 63.1%, linagliptin 60.3%), irrespective of the treatment groups. Serious adverse events were almost twice as frequent in patients taking insulin than in patients in SAF-2 (placebo 5.9%, linagliptin 4.8%). Similar differences were seen for adverse events of severe intensity. These findings may be related to the difference in demographic characteristics of the 2 analysis groupings. Patients in SAF-3 were on average about 2 years older, had been diagnosed with diabetes for a longer time (>5 years SAF-2: 57.5%, SAF-3: 86.7%), and had a substantially higher frequency of diabetic complications (e.g. diabetic neuropathy SAF-2: 16.8%, SAF-3: 31.8%). This notwithstanding, the frequencies of adverse events leading to premature discontinuation (SAF-2: placebo 4.4%, linagliptin 3.3%) and of (pre-specified) significant adverse events (SAF-2: placebo 2.1%, linagliptin 2.0%) were similar for patients predominantly taking oral antidiabetics or no additional antidiabetics (SAF-2) and for patients taking insulin (SAF-3).

For SAF-3, the most frequently reported adverse events were in the SOCs metabolism and nutrition disorders (placebo 42.1%, linagliptin 39.9%), followed by infections and infestations (placebo 33.0%, linagliptin 33.2%), gastrointestinal disorders (placebo 15.7%, linagliptin 19.3%), and musculoskeletal and connective tissue disorders (placebo 17.3%, linagliptin 17.1%) (see table below). Apart from infections and infestations, these conditions were also among the most frequent concomitant diagnoses at screening.

For most system organ classes and preferred terms, the frequencies were similar in both groups or higher in the placebo group than in the linagliptin group. Only gastrointestinal disorders (placebo 15.7%, linagliptin 19.3%) were considerably more frequent in the linagliptin group. This difference between treatment groups was mainly due to higher incidences of diarrhoea (placebo 3.9%, linagliptin 5.6%), nausea (placebo 1.9%, linagliptin 3.3%), and constipation (placebo 1.3%, linagliptin 2.8%) in the linagliptin group.

Only very few preferred terms exhibited frequencies that were more than 1% higher in the linagliptin group than in the placebo group. These were nasopharyngitis (placebo 7.4%, linagliptin 9.6%), diarrhoea (placebo 3.9%, linagliptin 5.6%), constipation (placebo 1.3%, linagliptin 2.8%), and nausea (placebo 1.9%, linagliptin 3.3%). The incidences of hypoglycaemia were similar between treatment groups. Among these adverse events, constipation was identified as a new side effect, potentially related to linagliptin as add-on to insulin.

**Table 27. Frequency of patients with adverse events occurring in more than 2.5% of patients in either treatment group at the PT or SOC level, sorted by frequency in the linagliptin group, for SAF-3 (placebo-controlled studies with insulin background) - TS**

| System organ class<br>Preferred term | Placebo<br><br>N (%) | Linagliptin<br>5 mg<br>N (%) |
|---|---|---|
| Patient years of exposure | 559.0 | 585.1 |
| Number of patients | 700 (100.0) | 720 (100.0) |
| Total with AEs | 523 (74.7) | 533 (74.0) |
| Metabolism and nutrition disorders | 295 (42.1) | 287 (39.9) |
| Hypoglycaemia | 199 (28.4) | 208 (28.9) |
| Hyperglycaemia | 93 (13.3) | 69 (9.6) |
| Hyperkalaemia | 20 (2.9) | 22 (3.1) |
| Infections and infestations | 231 (33.0) | 239 (33.2) |
| Nasopharyngitis | 52 (7.4) | 69 (9.6) |
| Urinary tract infection | 39 (5.6) | 32 (4.4) |
| Upper respiratory tract infection | 35 (5.0) | 31 (4.3) |
| Influenza | 27 (3.9) | 26 (3.6) |
| Bronchitis | 22 (3.1) | 21 (2.9) |
| Gastroenteritis | 21 (3.0) | 16 (2.2) |
| Gastrointestinal disorders | 110 (15.7) | 139 (19.3) |
| Diarrhoea | 27 (3.9) | 40 (5.6) |
| Nausea | 13 (1.9) | 24 (3.3) |
| Constipation | 9 (1.3) | 20 (2.8) |
| Musculoskeletal and connective tissue disorders | 121 (17.3) | 123 (17.1) |
| Back pain | 26 (3.7) | 28 (3.9) |
| Pain in extremity | 15 (2.1) | 20 (2.8) |
| Arthralgia | 26 (3.7) | 19 (2.6) |
| Nervous system disorders | 99 (14.1) | 98 (13.6) |
| Headache | 27 (3.9) | 29 (4.0) |
| Dizziness | 27 (3.9) | 28 (3.9) |
| General disorders and administration site conditions | 70 (10.0) | 76 (10.6) |
| Oedema peripheral | 16 (2.3) | 21 (2.9) |
| Injury, poisoning and procedural complications | 73 (10.4) | 72 (10.0) |
| Investigations | 62 (8.9) | 68 (9.4) |
| Skin and subcutaneous tissue disorders | 54 (7.7) | 57 (7.9) |
| Respiratory, thoracic and mediastinal disorders | 58 (8.3) | 56 (7.8) |

| | | |
|---|---|---|
| Cough | 23 (3.3) | 20 (2.8) |
| Vascular disorders | 48 (6.9) | 50 (6.9) |
| Hypertension | 29 (4.1) | 28 (3.9) |
| Renal and urinary disorders | 41 (5.9) | 49 (6.8) |
| Cardiac disorders | 42 (6.0) | 48 (6.7) |
| Eye disorders | 38 (5.4) | 43 (6.0) |
| Psychiatric disorders | 30 (4.3) | 29 (4.0) |
| Blood and lymphatic system disorders | 24 (3.4) | 17 (2.4) |
| Reproductive system and breast disorders | 19 (2.7) | 12 (1.7) |

## Adverse events in subgroups

As SAF-3 is the pool of studies comprising all patients who received concomitant treatment of linagliptin and insulin (or placebo and insulin), this is the most appropriate set for the analysis of subgroups. The following description focuses on imbalances disfavouring the linagliptin group.

**Age**

Four age subgroups were analysed (≤50, 51 to <65, 65 to <75, ≥75 years); the number of patients in the different categories varied from n=684 patients in the 51 to <65 years category to n=109 in the category of patients being 75 years of age or older. In all age categories were the overall incidences of adverse events similar in both treatment groups or higher with placebo than with linagliptin (for patients ≥75 years), and there was a modest tendency to higher overall frequencies of adverse event with more advanced age. For metabolism and nutrition disorders, the frequencies were similar between treatments or lower for linagliptin in all age categories. However, in the 51 to <65 year group, hypoglycaemia was somewhat more frequent in the linagliptin group (placebo 24.1%, linagliptin 28.4%). Consistent with the overall population, gastrointestinal disorders were more frequent in the linagliptin groups in all age categories but the group of the oldest patients (≥75 years). The largest treatment difference was seen in the ≤50 years age group (placebo 19.0%, linagliptin 24.0%). The differences were predominantly due to higher incidences of abdominal pain, constipation, diarrhoea, and nausea in the linagliptin groups. Higher frequencies of adverse events in the linagliptin group were seen for general disorders and administration site conditions in the ≥75 years category (11.1% vs. 18.2%) as well as for injury, poisoning, and procedural complications in the oldest patients (9.3% vs. 25.5%). Investigations were more frequent with linagliptin in the <50 years (6.0% vs. 10.6%) and the ≥75 years (3.7% vs. 14.5%) categories, without an obvious increase in a single preferred term. There was no obvious increase of renal and urinary disorders with age. In summary there is no evidence for an influence of age on the occurrence of adverse events with linagliptin treatment.

**Gender**

The overall incidences of adverse events were similar in men and women and generally incidences between treatment groups were also similar. While the frequencies in the SOC infections and infestations were similar between treatment groups in both men and women, a higher frequency of nasopharyngitis in the linagliptin group was observed in men (placebo 5.1%, linagliptin 11.3%) but not in women (placebo 10.1%, linagliptin 7.6%).

**Race**

SAF-3 predominantly comprised patients of White race (n=1143), whereas the numbers of patients of Asian (n=187) and especially Black race (n=90) were small. The overall incidences of adverse events appeared slightly lower in White patients (placebo 72.5%, linagliptin 73.2%) than in Asian (placebo 86.0%, linagliptin 73.4%) and Black patients (placebo 78.3%, linagliptin 86.4%), and the incidences in the treatment groups were balanced for White patients but not for Asian and Black patients. For all 3 race groups, gastrointestinal disorders were more frequent with linagliptin treatment (White: 14.4% vs. 17.0%, Black 13.0% vs. 20.5%) with the largest difference seen in Asian patients (24.7% vs. 33.0%).

**Ethnicity**

Most patients were Non-Hispanic/Latino (n=1139), and the group of Hispanic/Latino patients was comparatively small (n=281). Overall incidences of adverse events were similar in Non-Hispanic/Latino patients (placebo 74.3%, linagliptin 75.0%) and slightly lower in the linagliptin group of Hispanic/Latino patients (placebo 76.4%, linagliptin 69.9%). Nevertheless, eye disorders (placebo 4.1%, linagliptin 9.0%), in particular diabetic retinopathy (placebo 1.4%, linagliptin 3.8%), appeared to be more frequent with linagliptin in Hispanic patients, as were a few other adverse events such as dizziness (placebo 1.4%, linagliptin 4.5%).

**Geographic region**

The majority of patients in SAF-3 came from Europe (n=610) while the other regions were represented by smaller numbers of patients (South America n=327, North America n=303, Asia n=180). There appeared to be a certain degree of variation in the overall frequencies of adverse events with the lowest incidence in the linagliptin group for Europe (placebo 65.5%, linagliptin 67.0%) and the highest for South America (placebo 80.6%, linagliptin 80.2%). Some imbalances between treatments appear to be confined to certain regions and were generally in agreement with the analysis of the race and ethnicity subgroups. For gastrointestinal disorders a particularly large difference between treatment groups was seen in Asia (placebo 21.5%, linagliptin 33.3%) and to a minor extent in South America (placebo 13.3%, linagliptin 19.1%) and Europe (placebo 8.9%, linagliptin 12.1%) and in reverse for North America (placebo 29.7%, linagliptin 25.5%). The higher incidences with linagliptin were brought about by higher incidences of constipation and diarrhoea. The incidence of metabolism and nutrition disorders differed substantially between regions with the lowest incidences in Europe (placebo 32.6%, linagliptin 31.4%) and the highest incidence in South America (placebo 52.7%, linagliptin 48.8%); the treatment groups however were balanced in all regions. The incidences of hypoglycaemia varied greatly between regions with particularly high incidences in Asia (placebo 38.7%, linagliptin 36.8%) and low incidences in Europe (placebo 18.8%, linagliptin 22.2%). Imbalances disfavouring the linagliptin group were also seen for infections and infestations for Europe (placebo 26.0%, linagliptin 29.7%) and North America (placebo 37.7%, linagliptin 45.5%), predominantly caused by higher incidences of nasopharyngitis, sinusitis, and tooth abscess. The SOC eye disorders showed a higher incidence in the linagliptin group in South America (5.5% vs. 12.3%), mainly due to higher incidences of cataract, diabetic retinopathy, and reduced visual acuity. For vascular disorders, an imbalance was seen only in North America (placebo 4.3%, linagliptin 9.7%) predominantly based on higher incidences of hypertension (placebo 2.2%, linagliptin 4.8%). A similar imbalance for hypertension was also seen in Asia (placebo 1.1%, linagliptin 4.6%).

**BMI**

The BMI subgroups (<30 kg/$m^2$, ≥30 kg/$m^2$) were generally well balanced and both for the overall incidences and for most SOCs, no difference between treatment groups and BMI categories were observed.

