23 June 2011
EMA/604444/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trajenta

linagliptin

Procedure No.: EMEA/H/C/002110/0000

Note

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

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Boehringer Ingelheim International GmbH submitted on 30 June 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for linagliptin, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 March 2009.

The applicant applied for the following 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 contraindications or intolerance.

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

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/114/2009 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.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

New Active Substance status

The applicant requested the active substance linagliptin contained in the above medicinal product to be considered as a new active substance in itself.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 19 July 2007 and on 23 April 2008. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

Trajenta has been given a Marketing Authorisation in USA on 2 May 2011.

A new application was filed in the following countries: Australia, Canada, Japan, South, Indonesia, Argentina, Singapore, Colombia, Taiwan, Brazil, South Korea, Croatia, Mexico, Chile, Venezuela, Peru, Russia and India.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Pieter de Graeff** Co-Rapporteur: **Martina Weise**

- The application was received by the EMA on 30 June 2010.
- The procedure started on 21 July 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 October 2010. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 12 October 2010.
- During the meeting on 15-18 November 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 November 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 10 February 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 28 March 2011.
- During the CHMP meeting on 11-14 April 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 23 May 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Outstanding Issues to all CHMP members on 9 June 2011.
- During the meeting on 20-23 June 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Trajenta on 23 June 2011.

2. Scientific discussion

2.1. Introduction

Problem statement

Type 2 diabetes mellitus affects more than 180 million people worldwide and particularly in the industrialised countries the incidence of the disorder is increasing. Type 2 diabetes mellitus is characterised by multiple metabolic abnormalities involving insulin resistance, impaired insulin secretion, and increased glucose production. Morbidity and mortality associated with type 2 diabetes mellitus is caused by macrovascular complications such as cardiovascular disease and microvascular complications such as retinopathy, neuropathy, and nephropathy. In addition to diet and exercise, a number of medications are available to lower blood sugar levels. However, all of the established therapies have limitations including a range of safety and tolerability issues, limited extent and/or durability of efficacy, and inconvenience in dosing. The most common adverse events associated with currently used agents are hypoglycaemia (with sulfonylureas, meglitinides, insulin), weight gain (with sulfonylureas, meglitinides, insulin, thiazolidinediones [TZDs]), and gastrointestinal intolerance (with metformin, alpha-glucosidase inhibitors). Dipeptidyl-dipeptidase-4 (DPP-4) inhibitors are generally well tolerated; treatment with the currently marketed DPP-4 inhibitors (sitagliptin, saxagliptin, vildagliptin) was however associated with elevated incidences of infections and gastrointestinal disorders (compared with placebo). Sitagliptin, vildagliptin, and saxagliptin are either not indicated in patients with moderate to severe renal impairment or require dose adjustments in this patient population. Current regulatory guidelines emphasize the need for a thorough investigation of the cardiovascular risk profile of antidiabetic medications.

About the product

Linagliptin is a selective, orally administered, xanthine-based DPP-4 inhibitor. GLP-1 lowers blood glucose levels by augmenting the glucose-stimulated insulin release. Moreover, GLP-1 inhibits glucagon secretion, slows gastric emptying, and induces satiety. The plasma half-life of GLP-1 is limited to a few minutes because of rapid proteolytic degradation by the enzyme DPP-4. Inhibition of DPP-4 prolongs the half-life of active GLP-1 and thereby increases plasma insulin levels and lowers plasma glucose levels. Since GLP-1 activity ceases when the glucose concentration falls below 55 mg/dL, prolongation of the half-life of GLP-1 by DPP-4 inhibitors bears little risk of hypoglycaemia. Linagliptin is a selective, competitive, reversible inhibitor of human DPP-4 with a 50% Inhibitor Concentration (IC50) of 1 nM. The therapeutic dose of linagliptin will be 5 mg. Linagliptin is predominantly excreted unchanged via the faeces. Renal excretion is a minor pathway of elimination of linagliptin at therapeutic doses. Thus, linagliptin is especially suited for the treatment of patients with renal impairment without the need for dose adjustment.

The claim indication for linagliptin was:

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 contraindications or intolerance.

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 when diet and exercise plus a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate.

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

The approved indication for linagliptin is:

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."