**Renal function**

Patients were grouped according to their renal function based on MDRD staging into patients with normal renal function (≥90 mL/min) and mild (60 to <90 mL/min), moderate (30 to <60 mL/min), and severe (<30 mL/min) renal impairment/end-stage renal disease. The majority of patients had either normal renal function (n=561) or mild renal impairment (n=596). The subgroups of patients with moderate (n=162) and severe (n=101) renal impairment were small and hence more likely to exhibit imbalances between treatment groups. The subgroup of patients with severe renal impairment had the highest mean age (64.2 years) of all renal function subgroups and comprised the largest proportion of patients who had been diagnosed with T2DM for more than 5 years (94.1%). As expected, almost all patients in this subgroup were categorised as having diabetic nephropathy (91.1%), and a majority of patients had diabetic neuropathy (58.4%).

As expected, there was a tendency to higher incidences of adverse events with decreasing renal function but incidences were broadly well balanced between treatment groups. The lowest overall incidences were seen for patients with normal renal function (placebo 68.3%, linagliptin 71.0%) and the highest incidences in patients with severe renal impairment (placebo 95.7%, linagliptin 98.1%). With regards to gastrointestinal disorders, differences between treatment groups were observed in patients with normal renal function (placebo 12.9%, linagliptin 19.4%) and were particularly marked in patients with severe renal impairment (placebo 19.1%, linagliptin 33.3%). The differences were mainly due to higher incidences of constipation, diarrhoea, nausea, and dry mouth in the linagliptin groups. For patients with normal renal function, there was no other SOC that showed imbalances between treatment groups. For patients with mild renal impairment, only minor imbalances between placebo and linagliptin treatment were seen. In the group of patients with moderate renal impairment, differences between treatment groups were mainly seen for nasopharyngitis (placebo 7.1%, linagliptin 13.0%) and gastroenteritis (placebo 2.4%, linagliptin 6.5%). As expected from the low sample size (1 patient represents ~ 2% of treatment group), the group of patients with severe renal impairment showed the highest number of imbalances between treatment groups. While incidences were generally comparable for most SOCs, differences were seen for injury, poisoning and procedural complications (placebo 14.9%, linagliptin 24.1%) mainly due to a higher occurrence of contusion (placebo 0%, linagliptin 5.6%) and for metabolism and nutrition disorders (placebo 70.2%, linagliptin 81.5%) due to a higher incidence of hypoglycaemia in the linagliptin group (placebo 46.8%, linagliptin 63.0%). These observations were consistent with the almost identical SAF-5 grouping of patients with severe renal impairment and insulin background treatment from study 1218.43. Importantly, as analysed in SAF-5, the incidences of mild and moderate symptomatic hypoglycaemia as well as severe hypoglycaemia requiring assistance were very similar in both treatment groups. In summary, there are no grounds to conclude that linagliptin treatment results in higher incidences of adverse events in patients with various degrees of renal function impairment.

**Concomitant medications**

Since the proportions of patients using P-gp, CYP-3A4, or ACE inhibitors at screening in SAF-3 were too small to permit subgroup analyses (placebo 4.6%, linagliptin 7.1%), the analysis of the subgroup of patients taking P-gp or CYP-3A4 inhibitors was based on SAF-2 (placebo-controlled trials). Overall, there was no indication for any linagliptin-specific effects when given in combination with medications from these classes.

**Analysis of hypoglycaemia**

The analysis of hypoglycaemic events for the different safety groupings SAF-1 to SAF-3 demonstrates that treatment with linagliptin does not lead to an increase of hypoglycaemic events, neither based on reported adverse events nor on investigator-reported hypoglycaemic events. This was true for all hypoglycaemic events irrespective of severity and particularly also for severe hypoglycaemic events, i.e. those requiring assistance. However and not surprisingly, as seen in SAF-3 (patients with insulin background), the incidences of hypoglycaemic events were higher than in SAF-1 and SAF-2 regardless of treatment. This was observed for all severity grades of hypoglycaemic events including severe events. The analysis of hypoglycaemias is summarised in the table below. Also in SAF-6 (elderly patients with insulin background), incidences of hypoglycaemic events were comparable in both treatment groups, with numerically lower incidences in the linagliptin group. This was true irrespective of severity of the events and also for severe hypoglycaemic events requiring assistance.

**Table 28. Frequency of patients with hypoglycaemic events by treatment for SAF-1, SAF-2, and SAF-3 - TS**

| | SAF-1 Lina 5 mg N (%) | SAF-2 Placebo N (%) | Lina 5 mg N (%) | SAF-3 Placebo N (%) | Lina 5 mg N (%) |
|---|---|---|---|---|---|
| Patient years of exposure | 6965.9 | 1355.9 | 2284.0 | 559.0 | 585.1 |
| Number of patients | 5955 (100.0) | 2364 (100.0) | 4302 (100.0) | 700 (100.0) | 720 (100.0) |
| Patients with hypoglycaemic adverse events of SSC 'hypoglycaemia'[1] | 743 (12.5) | 275 (11.6) | 471 (10.9) | 202 (28.9) | 211 (29.3) |
| Patients with investigator reported hypoglycaemic adverse events[2] | n.a. | 286 (13.3) | 484 (11.8) | 207 (29.6) | 214 (29.7) |
| Patients with any severe or symptomatic hypoglycaemic event with PG ≤70 mg/dL | n.a. | 193 (8.9) | 292 (7.1) | 157 (22.4) | 153 (21.3) |
| Patients with any severe or symptomatic hypoglycaemic event with PG <54 mg/dL | n.a. | 105 (4.9) | 145 (3.5) | 90 (12.9) | 84 (11.7) |
| Patients with any hypoglycaemic event requiring assistance ("severe")[3] | n.a. | 20 (0.9) | 19 (0.5) | 17 (2.4) | 13 (1.8) |

n.a. = not available, PG = Plasma Glucose

1 SSC hypoglycaemia is composed of HLT 'hypoglycaemic conditions NEC' and MedDRA PT 'blood glucose decreased'

2 Studies 1218.2, 1218.3 (phase I trials), 1218.5, 1218.6, 1218.37 (phase II trials) are excluded from the presentation of SAF-2 because investigator-defined hypoglycaemia was not documented.

3 Event requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions

## Other adverse events of special interest

The analysis of adverse events of special interest performed over SAFs 1 to 3 shows very good overall agreement and consistency in the magnitude of the incidences of adverse events of special interest. Overall, the frequencies were low, and only small differences between the treatment groups were noted. Within SAF-2 and SAF-3, pancreatitis occurred in numerically more patients in the linagliptin group than in the placebo group. The results of the analyses of adverse events of special interest are summarized in the table below.

**Table 29. Frequency of patients with adverse events of special interest based on narrow SMQs by treatment for SAF-1, SAF-2, and SAF-3 - TS**

| | SAF-1 Lina 5 mg N (%) | SAF-2 Placebo N (%) | Lina 5 mg N (%) | SAF-3 Placebo N (%) | Lina 5 mg N (%) |
|---|---|---|---|---|---|
| Patient years of exposure | 6965.9 | 1355.9 | 2284.0 | 559.0 | 585.1 |
| Number of patients | 5955 | 2364 | 4302 | 700 | 720 |
| Patients with hepatic events[1] | 205 (3.4) | 47 (2.0) | 76 (1.8) | 11 (1.6) | 17 (2.4) |
| Patients with hypersensitivity reactions[2] | 72 (1.2) | 15 (0.6) | 32 (0.7) | 8 (1.1) | 8 (1.1) |
| Patients with renal events[3] | 38 (0.6) | 18 (0.8) | 22 (0.5) | 15 (2.1) | 13 (1.8) |
| Patients with severe cutaneous adverse reactions[4] | 1 (0.0) | 0 | 1 (0.0) | 0 | 0 |
| Patients with pancreatitis[5] | 10 (0.2) | 1 (0.0) | 5 (0.1) | 1 (0.1) | 3 (0.4) |

1 Based on SMQs 'liver-related investigations, signs and symptoms', 'cholestasis and jaundice of hepatic origin', 'hepatitis, non-infectious', and 'hepatic failure, fibrosis, cirrhosis and other liver damage-related conditions'
2 Based on SMQs 'anaphylactic reaction', 'angioedema', and 'asthma bronchospasm'
3 Based on SMQ 'acute renal failure'
4 Based on SMQ 'severe cutaneous adverse reactions'
5 Based on SMQ 'acute pancreatitis' and PT 'pancreatitis chronic'.

**Analysis of malignancies**

Malignancies were analysed as adverse events of special interest in SAF-2. In each treatment group, 0.5% of patients were reported with events contributing to this narrow SMQ. The only preferred term that was reported in more than 1 patient in the linagliptin group was thyroid neoplasms, which was reported by 5 patients (0.1%) in the linagliptin group but none in the placebo group. The reported terms of these events refer to a thyroid nodule and do not qualify as malignancies; yet since they are coded as thyroid neoplasm, they were identified by the SMQ search. Four of these 5 patients participated in study 1218.36 and one in study 1218.18. All 5 events were non-serious and of mild to moderate intensity, required no therapy and were not considered to be drug-related (for 1 patient the relatedness assessment was missing). Laboratory data describing thyroid function were not available for these patients. At the CHMP's request, the MAH provided extensive data related to thyroid neoplasm and thyroid cancer. The numerical imbalance for benign thyroid neoplasm will be studied in ongoing and planned long term safety studies (ongoing study 1218.74 and study 1218.22). The results of these studies will be submitted for CHMP review. Oncological AE is already included as important missing information in the RMP but in addition the topic 'thyroid neoplasm' will be discussed in future PSURs. This was considered acceptable by the CHMP.

**Analysis of photosensitivity**

Because photosensitivity-related questions were raised by the CHMP in a previous submission, a special search was made for photosensitivity events based on 4 preferred terms out of the MedDRA HLT photosensitivity conditions. In SAF-1, 4 patients (0.1%) treated with linagliptin (all received 5 mg) were reported with such events. In SAF-2, there were 1 patient in the placebo group and 2 patients in the linagliptin group with a photosensitivity reaction.

**Analysis of adverse events over long-term treatment**

The identification of adverse events that may emerge during long-term treatment was based on the pivotal study 1218.36 and analysed by comparing safety data from the first 24 weeks with safety data obtained up to the cut-off date for the interim analysis. The difference in the overall incidence of adverse events between the 24-week analysis (placebo 66.3%, linagliptin 63.7%) and the analysis up to the interim cut-off date (placebo 72.5%, linagliptin 71.8%) was in line with the difference in exposure between these analyses; the mean exposure to linagliptin up to the cut-off date was about 1.8 times greater than the mean exposure up to 24 weeks. This was also the case for drug-related adverse events, adverse events leading to discontinuation, and serious adverse events. Apart from the overall increase in incidence of adverse events with longer exposure, there were no discernible differences in the pattern of adverse events by SOC and PT up to 24 weeks vs. until the interim cut-off date. Similarly, there was no evidence of an increased risk of hypoglycaemic events for patients treated with linagliptin beyond 24 weeks.

In the period following the first 24 weeks, an additional 3 patients treated with linagliptin vs. none receiving placebo were reported with urticaria, which is a hypersensitivity reaction and therefore an adverse event of special interest (during the first 24 weeks, 1 patient per treatment group was reported with urticaria). However, no urticaria cases were considered by the investigator to be related to study medication.

Overall, the safety data from trial 1218.36 analysed up to 24 weeks vs. including the period beyond support the conclusion that long-term treatment with linagliptin in patients on basal insulin therapy does not lead to clinically relevant increases in particular adverse events.

**Summary of identified side effects**

A special exercise was undertaken to identify any side effects that are possibly associated with linagliptin treatment using the same algorithm as that used for the initial linagliptin submission:

- Adverse events with an incidence ≥2% with linagliptin and a 2-fold higher incidence than in the placebo group (or an incidence of zero in the placebo group), and/or
- Adverse events that were likely related based on medical plausibility, and/or
- Adverse events that had a consistent pattern over antidiabetic background treatments, i.e. the incidence in the linagliptin groups was consistently higher than in the placebo groups for every antidiabetic background medication
- Side effects identified based on post-marketing reports.

The analysis of side effects was conducted for each indication on the largest available placebo-controlled data set. The analysis included 766 patients treated with linagliptin (monotherapy) and 458 patients treated with placebo, 1322 patients treated with linagliptin as add-on to metformin compared with 583 patients treated with placebo as add-on to metformin, 786 patients treated with linagliptin as add-on to metformin plus SU compared with 263 patients treated with placebo as add-on to metformin plus SU, and 720 patients treated with linagliptin as add-on to insulin, compared with 700 patients treated with placebo as add-on to insulin.

The entries in the table below were obtained based on MedDRA preferred terms or, where appropriate, included additional terms in order to identify and display a particular medical concept.

**Table 30. Side effects identified as potentially related (based on data from clinical trials) to linagliptin monotherapy, as add-on to metformin, as add-on to metformin plus SU, and as add-on to insulin**

| SOC | Linagliptin (monotherapy) | Linagliptin add-on to metformin | Linagliptin add-on to metformin + SU | Linagliptin add-on to insulin |
|---|---|---|---|---|
| Infections and infestations | C<br>Nasopharyngitis | C<br>Nasopharyngitis | C<br>Nasopharyngitis | C<br>Nasopharyngitis |
| Immune system disorders | B<br>Hypersensitivity[1] | B<br>Hypersensitivity[1] | B<br>Hypersensitivity[1] | B<br>Hypersensitivity[1] |
| Metabolism and nutrition disorders | - | - | B<br>Hypoglycaemia[2] | - |
| Respiratory, thoracic and mediastinal disorders | C<br>Cough[3] | C<br>Cough[3] | A, C<br>Cough[3] | C<br>Cough[3] |
| Gastrointestinal disorders | B<br>Pancreatitis[4] | B<br>Pancreatitis[4] | B<br>Pancreatitis[4] | B<br>Pancreatitis[4] |
| | - | - | - | A<br>Constipation |

A Adverse events with an incidence ≥2% with linagliptin and a 2-fold higher incidence than in the placebo group (or an incidence of zero in the placebo group), and/or
B Adverse events that were likely related based on medical plausibility, and/or
C Adverse events that had a consistent pattern over antidiabetic background treatments, i.e. the incidence in the linagliptin groups was consistently higher than in the placebo groups for every antidiabetic background medication.
- The hyphen indicates no identified risk
1 'Hypersensitivity' included the narrow MedDRA SMQs for 'anaphylactic reaction' and 'asthma bronchospasm'
2 'Hypoglycaemia' included the MedDRA HLT 'hypoglycaemic conditions NEC' plus the MedDRA PT 'low blood glucose'
3 'Cough' included the MedDRA PTs 'cough' and 'productive cough'
4 'Pancreatitis' was calculated based on the narrow MedDRA SMQ 'acute pancreatitis' and the MedDRA PT 'pancreatitis chronic'.

Furthermore, the side effects angiooedema (based on the narrow MedDRA SMQ for 'angiooedema' minus the MedDRA PT 'urticaria') and urticaria were identified from post-marketing data (criterion D).

The side effects cough, hypersensitivity, nasopharyngitis and pancreatitis had already been described in the initial linagliptin submission as possibly associated with the use of linagliptin and are reflected in the SmPC for Trajenta. Hypoglycaemia had been identified as potential side effect only when linagliptin was given as add-on to metformin and sulphonylurea. The following potential side effects were newly identified in addition to the already described potential side effects for linagliptin therapy: angiooedema and urticaria for linagliptin alone and as add-on to background therapies and constipation when linagliptin was administered as add-on to insulin.

## *Serious adverse events*

**Deaths**

Of the 1420 patients in SAF-3, i.e. the patients receiving insulin background medication, 4 patients (0.6%) treated with linagliptin and 3 patients (0.4%) treated with placebo died. Three linagliptin-treated patients died from treatment-emergent adverse events, all of which were cardiac disorders (1 patient in study 1218.36: coronary artery arteriosclerosis; 2 patients in study 1218.43: cardiac arrest; acute myocardial infarction, acute cardiac failure, and congestive cardiac failure). The fourth patient in the linagliptin group (from study 1218.36) died of an adverse event (sudden death) during the post-treatment period. The 3 patients in the placebo group died of acute renal failure; cardiac death; and arrhythmia and myocardial infarction.

Among all 6602 linagliptin-treated patients with T2DM in the clinical trial program (SAF-1), 25 patients (0.4%) died: 21 patients died of treatment-emergent adverse events, and 4 patients died from adverse events with an onset during the post-treatment period. All 25 patients had received 5 mg linagliptin daily, with or without other antidiabetic medications. A further 11 patients, who had been randomised to comparator treatment groups in trials contributing to SAF-1, died (glimepiride: 5 patients, placebo: 6 patients). Of these, 10 patients died from treatment-emergent adverse events, and 1 patient died of an adverse event with an onset during the post-treatment period (after treatment with glimepiride).

None of the fatal adverse events were considered to be related to study medication. The incidence rates for death did not indicate an increased risk for linagliptin compared with placebo or a combined comparator group as shown in the table below.

**Table 31. Incidence rates of death (only treatment-emergent adverse events) per 1000 patient years of exposure for SAF-1, SAF-2, SAF-3, and for the pool of all controlled phase III studies - TS**

| Grouping | Treatment | Number of patients | Exposure [years] | Number of patients with fatal AE | Time at risk [years] | Incidence rate [per 1000 years at risk] |
|---|---|---|---|---|---|---|
| SAF-1 | Linagliptin 5 mg | 5955 | 6965.9 | 21 | 7067.3 | 2.97 |
| | Linagliptin total | 6602 | 7243.0 | 21 | 7356.8 | 2.85 |
| SAF-2 | Placebo | 2364 | 1355.9 | 6 | 1375.7 | 4.36 |
| | Linagliptin 5 mg | 4302 | 2284.0 | 9 | 2321.9 | 3.88 |
| SAF-3 | Placebo | 700 | 559.0 | 3 | 561.8 | 5.34 |
| | Linagliptin 5 mg | 720 | 585.1 | 3 | 587.8 | 5.10 |
| Controlled Phase III trials[1] | Comparator[2] | 3051 | 2716.8 | 10 | 2746.6 | 3.64 |
| | Linagliptin 5 mg | 4548 | 3646.9 | 13 | 3691.3 | 3.52 |

[1] Includes data from the following trials (without leading 1218): .15, .16, .17, .18, .20, .23, .35, .36, .43, .46, .50, .52, .63

[2] Includes placebo, glimepiride, and voglibose

**Serious adverse events**

The analyses of serious adverse events include all deaths.

In SAF-3 (patients with insulin background), the frequencies of patients with treatment-emergent serious adverse events were similar in both treatment groups (placebo 11.7%, linagliptin 10.8%). Cardiac disorders were the system organ class with the highest incidences. Based on preferred terms, serious adverse events with an incidence of more than 0.5% (i.e. 4 or more patients) in either treatment group and occurring more frequently in the linagliptin group than the placebo group were pneumonia, acute myocardial infarction, fall, and hypoglycaemia. Serious adverse events belonging to the system organ class benign, malignant, and unspecified neoplasms were reported for 6 (0.9%) patients in the placebo group and 2 patients (0.3%) in the linagliptin group; the 2 linagliptin-treated patients had lung adenocarcinoma and ovarian adenoma.

The table below summarises the most frequently reported serious adverse events in SAF-3. During the post-treatment period, 6 patients (4.1%) in the placebo group and 4 patients (2.8%) in the linagliptin group were reported with serious adverse events.

**Table 32. Frequency of patients with serious adverse events occurring with incidence greater than 0.5% in PT or SOC, sorted by frequency in the linagliptin group, for SAF-3 (placebo-controlled studies with insulin background) - TS**

| | Placebo N (%) | Linagliptin 5 mg N (%) |
|---|---|---|
| Patient years of exposure | 559.0 | 585.1 |
| Number of patients | 700 (100.0) | 720 (100.0) |
| Total with serious AEs | 82 (11.7) | 78 (10.8) |
| Cardiac disorders | 19 (2.7) | 23 (3.2) |
| Acute myocardial infarction | 1 (0.1) | 4 (0.6) |
| Angina pectoris | 4 (0.6) | 3 (0.4) |
| Infections and infestations | 19 (2.7) | 12 (1.7) |
| Pneumonia | 3 (0.4) | 5 (0.7) |
| Injury, poisoning and procedural complications | 7 (1.0) | 10 (1.4) |
| Fall | 3 (0.4) | 4 (0.6) |
| Renal and urinary disorders | 12 (1.7) | 8 (1.1) |
| Acute renal failure | 6 (0.9) | 2 (0.3) |
| Metabolism and nutrition disorders | 7 (1.0) | 7 (1.0) |
| Hypoglycaemia | 2 (0.3) | 4 (0.6) |
| Gastrointestinal disorders | 7 (1.0) | 7 (1.0) |
| Respiratory, thoracic and mediastinal disorders | 10 (1.4) | 6 (0.8) |
| Nervous system disorders | 6 (0.9) | 5 (0.7) |
| Musculoskeletal and connective tissue disorders | 4 (0.6) | 5 (0.7) |
| Neoplasms benign, malignant and unspecified (incl. cysts and polyps) | 6 (0.9) | 2 (0.3) |
| Vascular disorders | 6 (0.9) | 2 (0.3) |

In the pivotal study 1218.36 (SAF-4), the incidences of serious adverse events (placebo 9.2%, linagliptin 8.7%) were somewhat lower than in SAF-3. This difference is explained by the additional patients included in SAF-3: patients with renal impairment from study 1218.43 and elderly patients from study 1218.63. Especially the small group of patients with severe renal impairment in SAF-5 (from study 1218.43), a subgroup of the patients in SAF-3, had high serious adverse event incidences (placebo 40.0%, linagliptin 37.0%).

Compared with the patient population evaluated for the initial linagliptin application, the incidences of serious adverse events were generally higher for the patient populations assessed for the present submission. Thus, for the placebo-controlled studies in the initial linagliptin submission (SAF-2), the frequencies of patients with serious adverse events were 2.5% (placebo) and 2.7% (linagliptin), while frequencies were 5.9% (placebo) and 4.8% (linagliptin) in SAF-2 for the present evaluation. The difference was expected because the patients newly added to SAF-2 are mainly patients with more advanced T2DM, i.e. patients with background insulin therapy, or otherwise higher propensity for serious adverse events (patients with renal impairment, elderly patients). Consistent with this observation, incidences of serious adverse events in SAF-3 to SAF-6 of the current package were considerably higher than in the current SAF-2. In each of these SAFs, the incidence of serious adverse events was higher in the placebo group than in the linagliptin group.

The patterns of reported serious adverse events in SAF-2 and SAF-3 were compared to check for any events specific for treatment with linagliptin and insulin as opposed to treatment with linagliptin alone or combined with oral antidiabetics. This is an appropriate comparison since SAF-3 comprises less than a quarter (21%) of all patients included in SAF-2; the remaining patients took oral antidiabetic medications on top of study medication or study medication alone. Apart from the generally lower incidences of serious adverse events in SAF-2 than in SAF-3 (for most system organ classes and preferred terms), no meaningful differences could be identified. However, because of the relatively small numbers of patients with individual serious adverse events, no solid conclusions are possible.

Serious adverse events were also assessed for a range of subgroups in SAF-2 and SAF-3. Overall incidences of serious adverse events were generally higher in subgroups of SAF-3 than in subgroups of SAF-2, consistent with the overall incidences in both SAFs. The following noteworthy observations were made for SAF-3; there were similar trends in SAF-2 unless otherwise indicated. Because of the relatively low incidence of serious adverse events, only overall incidences are compared rather than specific system organ classes or preferred terms.

**Age**

Incidences of serious adverse events increased with age. Patients 50 years of age or younger had low incidences (placebo 3.0%, linagliptin 11.5%), whereas patients with an age of at least 75 years reported the highest incidences (placebo 31.5%, linagliptin 16.4%). However, there were relatively few patients in this latter age subgroup (109 patients overall) and therefore no clear differences between the treatment groups.

**Race**

For patients of Black race, almost twice as many patients in the linagliptin group reported serious adverse events than in the placebo group (placebo 10.9%, linagliptin 20.5%). With 90 patients overall this subgroup was small. An additional study 1218.75 was submitted by the MAH during the evaluation. This was a Phase III, 24-week, randomised, placebo-controlled, double-blind efficacy and safety trial in Black/African American T2DM patients. The primary endpoint in study 1218.75 was the change of HbA1c (HbA1c after 24 weeks of treatment minus HbA1c at baseline) in Black/African American patients. The difference between the treatment groups in adjusted mean change in HbA1c from baseline at Week 24 was - 0.58% (95% CI: [-0.91, -0.26]; p = 0.0005), demonstrating a modest, but clinically relevant effect of linagliptin in reduction of HbA1c after 24 weeks of treatment in Black/African American patients. Sensitivity analyses confirmed the results of the primary analysis. Secondary endpoints were also in line with the primary endpoints. In this study 1/106 (0.9%) patients in the linagliptin group versus 2/120 (1.7%) patients in the placebo group experienced serious AEs. The subject in the linagliptin group was reported with non-fatal myocardial infarction. Severe AEs were reported for 4/106 (3.8%) patients in the linagliptin group, versus 4/120 (3.3%) in the placebo group. In the linagliptin group, besides the already mentioned patient with the acute non-fatal myocardial infarction, one patient was reported with localized infection, one patient was reported with bite and gout, and the last patient was reported with migraine and hypertonic bladder. In conclusion, no clustering of SAE were shown in the linagliptin group in study 1218.75. Furthermore, both the efficacy and safety results were in line with previously submitted studies performed in other races. Although, study 1218.75 only included Black/African American patients, and therefore, no comparison can be made between different races, no evidence could be found to support a possible increased safety risk for Black/African American patients based on their race. No new safety signals were seen in this study with Black/African American T2DM patients, compared to earlier submitted studies.

**Region**

Patients from Asia (placebo 18.3%, linagliptin 17.2%) and North America (placebo 18.1%, linagliptin 14.5%) more frequently reported serious adverse events than patients from Europe (10.2% vs. 9.2%) and South America (5.5% vs. 6.8%), with no imbalances between treatment groups. Also in SAF-2, relatively high incidences were reported for North American patients (placebo 9.4%, linagliptin 6.6%) but patients from Asia reported serious adverse events with a similarly low frequency as patients from Europe and South America.

**Renal impairment (MDRD)**

Patients with worse renal function generally had more serious adverse events than patients with higher MDRD values. Incidences of serious adverse events were 7.2% (placebo) and 7.8% (linagliptin) in patients with normal renal function (≥90 mL/min). For the relatively small group of patients (n=101) with severe or end-stage renal impairment (<30 mL/min), serious adverse events were reported for 44.7% of patients in the placebo group and 38.9% of linagliptin-treated patients. This latter group is almost identical with the group of patients in SAF-5.

**Concomitant medications**

Subgroup analyses according to intake of P-gp inhibitors, CYP-3A4 inhibitors, and ACE inhibitors were only done for SAF-2. Patients who took medications from any of the 3 classes generally reported more serious adverse events than patients without such medications. This likely reflects the more frequent occurrence of concomitant diagnoses and more advanced disease states in patients with such medications. There were no obvious differences between the treatment groups in any of these subgroups.

**Other subgroups**

Within the subgroups by gender, ethnicity, and BMI, no clear trends or differences between treatment groups were identified.

**Pooled cardiovascular safety analysis**

Cardiovascular (CV) safety is of interest in the development of any new antidiabetic drug. Therefore, in line with recent regulatory requirements, a formal pre-specified CV safety analysis was performed in 2010 (data cut-off in February 2010) which was submitted with the initial MAA for Trajenta. This analysis included data from 8 Phase III trials. According to that analysis, treatment with linagliptin was not associated with an increased cardiovascular risk compared with a pooled comparator group (placebo, glimepiride, and voglibose). An updated version of this pooled CV analysis (data cut-off in April 2011) was submitted with this extension of indication which has already been assessed as part of Trajenta MEA 010. This updated cardiovascular safety analysis included data from 13 Phase III trials and 7907 patients in total (4891 patients treated with linagliptin and 3016 treated with comparator).

Another updated version of this pooled CV safety analysis (data cut-off in March 2012) was submitted by the MAH during the evaluation. The updated cardiovascular safety analysis included 5282 patients treated with linagliptin and 3340 patients treated with comparators (placebo: 2403 patients, active comparators glimepiride or voglibose: 937 patients). The total exposure to linagliptin amounted to 4133.7 patient years. The primary endpoint was based on adjudicated events and was a composite endpoint consisting of cardiovascular death (including fatal stroke and fatal MI), non-fatal MI, non-fatal stroke, and hospitalisation due to unstable angina.

Overall, 212 linagliptin-treated patients and 190 patients treated with comparators had events that triggered adjudication. Events adjudicated and confirmed as primary endpoint events occurred in 56 (1.06%) linagliptin patients and 55 patients (1.65%) treated with comparator medications (placebo: 1.21%, active comparators: 2.8%). Incidence rates of the primary endpoint (per 1000 patient years at risk) were numerically lower for linagliptin (13.4) than for the combined comparator group (17.6). The difference between these 2 treatment groups was not statistically significant, whether it was expressed as Cox regression hazard ratio (0.83 with 95% CI 0.57, 1.21), Poisson regression risk ratio (0.83 with 95% CI 0.56, 1.23), odds ratio for stratified exact test (0.86 with 95% CI 0.58, 1.28), or incidence ratio for stratified Cochran-Mantel-Haenszel test with treatment arm continuity correction (0.89 with 95% CI 0.62, 1.28). Results for the secondary and tertiary endpoints confirmed the primary endpoint results. Thus, also the updated CV safety analysis showed no evidence of an increased CV risk with linagliptin compared with a pooled comparator group.

In the interim analysis of study 1218.36, a total of 10 patients (1.6%) in the linagliptin group and 5 patients (0.8%) in the placebo group had confirmed cardiovascular death, myocardial infarction, stroke, or hospitalisation due to unstable angina (primary endpoint for the CV safety analysis). In the final CV safety analysis for study 1218.36, the difference between linagliptin and placebo was smaller: 18 patients (2.9%) in the linagliptin group and 11 patients (1.7%) in the placebo group had confirmed cardiovascular events. The numbers of patients with confirmed events in the period between the interim and final analyses were similar in both treatment groups (linagliptin: 8 patients; placebo: 6 patients). There was no temporal relationship observed with the occurrence of hypoglycaemic events; only 1 patient (in the linagliptin group) had a hypoglycaemic episode up to 2 weeks before a confirmed cardiovascular event. Although the demographic characteristics of the study population in study 1218.36 were generally comparable between treatment groups, there were some differences that might be related to potential cardiovascular risk. For example, while smoking history was broadly similar between treatment groups, a higher proportion of patients treated with linagliptin (16.2%) than receiving placebo (13.8%) were current smokers. Furthermore, a lower proportion of patients treated with linagliptin than receiving placebo were taking lipid-lowering drugs (placebo: 59.8%; linagliptin 54.5%) at baseline including statins (placebo: 54.0%; linagliptin 48.2%). Of note the majority of patients who had confirmed cardiovascular death, myocardial infarction, stroke, or hospitalisation due to unstable angina already had a medical history suggestive of increased cardiovascular risk. The final analysis of study 1218.36 shows that during the latter part of the trial, there was no marked difference between treatment groups in the number of additional patients with cardiovascular events.

To evaluate the cardiovascular safety of linagliptin as add-on to insulin, a subgroup analysis by use of insulin was performed by the MAH. This subgroup analysis included patients from studies 1218.36, 1218.43, 1218.63 and 1218.64 who were taking insulin as background therapy. In total, this subgroup included 818 patients treated with linagliptin and 808 patients treated with placebo. Events adjudicated and confirmed as primary endpoint events occurred in 24 patients (2.93%) treated with linagliptin and 20 patients (2.48%) treated with placebo. The difference between the linagliptin and the placebo groups was not statistically significant. In study 1218.43 comprising patients with severe chronic renal impairment, the incidence rates of the primary endpoint for the cardiovascular analysis were 120.2 for linagliptin (7 patients) and 148.1 for placebo (8 patients). The statistical tests (same as above for the pooled analysis) did not indicate a statistically significant treatment difference. Of the 7 patients in the linagliptin group, 4 were reported with non-fatal myocardial infarction, 1 with stroke, and 2 with cardiac death; all 7 patients were receiving insulin as background therapy. Of the 8 patients in the placebo group, 3 were reported with unstable angina leading to hospitalisation, 1 with myocardial infarction, 1 with stroke, and 3 with cardiac death. Six of these 8 patients in the placebo group were receiving insulin as background medication (2 of the patients with cardiac death had not received insulin).

Study 1218.63, which comprised elderly patients, was completed after the cut-off date for the updated CV safety analysis and was therefore not included in the latter analysis. In this study, 2 patients, both in the linagliptin group (1.2%), had adjudicated and confirmed cardiac or cerebrovascular events. For one patient, the confirmed event was an ischemic stroke, the other patient was hospitalised due to unstable angina. Neither of the 2 patients were receiving insulin background therapy.

### *Clinical laboratory evaluation and vital signs*

Overall, the safety laboratory data revealed no clear trends of clinical relevance. In SAF-3 and SAF-4, mean changes from baseline were generally small and did not provide reason to assume any clinically relevant differences between the treatment groups for any of the measured clinical laboratory parameters.

Among the patients with insulin background therapy (SAF-3), the most prominent differences between treatment groups in terms of possibly clinically significant laboratory abnormalities were observed for the following 2 parameters: decreases in haemoglobin values (placebo 4.0% of patients, linagliptin 7.4%) and increases of amylase concentrations (placebo 3.3%, linagliptin 5.9%). In the larger SAF-2 set (placebo-controlled trials), such treatment differences were either not observed (haemoglobin: placebo 2.9%, linagliptin 2.7%) or to a smaller extent (amylase: placebo 2.3%, linagliptin 3.2%). The data for mean changes from baseline and transitions relative to reference range for haemoglobin levels in SAF-2 and SAF-3 did not confirm the observation for the possibly clinically significant abnormalities, suggesting that the haemoglobin changes are not of clinical relevance. With regard to amylase, transitions from normal to high levels were observed more frequently in the linagliptin groups of both SAF-3 (placebo 2.5%, linagliptin 4.9%) and SAF-2 (3.7% vs. 5.1%). Also the mean changes from baseline to last value on treatment in SAF-3 indicated a potential treatment difference (placebo -1 U/L, linagliptin +6 U/L). Nevertheless, for the 3 linagliptin-treated patients in SAF-3, who had pancreatitis, recorded amylase levels (at the planned study visits) were always within the reference range. Taken together, the increases in amylase concentrations do not seem to be clinically relevant. The analyses of transitions relative to the reference range and of possibly clinically significant abnormalities (SAF-1 to SAF-3) did not reveal clinically meaningful differences between the treatment groups for any other parameters.

There were no potential Hy's law cases among all the linagliptin-treated patients (SAF-1). Considering the observed changes in liver function parameters, the potential for linagliptin to induce liver toxicity is judged to be very low, also in combination with insulin treatment. Renal function was analysed by shifts in renal impairment stage from baseline to last value on treatment (SAF-1 to SAF-3). Overall, no clinically relevant changes from baseline or between treatment groups were observed.

In SAF-2 to 4, there were no clinically relevant linagliptin-specific changes in vital signs (blood pressure, pulse rate) over time. Only few patients had marked increases in blood pressure or marked outliers of their blood pressure or pulse rate values.

A reduction in haemoglobin (Hb) was observed in SAF-3 (placebo controlled trials with insulin background therapy) in the data set of possible clinically significant abnormalities (PCSA). From 672 patients treated with placebo, 27 (4.0%), and from 699 patients treated with linagliptin, 52 (7.4%) experienced a decrease in Hb according to the definition of PCSA values. The reference range for haemoglobin PCSA was defined as decrease below 11.5 g/dL for males and 9.5 g/dL for females. Numerical imbalances towards linagliptin as well towards placebo were described in the further analyses conducted by the MAH during the evaluation. However the analysis of the absolute changes by descriptive statistics did not show a clinical meaningful difference between the treatments. Further, a small numerical imbalance disfavouring linagliptin compared to placebo with respect to severe renal impairment was observed in the selected population. Because chronic kidney disease stage is linked to decreased Hb levels, this numerical imbalance may be a contributing factor towards the observed variability. Overall, the presented and analysed data do not indicate a clinical meaningful effect of linagliptin treatment on Hb values.

**Use of linagliptin in elderly patients: study 1218.63**

### *Exposure*

All 241 randomised patients received at least one dose of study medication and were included in the Treated Set: 79 patients received placebo and 162 patients received linagliptin. Mean exposure to study medication was 163.8 days for patients randomised to placebo and 159.7 days for patients randomised to linagliptin. Cumulative patient exposure in the linagliptin group was 70.9 patient years, see table below.

**Table 33. Exposure to randomised study drug – Treated set**

| | Placebo | Linagliptin |
|---|---|---|
| Number of patients, N (%) | 79 (100.0) | 162 (100.0) |
| Exposure categories, N (%) | | |
| 0 to 4 weeks | 1 (1.3) | 4 (2.5) |
| >4 to 8 weeks | 1 (1.3) | 2 (1.2) |
| >8 to 14 weeks | 0 (0.0) | 3 (1.9) |
| >14 to 20 weeks | 2 (2.5) | 5 (3.1) |
| >20 to 26 weeks | 75 (94.9) | 147 (90.7) |
| >26 weeks | 0 (0.0) | 1 (0.6) |
| Exposure | | |
| Median [days] | 168.0 | 168.0 |
| Mean [days] | 163.8 | 159.7 |
| Sum [years] | 35.4 | 70.9 |

### *Adverse events*

Overall, 60 patients (75.9%) were reported with AEs in the placebo group and 123 patients (75.9%) were reported with AEs in the linagliptin group. The majority of the AEs were of mild or moderate intensity. Severe AEs were reported for 3 patients (3.8%) treated with placebo and 9 patients (5.6%) treated with linagliptin. Serious adverse events (SAEs) were reported for 5 patients (6.3%) in the placebo group and 14 patients (8.6%) in the linagliptin group. No patients died during the study. A summary of the different AE categories is provided in the table below.

AEs that were assessed by the investigators as being drug-related were reported in 13.9% of patients in the placebo group and 21.0% of patients in the linagliptin group. The most common preferred terms (PTs) of drug-related AEs were hypoglycaemia (8.9% placebo; 14.2% linagliptin group), followed by diarrhoea (0.0% placebo; 1.2% linagliptin). All other drug-related AEs occurred in only one patient each.

AEs led to discontinuation of study medication in 1.3% of patients in the placebo group and 4.9% of patients in the linagliptin group. One of the AEs that led to discontinuation of linagliptin medication was considered drug-related: insomnia.

**Table 34. Adverse event overall summary – Treated set**

| | Placebo N (%) | Linagliptin N (%) |
|---|---|---|
| Number of patients | 79 (100.0) | 162 (100.0) |
| Patients with any AE | 60 (75.9) | 123 (75.9) |
| Patients with severe AEs | 3 (3.8) | 9 (5.6) |
| Patients with investigator-defined drug-related AEs | 11 (13.9) | 34 (21.0) |
| Patients with significant AEs (pre-specified events) [1] | 0 (0.0) | 4 (2.5) |
| Patients with other significant AEs (ICH E3) | 1 (1.3) | 4 (2.5) |
| Patients with AEs leading to discontinuation of trial drug | 1 (1.3) | 8 (4.9) |
| Patients with serious AEs[2] | 5 (6.3) | 14 (8.6) |
| Requiring hospitalisation | 4 (5.1) | 14 (8.6) |
| Other | 2 (2.5) | 0 (0.0) |

1 i.e. hypersensitivity reactions, renal AEs, and increased liver enzymes (all based on investigator reporting); excluding severe cutaneous reactions and pancreatitis
2 Note: A patient may be counted in more than one seriousness criterion.
Note: Percentages were calculated using total number of patients per treatment as the denominator.

The most frequently reported AEs across both treatment groups were in the system organ classes (SOCs) infections and infestations (35.4% placebo; 29.6% linagliptin), followed by metabolism and nutrition disorders (24.1% placebo; 26.5% linagliptin), gastrointestinal disorders (16.5% placebo; 13.6% linagliptin), nervous system disorders (15.2% placebo; 9.9% linagliptin), and musculoskeletal and connective tissue disorders (10.1% placebo; 14.8% linagliptin). The most commonly reported AEs on preferred term (PT) level were hypoglycaemia (16.5% placebo; 22.8% linagliptin), followed by nasopharyngitis (8.9% placebo; 10.5% linagliptin), hyperglycaemia (10.1% placebo; 5.6% linagliptin), urinary tract infection (6.3% placebo; 4.3% linagliptin), and upper respiratory tract infection (6.3% placebo; 3.7% linagliptin).

Less common AEs on PT level that were reported in a greater proportion of patients in the linagliptin group than in the placebo group were: diarrhoea (2.5% placebo; 5.6% linagliptin), fall (2.5% placebo; 4.3% linagliptin), pain in extremity (2.5% placebo; 3.1% linagliptin), back pain (0.0% placebo; 4.3% linagliptin), oropharyngeal pain (1.3% placebo; 2.5% linagliptin), pneumonia (1.3% placebo; 2.5% linagliptin), vertigo (0.0% placebo; 3.1% linagliptin), arthralgia (0.0% placebo; 3.1% linagliptin), cystitis (0.0% placebo; 2.5% linagliptin), and peripheral oedema (0.0% placebo; 2.5% linagliptin). None of the episodes of peripheral oedema were serious and none led to withdrawal. The four episodes of peripheral oedema could not be confirmed to be cardiovascular events.

**Table 35. Number of patients with AEs occurring with an incidence in preferred term of greater than 2% by treatment, primary system organ class and preferred term – Treated set**

| System organ class/ Preferred term | Placebo N (%) | | Linagliptin N (%) | |
|---|---|---|---|---|
| Number of patients | 79 | (100.0) | 162 | (100.0) |
| Total with adverse events | 60 | (75.9) | 123 | (75.9) |
| Infections and infestations | 28 | (35.4) | 48 | (29.6) |
| Nasopharyngitis | 7 | (8.9) | 17 | (10.5) |
| Urinary tract infection | 5 | (6.3) | 7 | (4.3) |
| Upper respiratory tract infection | 5 | (6.3) | 6 | (3.7) |
| Influenza | 3 | (3.8) | 3 | (1.9) |
| Lower respiratory tract infection | 3 | (3.8) | 1 | (0.6) |
| Pneumonia | 1 | (1.3) | 4 | (2.5) |
| Cystitis | 0 | (0.0) | 4 | (2.5) |
| Metabolism and nutrition disorders | 19 | (24.1) | 43 | (26.5) |
| Hypoglycaemia | 13 | (16.5) | 37 | (22.8) |
| Hyperglycaemia | 8 | (10.1) | 9 | (5.6) |
| Gastrointestinal disorders | 13 | (16.5) | 22 | (13.6) |
| Diarrhoea | 2 | (2.5) | 9 | (5.6) |
| Dry mouth | 2 | (2.5) | 1 | (0.6) |
| Gastrooesophageal reflux disease | 2 | (2.5) | 0 | (0.0) |
| Gingivitis | 2 | (2.5) | 0 | (0.0) |
| Nervous system disorders | 12 | (15.2) | 16 | (9.9) |
| Dizziness | 4 | (5.1) | 6 | (3.7) |
| Headache | 3 | (3.8) | 6 | (3.7) |
| Musculoskeletal and connective tissue disorders | 8 | (10.1) | 24 | (14.8) |
| Pain in extremity | 2 | (2.5) | 5 | (3.1) |
| Musculoskeletal pain | 3 | (3.8) | 1 | (0.6) |
| Back pain | 0 | (0.0) | 7 | (4.3) |
| Arthralgia | 0 | (0.0) | 5 | (3.1) |
| Respiratory, thoracic and mediastinal disorders | 5 | (6.3) | 14 | (8.6) |
| Cough | 2 | (2.5) | 4 | (2.5) |
| Oropharyngeal pain | 1 | (1.3) | 4 | (2.5) |
| Skin and subcutaneous tissue disorders | 5 | (6.3) | 14 | (8.6) |
| Rash | 2 | (2.5) | 1 | (0.6) |
| General disorders and administration site conditions | 6 | (7.6) | 11 | (6.8) |
| Fatigue | 3 | (3.8) | 2 | (1.2) |
| Chest pain | 2 | (2.5) | 1 | (0.6) |
| Oedema peripheral | 0 | (0.0) | 4 | (2.5) |
| Injury, poisoning and procedural complications | 4 | (5.1) | 11 | (6.8) |
| Fall | 2 | (2.5) | 7 | (4.3) |
| Investigations | 2 | (2.5) | 10 | (6.2) |
| Lipase increased | 2 | (2.5) | 0 | (0.0) |

| | | | | |
|---|---|---|---|---|
| Ear and labyrinth disorders | 1 | (1.3) | 5 | (3.1) |
| Vertigo | 0 | (0.0) | 5 | (3.1) |
| Vascular disorders | 2 | (2.5) | 3 | (1.9) |
| Hypotension | 2 | (2.5) | 1 | (0.6) |
| Blood and lymphatic system disorders | 2 | (2.5) | 2 | (1.2) |
| Anaemia | 2 | (2.5) | 1 | (0.6) |

The number of patients specified for each SOC is the total number of patients for whom an AE in that SOC was reported, including patients for whom an AE was reported that did not have an incidence in PT > 2%. Within each SOC only those PTs are listed that have an incidence of more than 2%

**Hypoglycaemia**

There were 13 patients (16.5%) in the placebo group and 39 patients (24.1%) in the linagliptin group with an investigator-defined hypoglycaemic episode, see table below. Of the patients with hypoglycaemia, asymptomatic hypoglycaemia was reported with a higher incidence in the placebo group than in the linagliptin group (38.5% placebo; 25.6% linagliptin), as was symptomatic (moderate) hypoglycaemia with plasma glucose <54 mg/dL (38.5% placebo; 28.2% linagliptin), whereas symptomatic (mild) hypoglycaemia with plasma glucose ≥54 to ≤70 mg/dL more common in the linagliptin group than in the placebo group (38.5% patients with hypoglycaemia on placebo; 71.8% patients with hypoglycaemia on linagliptin).

**Table 36. Number of patients with investigator-defined hypoglycaemia by treatment and by background glucose-lowering medication – Treated set**

| | Placebo | Linagliptin |
|---|---|---|
| Number of patients, N (%) | 79 (100.0) | 162 (100.0) |
| Number of patients with any investigator-defined hypoglycaemia, N (% of patients treated)[1] | 13 (16.5) | 39 (24.1) |
| Any asymptomatic hypoglycaemia[2], N (% of patients with hypoglycaemia) | 5 (38.5) | 10 (25.6) |
| Any documented symptomatic (mild) hypoglycaemia[3] and measured plasma glucose ≥54 mg/dL and ≤70 mg/dL, N (% of patients with hypoglycaemia) | 5 (38.5) | 28 (71.8) |
| Any documented symptomatic(moderate) hypoglycaemia[4] and measured plasma glucose <54 mg/dL, N (% of patients with hypoglycaemia) | 5 (38.5) | 11 (28.2) |
| Any severe hypoglycaemic episode[5], N (% of patients with hypoglycaemia) | 0 (0.0) | 1 (2.6) |
| Number of hypoglycaemic episodes per patient, N (% of patients with hypoglycaemia) | | |
| 1 | 7 (53.8) | 17 (43.6) |
| 2 to 3 | 4 (30.8) | 9 (23.1) |
| ≥4 | 2 (15.4) | 13 (33.3) |
| Background antidiabetes medication [N (%)] | | |
| Metformin | 0 (0.0) | 2 (5.1) |
| SU with or without metformin | 7 (53.8) | 24 (61.5) |
| Insulin | 6 (46.2) | 13 (33.3) |

1 Note that patients may have had events of more than one category or events that are not covered by the 4 categories. Thus the sum of patients with events in the 4 categories may differ from the number of patients with any hypoglycaemic event.
2 not accompanied by typical symptoms of hypoglycaemia but with a measured plasma glucose concentration ≤70 mg/dL
3 accompanied by typical symptoms of hypoglycaemia
4 accompanied by typical symptoms of hypoglycaemia but no need for external assistance
5 requiring the assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions

One 75-year-old patient in the linagliptin group (on background antidiabetes medication of metformin and SU) had a severe episode of hypoglycaemia. The episode of hypoglycaemia was graded as moderate, plasma glucose was <54 mg/dL, and the patient required assistance; therefore the episode was severe overall.

The proportion of patients reported with investigator-defined hypoglycaemia by age group was similar for the two treatment groups in patients younger than 75 years of age (23.3% placebo; 25.3% linagliptin), but was low in the placebo group in patients aged 75 years or older (8.3% placebo; 22.5% linagliptin).

Logistic regression of the occurrence of hypoglycaemia indicated that treatment group was not associated with a significant difference in the odds of having a hypoglycaemic event (odds ratio 1.577, 95% CI [0.776; 3.208], p = 0.2083), whereas if a patient had insulin as part of their background therapy, there was a significant increase in the odds of having a hypoglycaemic event (odds ratio 2.869, 95% CI [1.433; 5.745], p = 0.0029). An additional logistic regression, including age group and background medication class explanatory variables, showed that age was not a significant factor (odds ratio 1.490, 95% CI [0.765; 2.905], p = 0.2414). Background antidiabetes medication (particularly SU and insulin) was significant (p = 0.0005). The odds ratios for metformin:SU with or without metformin was 0.090, 95% CI [0.021; 0.391] and for metformin:insulin was 0.049, 95% CI [0.011; 0.227].

**Significant adverse events (protocol-specified events)**

Due to regulatory recommendation based on the experience with other compounds in the DPP-4 inhibitor class, the SMQs 'severe cutaneous adverse reactions' and 'pancreatitis' were added to the significant AEs.

In the linagliptin group there was 1 patient who had moderate contact dermatitis (censored after 47 days, considered drug-related); 1 patient with moderate eczema (censored after 143 days, considered not drug-related); 1 patient with mild acute renal failure (resolved after 3 days, not considered drug-related); and 1 patient with moderate increased blood creatinine (resolved after 43 days, not considered drug-related). There were no cases of pancreatitis.

**Adverse events of severe intensity**

In the linagliptin group, 9 patients (5.6%) were reported with 10 AEs of severe intensity. One patient was reported with 2 severe AEs (fall, and lower limb fracture), while the remaining 8 patients were reported with 1 severe AE each (atrial fibrillation, atrioventricular block complete, chest pain, pneumonia, back pain, cerebrovascular accident, dizziness, and urinary retention). In the placebo group, 3 patients (3.8%) were reported with 1 severe adverse event each. The severe AEs in the placebo group were lower respiratory tract infection, lung adenocarcinoma, and urinary bladder polyp.

**Serious adverse events**

There were no fatal cases in this study. There were 5 patients (6.3%) in the placebo group and 14 patients (8.6%) in the linagliptin group who were reported with SAEs during the treatment period. None of the SAEs were considered related to trial medication. In the linagliptin treatment group, SAEs were reported in the SOCs cardiac disorders (4 patients), gastrointestinal disorders (1 patient), infections and infestations (4 patients), injury, poisoning and procedural complications (3 patients), metabolism and nutrition disorders (1 patient), and nervous system disorders (2 patients).

In the placebo group, SAEs were reported in the SOCs infections and infestations (1 patient), neoplasms benign, malignant and unspecified (including cysts and polyps) (3 patients), and renal and urinary disorders (1 patient).

**Laboratory evaluation and vital signs**

Laboratory analyses (haematology, clinical chemistry, and urinalysis) did not reveal any clinically significant findings compared to baseline. Few patients were reported with possibly clinically significant abnormalities: In the linagliptin group 9/157 (5.7%) patients had a decrease in haemoglobin, compared to 1/77 (1.3%) in the placebo group. Creatinine increased in 12/157 (7.6%) patients in the linagliptin group, versus 3/77 (3.9%) in the placebo group. Amylase increased in 5/157 (3.2%) subjects in the linagliptin group, versus 1/77 (1.3%) in the control group. No notable differences in changes in renal or liver function were observed between treatment groups.

Furthermore, no clinically significant differences between the treatment groups were observed in blood pressure and pulse rate from baseline to end of treatment.

### *Post-marketing experience*

Linagliptin received its first worldwide marketing approval from the FDA on 02 May 2011. At the time of data cut-off for the evaluation of post-marketing experience, approval had been received in Japan, the European Union, Brazil, Mexico, Canada, and South Korea. Since first launch, some 19822 patient years of exposure are available for the period of 02 May to 31 October 2011. The post-marketing experience summarises all spontaneous cases (spontaneous reports, health authorities, observational studies, registries, literature) received from health professionals and non-health professionals as well as cases from clinical trials during the period from 02 May to 2 November 2011. The source for the data evaluation was the BI Global Drug Safety Database. In total, 177 cases (confirmed by healthcare professionals and non-confirmed cases) were reported, of which 23 cases were serious and 154 cases were non-serious. Overall, 264 suspected adverse drug reactions (confirmed by healthcare professionals and non-confirmed cases) were reported, from which 36 suspected adverse drug reactions were serious and 228 were non-serious.

From spontaneous sources, 8 events of pancreatitis were reported in 7 patients. In relation to the estimated patient exposure, this corresponds to a reporting rate of 0.4 per 1000 patient years. None of these events were fatal, haemorrhagic, or necrotizing. Therefore, the reporting frequency as well as the intensity of the pancreatitis events among the post-marketing data is consistent with the data derived from controlled clinical trials. Pancreatitis is a risk identified with other DDP-4 inhibitors and should be included in the Trajenta SmPC in section 4.4.

Based on the available data from spontaneous sources concerning swellings in the oropharynx and face as well as reports of hives, angioedema and urticaria are considered to be hypersensitivity side effects potentially associated with the use of linagliptin.

## Discussion on clinical safety

**Add-on to insulin extension of indication**

In line with its already established safety profile, gastrointestinal disorders and nasopharyngitis occurred more with linagliptin. There were new potential adverse events identified: angiooedema and urticaria for linagliptin alone and as add-on to background therapies and constipation when linagliptin was administered as add-on to insulin.

In the small subgroup of Black patients (in total n=90) the frequency of premature discontinuation was lower with placebo (10.9%) than with linagliptin (15.9%). Compared to placebo, linagliptin was associated with more adverse events, and especially more serious adverse events in Blacks, but not in Whites and Asians. However, there was only a small number of Black patients in SAF-3 (placebo: n=46 and linagliptin: n=44), and therefore data should be interpreted with caution. Further analysis of SAF-3, indicated that there was no specific pattern of SAEs towards a medical concept or a specific safety concern. Furthermore, in study 1218.75, a Phase III, 24-week, randomised, placebo-controlled, double-blind efficacy and safety trial in Black/African American T2DM patients, no evidence could be found to support a possible increased safety risk for Black/African American patients based on their race. In this study, 1/106 (0.9%) patients in the linagliptin group versus 2/120 (1.7%) patients in the placebo group experienced serious AEs. Severe AEs were reported for 4/106 (3.8%) patients in the linagliptin group, versus 4/120 (3.3%) in the placebo group. No clustering of SAE were shown in the linagliptin group in study 1218.75. Furthermore, both the efficacy and safety results were in line with previously submitted studies performed in other races. Considering this, the safety results in SAF-3 regarding black patients were most-likely caused by chance, due to the limited number of Black patients.

The only preferred term that was reported in more than 1 patient in the linagliptin group was thyroid neoplasm, which was reported by 5 patients (0.1%) in the linagliptin group but none in the placebo group. The reported terms of these events refer to a thyroid nodule and do not qualify as malignancies; yet since they are coded as thyroid neoplasm, they were identified by the SMQ search. All 5 events were non-serious and of mild to moderate intensity, required no therapy and were not considered to be drug-related (for 1 patient the relatedness assessment was missing). Linagliptin containing medicinal products will be used chronically, and the clinical experience, in particular long term use, with linaglitpin is limited. Even though the above findings were considered not drug-related and non-malignant, it should be noted that they were reported in the linagliptin group only. Oncological AE is already included as important missing information in the RMP. But taking the aforementioned and the mechanism of action into consideration, the MAH should discuss this in future PSURs.

An important goal in the treatment of diabetes is the prevention of cardiovascular disease. In the cardiovascular safety analysis of study 1218.36, the main study for this application, the rate of the primary endpoint (CV death, MI, stroke or hospitalisation due to unstable angina) was higher in the linagliptin group than in the comparator group: 18 patients (2.9%) versus 11 patients (1.7% respectively). An updated cardiovascular meta-analysis of studies investigating linagliptin in combination with other oral antidiabetic medications was submitted by the MAH with this application. In comparison to placebo and active comparators combined, linagliptin was not associated with an increased cardiovascular risk (HR 0.83 with 95% CI 0.57,1.21).In a subgroup analysis including all the studies including patients taking insulin as background therepayi, cardiovascular events were slightly higher with linagliptin than with placebo only (24 patients [2.93%] with linagliptin versus 20 patients [2.48%] with placebo). These data were not statistically significant and the absolute numbers are low. A cardiovascular outcome study to further clarify the cardiovascular safety of linagliptin was requested by the CHMP at the time of the initial MAA for Trajenta and is currently ongoing and included already in the RMP.

**Use of linagliptin in elderly patients**

The safety analyses of study 1218.63 revealed no new unexpected safety issues. The overall rate of AEs was higher than in most previous clinical trials with linagliptin, but the differences between placebo and treatment group were small, including SAEs, suggesting that this is related to the age of the study population. The increase in amylase levels has been included as an ADR in section 4.8 "Undesirable effects" of the SmPC. As other DPP-4 inhibitors, linagliptin is associated with an increased risk for pancreatitis and this has been reflected in section 4.4 of the SmPC.

### *Conclusion on clinical safety*

In general linagliptin was well tolerated as add-on to insulin and in elderly patients, and the incidences of adverse events were usually not importantly different between treatment groups. As could be expected on the basis of previous trials with linagliptin, gastrointestinal disorders and nasopharyngitis occurred more frequently with linagliptin than with placebo. There was an increase in amylase levels with linagliptin. As other DPP-4 inhibitors, linagliptin is associated with an increased risk for pancreatitis. These ADR have been reflected in the SmPC.

Thyroid neoplasm was reported by 5 patients (0.1%) in the linagliptin group but none in the placebo group. Even though the above findings were considered not drug-related and non-malignant, it should be noted that they were reported in the linagliptin group only. Oncological AE is already included as important missing information in the RMP. But taking the aforementioned and the mechanism of action into consideration, the MAH should discuss this in future PSURs.

In the cardiovascular safety analysis of study 1218.36, the main study for this application, the rate of the primary endpoint (CV death, MI, stroke or hospitalisation due to unstable angina) was higher in the linagliptin group than in the comparator group: 18 patients (2.9%) versus 11 patients (1.7% respectively) but the difference between the two groups was not statistically significant. However in comparison to placebo and active comparators combined, linagliptin was not associated with an increased cardiovascular risk in the updated cardiovascular meta-analysis submitted with this application (HR 0.83 with 95% CI 0.57,1.21). Nevertheless, as this cardiovascular meta-analysis including all the linagliptin trials, having more events collected, needs to be considered as more relevant to define the actual CV risk of linagliptin, the CHMP considers that the results from one single study analysis, whilst in need of further investigation, do not already allow the conclusion on a CV risk associated with the use of the medicinal product. A cardiovascular outcome study to further clarify the cardiovascular safety of linagliptin is currently ongoing and is included already in the RMP.

## *2.4. Risk management plan*

The MAH submitted an updated Risk Management Plan within this variation procedure.

**Table 37. Summary of the risk management plan**

| Safety concern | Proposed pharmacovigilance activities (routine and additional) | Proposed risk minimization activities (routine and additional) |
|---|---|---|
| **Important identified risk** | | |
| Hypoglycaemia | Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data | *4.2 Posology and method of administration*<br>When linagliptin is used in combination with a SU or with insulin, a lower dose of the SU or insulin, may be considered to reduce the risk of hypoglycaemia<br>*4.4 Special warnings and precautions for use*<br>Hypoglycaemia<br>When linagliptin is used with SU or insulin, caution is advised. A dose reduction of SU or insulin may be considered.<br>*4.8 Undesirable effects*<br>Hypoglycaemia is listed as very common adverse reaction when linagliptin is combined with metformin and a SU. |
| Pancreatitis | Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data | *4.4 Special warnings and precautions for use*<br>Information on post-marketing reports of acute pancreatitis for linagliptin. In addition, signs and symptoms indicative of pancreatitis are provided.<br>*4.8 Undesirable effects*<br>Pancreatitis is listed as adverse reaction for linagliptin |
| Angioedema/urticaria and hypersensitivity | Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data | *4.8 Undesirable effects*<br>Angioedema, urticaria are listed for linagliptin, based on post-marketing reports.<br>Hypersensitivity is listed as adverse reaction for linagliptin. |
| **Important potential risks** | | |

| Safety concern | Proposed pharmacovigilance activities (routine and additional) | Proposed risk minimization activities (routine and additional) |
|---|---|---|
| Skin lesions | Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data | Not applicable. |
| | | |
| Infections | Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data | Not applicable. |
| Worsening of renal function | Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data | Not applicable. |
| **Important missing information** | | |
| **Safety in subpopulations** | | |
| High risk patients with recent CV events | Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data (planned CV-safety study and final data of study 1218.63) which includes the analysis of available data for patients concomitantly treated with linagliptin and insulin in both CV safety studies. Ongoing CV meta-analyses of Phase III and IV programme | *Section 5.1 Pharmacodynamic properties*<br>Cardiovascular risk<br>Information on the results of the pre-specified cardiovascular meta-analysis is provided. To date, no evidence for an increased CV risk is seen, however the number of events in the clinical studies was low, precluding firm conclusions. |

| Safety concern | Proposed pharmacovigilance activities (routine and additional) | Proposed risk minimization activities (routine and additional) |
|---|---|---|
| Old patients (>80 years) | Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data (planned CV safety study and final data of study 1218.63 | *Section 4.2 'Special populations'*<br>Elderly<br>No dose adjustment is necessary based on age.<br>*Section 5.2 'Pharmacokinetic properties'*<br>Geriatric<br>No dosage adjustment is required based on age up to 80 years, as age did not have a clinically relevant impact on the pharmacokinetics of linagliptin. |
| Severe renally impaired patients | Routine pharmacovigilance and analysis of final data of study 1218.43 | *Section 4.2 'Special populations'*<br>Renal impairment<br>For patients with renal impairment, no dose adjustment for linagliptin is required.<br>*5.2 'Pharmacokinetic properties'*<br>Renal insufficiency<br>Information on pharmacokinetics of linagliptin (5 mg dose) in patients with varying degrees of chronic renal insufficiency is provided. Based on the data, no dose adjustment of linagliptin in this population is necessary. |
| Paediatric use | Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data | *Section 4.2 'Special populations'*<br>Paediatric population<br>The safety and efficacy of linagliptin in children and adolescents has not yet been established. No data are available.<br>*Section 5.2 'Pharmacokinetic properties'*<br>Paediatric population<br>Studies characterising the pharmacokinetics of linagliptin in paediatric patients have not been yet performed. |

| Safety concern | Proposed pharmacovigilance activities (routine and additional) | Proposed risk minimization activities (routine and additional) |
|---|---|---|
| Pregnant and lactating patients | Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data | *Section 4.6 'Fertility, pregnancy and lactation'*<br>Pregnancy<br>The use of linagliptin has not been studied in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive As a precautionary measure, it is preferable to avoid the use of linagliptin during pregnancy.<br><br>Breast-feeding<br>Available pharmacokinetic data in animals have shown excretion of linagliptin/metabolites in milk. A risk to the breast-feed child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from linagliptin therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. |
| Hepatic impaired patients | Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data | *Section 4.2 'Special populations'*<br>Hepatic impairment<br>Pharmacokinetic studies suggest that no dose adjustment is required for patients with hepatic impairment but clinical experience in such patients is lacking.<br>*Section 5.2 'Pharmacokinetic properties'*<br>Hepatic impairment<br>The available PK data support no dose adjustment for linagliptin for patients with mild, moderate or severe hepatic impairment. |
| Oncological adverse reactions | Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data | Not applicable. |
| Idiosyncratic adverse reactions | Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data | Not applicable. |

| Safety concern | Proposed pharmacovigilance activities (routine and additional) | Proposed risk minimization activities (routine and additional) |
|---|---|---|
| Immunological adverse reactions | Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data | Not applicable. |
| Concomitant P-gp and CYP3A4 inhibitors | Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data | Not applicable. |

The CHMP, having considered the data submitted, was of the opinion that no additional pharmacovigilance activities in addition to the use of routine pharmacovigilance activities and the already agreed additional pharmacovigilance activities detailed in the pharmacovigilance plan of the RMP are needed to investigate further some of the safety concerns.

Agreed additional pharmacovigilance activities:

| Description | Due date |
|---|---|
| Study 1218.74:<br>CV outcome study | Interim analysis (DMC safety assessemnt only):<br>event driven, ≥ 80 adjudicated primary outcome events, and minimum duration of 1.5 years:<br>January 2014<br><br>Final analysis due date event driven, 631 adjudicated primary outcome events<br>December 2018 |
| CV meta-analyses of phase 3 and 4 program at appropriate time points | 31-Jan-2013 |

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

## *2.5. Changes to the Product Information*

The MAH proposed the following changes to the Product Information (PI) (underlined = new text, strikethrough = deleted text), to which the CHMP agreed:

**Section 4.2 Posology and method of administration of the SmPC**

Posology
The dose of linagliptin is 5 mg once daily. When linagliptin is added to metformin, the dose of metformin should be maintained, and linagliptin administered concomitantly.
When linagliptin is used in combination with a sulphonylurea or with insulin, a lower dose of the sulphonylurea or insulin, may be considered to reduce the risk of hypoglycaemia (see section 4.4)

**Section 4.4 Special warnings and precautions for use of the SmPC**

Hypoglycaemia
Sulphonylureas and insulin are known to cause hypoglycaemia. Therefore, caution is advised when linagliptin is used in combination with a sulphonylurea and/or insulin. A dose reduction of the sulphonylurea or insulin, may be considered (see section 4.2).

**Section 4.8 Undesirable effects of the SmPC**

Summary of the safety profile
The safety of ~~TRAJENTA®~~Trajenta has been evaluated overall in ~~4,687~~6,602 patients with T2DM of which ~~4,040~~5,955 patients received the target do~~si~~se of 5 mg.

In placebo-controlled studies, ~~3,749~~6,666 patients were included and ~~2,566~~4,302 patients were treated with the therapeutic dose of 5 mg linagliptin. ~~2,3603~~3,964 patients were exposed to linagliptin 5 mg once daily for ≥ 12 weeks.

In the pooled analysis of the placebo-controlled trials, the overall incidence of adverse events in patients treated with placebo was similar to linagliptin 5 mg (~~53.8% versus 55.0%~~63.1% versus 60.3%).
Discontinuation of therapy due to adverse events was higher in patients who received placebo as compared to linagliptin 5 mg (~~3.6% versus 2.3%~~4.4% versus 3.3%).

The most frequently reported adverse reaction was hypoglycaemia observed under the triple combination, linagliptin plus metformin plus sulphonylurea 14.6% versus 7.6% in placebo.

In the placebo controlled studies 6.2% of patients experienced "hypoglycaemia" as an adverse reaction under linagliptin. ~~86.8% of these were mild and 13.2% were moderate.~~ Of these, 5.1% were mild and 1.0% were moderate and 0.1% were classified as severe. ~~None of the hypoglycaemias was classified as severe.~~ Pancreatitis was reported more often in patients randomized to linagliptin (~~2~~5 events in ~~2,566~~4,302 patients receiving linagliptin versus ~~zero~~1 event in ~~1,183~~2,364 patients receiving placebo).

Tabulated list of adverse reactions
Due to the impact of the background therapy on adverse reactions (e.g. on hypoglycaemias), adverse reactions were analysed and displayed based on the respective treatment regimens (monotherapy, add on to metformin, ~~and~~ add on to metformin plus sulphonylurea, and add on to insulin).

**Section 5.1 Pharmacodynamic properties of the SmPC**

*Linagliptin as add on to insulin therapy*
The efficacy and safety of the addition of linagliptin 5 mg to insulin alone or in combination with metformin and/or pioglitazone has been evaluated in a double blind placebo controlled study of 24 weeks duration. Linagliptin provided significant improvements in HbA1c (-0.65% compared to placebo) from a mean baseline HbA1c of 8.3 %. Linagliptin also provided significant improvements in fasting plasma glucose (FPG), and a greater proportion of patients achieved a target HbA1c of < 7.0%, compared to placebo. This was achieved with a stable insulin dose (40.1 UI). Body weight did not differ significantly between the groups. Effects on plasma lipids were negligible. The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo (22.2% linagliptin; 21.2% placebo).

**Section 1 What Trajenta is and what it is used for of the Package Leaflet**

Trajenta is used for 'type 2 diabetes' in adults, if the disease cannot be adequately controlled with one oral anti-diabetic medicine (metformin or sulphonylureas) or diet and exercise alone. Trajenta may be used together with other anti-diabetic medicines (insulin, metformin or sulphonylureas e.g. glimepiride, glipizide).

**Section 4 Possible side effects of the Package Leaflet**

Like all medicines, ~~Trajenta~~this medicine can cause side effects, although not everybody gets them.

Some symptoms need immediate medical attention
You should stop taking Trajenta and see your doctor immediately if you experience the following symptoms of low blood sugar: trembling, sweating, anxiety, blurred vision, tingling lips, paleness, mood change or confusion (hypoglycaemia). Hypoglycaemia (frequency: very common, may affect~~s~~ more than ~~one~~1 in 10 people) is an identified side effect for the combination of Trajenta plus metformin and plus ~~sulfonylurea~~sulphonylurea.

Some patients have experienced allergic reactions (hypersensitivity; for frequency ~~see below~~not known), which may be serious, including rash, hives, and swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing (angioedema, urticaria), and wheezing and shortness of breath (bronchial hyperreactivity).

Some patients have experienced inflammation of the pancreas (pancreatitis; frequency not known, frequency cannot be estimated from the available data). Call your doctor if you experience severe and persistent stomach ache, with or without vomiting, because you could have pancreatitis. ~~Inflammation of the pancreas, irrespective of other therapy with other oral glucose lowering agents (pancreatitis; frequency not known, cannot be estimated from the available data.)~~

Some patients have had the following side effects while taking Trajenta alone:
- Uncommon (may affect~~s~~ up to 1 ~~to~~in 100 ~~users~~people ~~in 1000~~): inflamed nose or throat (nasopharyngitis), cough, blood enzyme amylase increased.
- Not known (frequency cannot be estimated from the available data): allergic reactions (hypersensitivity).

Some patients have had the following side effects while taking Trajenta and metformin:

- Uncommon: inflamed nose or throat (nasopharyngitis), allergic reactions (hypersensitivity), cough.

Some patients have had the following side effects while taking Trajenta and insulin:
- Uncommon: inflamed nose or throat (nasopharyngitis), cough, pancreatitis, constipation, blood enzyme amylase increased.
- Not known: allergic reactions (hypersensitivity).

Some patients have had the following side effects while taking Trajenta, metformin and a sulphonylurea:
- Not known: inflamed nose or throat (nasopharyngitis), allergic reactions (hypersensitivity), cough, blood enzyme amylase increased.

If you get any ~~of the~~ side effects talk to your doctor, pharmacist or nurse. This includes any possible ~~gets serious, or if you notice any~~ side effects not listed in this leaflet~~, please tell your doctor or pharmacist~~.

During the procedure, the CHMP requested further amendments to the PI as discussed in detail above:

**Section 4.1 Therapeutic indications of the SmPC**

Trajenta is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults:

as **monotherapy**
- in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment.

as **combination therapy**
- in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.
- in combination with insulin with or without metformin, when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.

**Section 4.2 Posology and method of administration of the SmPC**

*Elderly patients*
No dose adjustment is necessary based on age.

However, clinical experience in patients > ~~75~~80 years of age is limited and caution should be exercised when treating this population.

**Section 4.4 Special warnings and precautions for use of the SmPC**

Pancreatitis

In post-marketing experience of linagliptin there have been spontaneously reported adverse reactions of acute pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. Resolution of pancreatitis has been observed after discontinuation of linagliptin. If pancreatitis is suspected, Trajenta should be discontinued.

**Section 4.7 Effects on ability to drive and use machines of the SmPC**

~~No studies on the effects on the ability to drive and use machines have been performed.~~ Trajenta has no or negligible influence on the ability to drive and use machines. However patients should be alerted to the risk of hypoglycaemia especially when combined with sulphonylurea and/or insulin.

**Section 4.8 Undesirable effects of the SmPC**

Table 1 Adverse reactions reported in patients who received linagliptin 5 mg daily as monotherapy or as add-on therapies (pooled analysis of placebo-controlled studies)

| | Adverse reactions by treatment regimen | | | |
|---|---|---|---|---|
| System organ class<br>Adverse reaction | Linagliptin monotherapy | Linagliptin + Metformin | Linagliptin + Metformin + Sulphonylurea | Linagliptin + Insulin |
| Infections and infestations | | | | |
| *Nasopharyngitis* | uncommon | uncommon | not known | uncommon |
| Immune system disorders | | | | |
| *Hypersensitivity (e.g. bronchial hyperreactivity)~~Hypersensitivity~~* | not known | uncommon | not known | not known |
| Metabolism and nutrition disorders | | | | |
| *Hypoglycaemia* | | | very common | |
| Respiratory, thoracic and mediastinal disorders | | | | |
| *Cough* | uncommon | uncommon | not known | uncommon |
| Gastrointestinal disorders | | | | |
| *Pancreatitis* | not known | not known | not known | uncommon |
| *Constipation* | | | | uncommon |
| Investigations | | | | |
| *Amylase increased* | uncommon | uncommon | Not known | not known |

**Section 5.1 Pharmacodynamic properties of the SmPC**

In an updated prospective, pre-specified meta-analysis analysis of independently adjudicated cardiovascular events from 15 phase III clinical studies (ranging from 18 weeks to 24 months duration) involving 8622 patients with type 2 diabetes, linagliptin treatment was not associated with an increase in cardiovascular risk. The primary endpoint, the composite of: the occurrence or time to first

occurrence of CV death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for unstable angina, was non-significantly lower for linagliptin versus combined active and placebo comparators [Hazard ratio 0.83 (95% confidence interval 0.57;1.21)]. In total there were 56 primary events on linagliptin and 55 on comparators. To date there is no evidence for an increased CV risk but the number of events in the clinical studies precludes firm conclusions. However, cardiovascular events were similar between linagliptin and placebo (1.06% with lina vs 1.21% with placebo).~~In a prospective, pre-specified meta-analysis analysis of independently adjudicated cardiovascular events from 8 phase III clinical studies (ranging from 18 weeks to 12 months duration) involving 5239 patients with type 2 diabetes, linagliptin treatment was not associated with an increase in cardiovascular risk. The primary endpoint, the composite of: the occurrence or time to first occurrence of CV death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for unstable angina, was significantly lower for linagliptin versus combined active and placebo comparators [Hazard ratio 0.34 (95% confidence interval 0.17;0.70)]. In total there were 11 primary events on linagliptin and 23 on comparators. To date there is no evidence for an increased CV risk but the number of events in the clinical studies was low, precluding firm conclusions.~~

**Section 2 What you need to know before you take Trajenta of the PIL**

**Driving and using machines**

Trajenta has no known influence on the ability to drive and use machines.

Taking Trajenta in combination with medicines called sulphonylureas and/or insulin can cause too low blood sugar levels (hypoglycaemia), which may affect your ability to drive and use machines or work without safe foothold.

Changes were also made to the PI to bring it in line with the current Agency/QRD template, SmPC guideline and other relevant guideline(s), which were reviewed by QRD and accepted by the CHMP.

In addition, the MAH took the opportunity to include the Marketing Authorisation numbers in the SmPC and Labelling and to make linguistic corrections in the Spanish Annexes.

# 3. Benefit-Risk Balance

## *Benefits*

### Beneficial effects

The efficacy of linagliptin as add-on to insulin was modest but statistically significant and clinically relevant. The decrease in HbA1c was similar compared to other studies using linagliptin. Linagliptin add-on to insulin was weight neutral. The beneficial blood glucose lowering effects of linagliptin in the elderly population was demonstrated in study 1218.63.

### Uncertainty in the knowledge about the beneficial effects

Linagliptin is not approved for use in combination with pioglitazone or SU. In the current application, most patients in the pivotal study 1218.36 were taking metformin monotherapy (75.1% of all patients

in EFF-1) in combination with insulin. Only 1.0% of patients were taking pioglitazone but not metformin, while 7.3% of were taking both metformin and pioglitazone. No patients were using SU in the major study and its use is limited to small number of patients in the other two studies.

Efficacy was similar is most subgroups. As most patients who will be treated with linagliptin in combination with insulin will have diabetes duration of more than one year, the observed smaller reduction of HbA1c in the subgroup of patients with diabetes duration of less than one year is not of concern in clinical practice.

For the patients with renal impairment, the effect of linagliptin on fasting plasma glucose was small, but the decrease in HbA1c was clinically relevant.

# *Risks*

## Unfavourable effects

In general linagliptin was well tolerated, and the incidences of adverse events were usually not importantly different between treatment groups. As could be expected on the basis of previous trials with linagliptin, gastrointestinal disorders and nasopharyngitis occurred more with linagliptin.

There was an increase in amylase levels with linagliptin in study 1218.63, the study conducted in elderly patients. As other DPP-4 inhibitors, linagliptin is associated with an increased risk for pancreatitis.

## Uncertainty in the knowledge about the unfavourable effects

An important goal in the treatment of diabetes is the prevention of cardiovascular disease. In the cardiovascular safety analysis of study 1218.36, the main study for this application, the rate of the primary endpoint (CV death, MI, stroke or hospitalisation due to unstable angina) was higher in the linagliptin group than in the comparator group: 18 patients (2.9%) versus 11 patients (1.7% respectively). An updated cardiovascular meta-analysis of studies investigating linagliptin in combination with other oral antidiabetic medications was submitted by the MAH with this application. In comparison to placebo and active comparators combined, linagliptin was not associated with an increased cardiovascular risk (HR 0.83 with 95% CI 0.57,1.21).In a subgroup analysis including all the studies including patients taking insulin as background therapy, cardiovascular events were slightly higher with linagliptin than with placebo only (24 patients [2.93%] with linagliptin versus 20 patients [2.48%] with placebo). These data were not statistically significant and the absolute numbers are low. A cardiovascular outcome study to further clarify the cardiovascular safety of linagliptin was requested by the CHMP at the time of the initial MAA for Trajenta and is currently ongoing and included already in the RMP.In Study SAF-3, linagliptin was, compared to placebo, associated with more adverse events in Blacks, but not in Whites and Asians. In addition, in Blacks, linagliptin was associated with more serious adverse events. In study 1218.75, a Phase III, 24-week, randomised, placebo-controlled, double-blind efficacy and safety trial in Black/African American T2DM patients, 1/106 (0.9%) patients in the linagliptin group versus 2/120 (1.7%) patients in the placebo group experienced serious AEs. Severe AEs were reported for 4/106 (3.8%) patients in the linagliptin group, versus 4/120 (3.3%) in the placebo group. No clustering of SAE were shown in the linagliptin group in study 1218.75. Furthermore, both the efficacy and safety results were in line with previously submitted studies performed in other races. Considering this, the safety results in SAF-3 regarding black patients was most-likely caused by chance, due to the limited number of Black patients participating in that study.

The only preferred term that was reported in more than 1 patient in the linagliptin group was thyroid neoplasm, which was reported by 5 patients (0.1%) in the linagliptin group but none in the placebo group. The reported terms of these events refer to a thyroid nodule and do not qualify as malignancies; yet since they are coded as thyroid neoplasm, they were identified by the SMQ search. All 5 events were non-serious and of mild to moderate intensity, required no therapy and were not considered to be drug-related (for 1 patient the relatedness assessment was missing). Linagliptin containing medicinal products will be used chronically, and the clinical experience, in particular long term use, with linaglitpin is limited. Even though the above findings were considered not drug-related and non-malignant, it should be noted that they were reported in the linagliptin group only. Oncological AE is already included as important missing information in the RMP. But taking the aforementioned and the mechanism of action into consideration, the MAH should discuss this in future PSURs.

# *Benefit-risk balance*

## Importance of favourable and unfavourable effects

The efficacy of linagliptin as add-on to insulin is modest, but statistically significant, clinically relevant and comparable to its efficacy as add-on to other antidiabetic drugs.

The number of patients using linagliptin with insulin in combination with pioglitazone and SU was low. However the new indication is limited to "in combination with insulin with or without metformin" only.

In individuals with diabetes duration less than 1 year, the treatment effect of linagliptin was small. However, this is not a major issue, as most patients that will be treated with a combination of linagliptin and insulin will have longer diabetes duration.

Most adverse events were non-serious. As not enough events have been collected during the clinical trials to draw firm conclusions on the CV risk with linagliptin, its cardiovascular safety will be further clarified with the currently ongoing CV outcome study (study 1218.74) (see RMP).

In addition, the risk of pancreatitis was increased with linagliptin and also amylase levels were increased in the linagliptin group. Both issues have been included in the Trajenta SmPC.

The higher incidence of adverse events and serious adverse events seen in Blacks in study SAF-3 were based on a small number of subjects. Furthermore, an additional study in only Black/African Americans did not support an increased risk in Black patients.

The reduction in Hb was small, but may be important with long term treatment.

The benefit/risk balance in the elderly population age group was comparable to the younger T2DM age groups.

## Benefit-risk balance

The numerical increase in cardiovascular events observed with the combination therapy of linagliptin with insulin has been discussed further by the MAH and an updated meta-analysis was performed. Compared to the combination of placebo and active comparator cardiovascular events in the group of patients treated with linagliptin were lower but still slightly higher compared to placebo. However, the absolute number in events was low and results were considered inconclusive. Further data from the ongoing cardiovascular outcome study (study 1218.74) is awaited.

The risk of pancreatitis is in line with previous findings with linagliptin and other DPP-4 inhibitors. This risk has been added to paragraph 4.4 "Special warnings and precautions for use". The increase in amylase levels should be mentioned in section 4.8 "Undesirable effects".

The higher incidence of adverse events and serious adverse events in Blacks were based on a small number of subjects. However, there was no specific pattern of SAEs towards a medical concept or a specific safety concern. Furthermore, an additional larger study in only Black/African Americans (n=106 linagliptin, versus n=120 placebo) did not support an increased safety risk in Black patients.

### Discussion on the benefit-risk balance

The overall benefit/risk of linagliptin is considered positive for the indication:

*Trajenta is indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults:*

*as **monotherapy***

- *in patients inadequately controlled by diet and exercise alone and for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment.*

*as **combination therapy***

- *in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.*
- *in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.*
- *in combination with insulin with or without metformin, when this regimen alone, with diet and exercise, does not provide adequate glycaemic control.*

# 4. Recommendations

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

| **Variations accepted** | | **Type** |
|---|---|---|
| C.I.6.a | Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one | II |
| C.I.4 | Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data | II |

Update of sections 4.1, 4.2, 4.4, 4.7, 4.8 and 5.1 of the SmPC: extension of indication for the treatment of type 2 diabetes in combination with insulin (with or without metformin) when this regimen alone, with diet and exercise, does not provide adequate glycaemic control. Sections 1, 2 and 4 of the Package Leaflet are updated accordingly.

Update of sections 4.2, 4.8 and 5.1 of the SmPC to include the results of study 1218.63, a study conducted in elderly patients.

In addition, the MAH took the opportunity to include the Marketing Authorisation numbers in the SmPC and Labelling and to make linguistic corrections in the Spanish Annexes.

Furthermore, the PI is being brought in line with the latest QRD template version 8.

The requested group of variations proposed amendments to the Update of Summary of Product Characteristics, Annex II, Labelling and Package Leaflet.