Type of Application and aspects of the development

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application (new active substance)

Initial scientific advice was sought from the CHMP for clinical issues on 16 May 2007 (EMEA/CHMP/SAWP/ 385760/2007). Subsequently, the clinical program was revised and a follow-up Scientific Advice was sought on 23 April 2008. (EMEA/CHMP/ SAWP/311988/2008). The emphasis of the meetings was on the design features of the phase III trials, particularly dosing, the adequacy of the safety database, and the non-inferiority margin in the active-controlled 1218.20 trial.

2.2. Quality aspects

2.2.1. Introduction

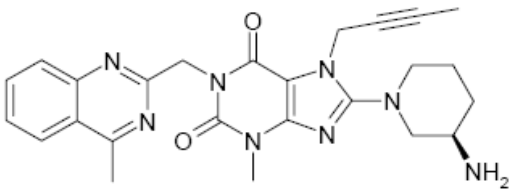
Composition
Trajenta is presented as light red, round, biconvex immediate release film-coated tablets containing 5 mg of linagliptin as the active substance.

Other ingredients include mannitol, pregelatinised starch, maize starch, copovidone, magnesium stearate in the tablet core and hypromellose, titanium dioxide, talc, macrogol 6000 and red iron oxide for the film coating.

The finished product is packed in aluminium/aluminium blisters.

2.2.2. Active Substance

The chemical name of linagliptin is 8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1-[(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione. The structural formula is shown below:



The structure has been confirmed by means of UV, IR, 1H- and 13C-NMR spectroscopy and mass spectrometry. The content of carbon, hydrogen and nitrogen have been determined by elemental analysis.

Linagliptin has one chiral centre at the 3-aminopiperidine moiety. The active substance corresponds to the R-enantiomer. The absolute configuration of the active substance at the chiral carbon has been determined by means of single X-ray crystallography.

It is a white to yellowish crystalline solid substance. It is slightly hygroscopic, but water uptake does not change the crystal modification. It is very soluble in aqueous media (> 1 mg/ml) over the entire physiological pH range. It is soluble in methanol, sparingly soluble in ethanol and very slightly soluble in isopropanol and acetone.

The active substance simultaneously exists in two polymorphic forms, which are enantiotropically related and which reversibly convert into each other approximately at room temperature. The two polymorphic forms do not differ with regard to biopharmaceutical properties.

Manufacture

The synthetic process for linagliptin consists of three steps and then a milling step follows.

The manufacturing process has been described in sufficient detail including suitable reaction schemes. The amounts of raw materials, yields, and equipment have been specified, and the in-process controls have been well described.

The levels of the impurities with an acceptance criterion higher than max. 0.15% are supported by the results of toxicological studies and appropriate specifications have been set. There are no impurities arising from the starting materials.

The synthetic process does not involve Class 1 solvents or metal catalysts. The Class 2 and the Class 3 solvents used in the synthesis have been shown to be efficiently removed during the process and appropriate specifications have been set in accordance with the Note for Guidance on Impurities: Residual Solvents.

Specification

The specifications of the active substance contains tests with suitable limits for appearance (visually), identification (IR spectrum, Chiral HPLC, Melting point), impurity (GC, HPLC, Chiral-HPLC), residual solvents (GC), water content (KF), sulphated ash (weighing), particle size (Laser-beam diffraction) and Assay (HPLC)

The analytical methods used have been adequately validated in accordance with the Note for Guidance on Validation of Analytical Methods: Definitions and Terminology / Methodology.

Batch analysis results have been provided for 14 batches manufactured according to the proposed synthetic process. In all cases the results demonstrate compliance with the proposed active substance specifications.

Stability
Stability studies have been conducted in accordance with ICH requirements on three commercial batches manufactured with the proposed route of synthesis. The samples were stored for up to 36 months under the conditions for long term storage and up to 6 months under accelerated conditions. The parameters tested included appearance, melting temperature, organic impurities, enantiomeric purity, water content, assay and particle size. The analytical methods used were stability indicating. In all cases the stability results presented were satisfactory and support the proposed retest period.

In addition, one batch was subjected to stress studies at elevated temperature, humidity, pH, oxidative conditions and light in the solid state and in solution. Photostability testing of the solid active substance was also performed according to ICH guideline Q1B. The parameters tested included appearance, melting temperature, organic impurities, enantiomeric purity, water content and assay.

The results of the stress studies demonstrated that in solid form, the active substance is very stable at elevated temperatures, high humidity and the combined effect of both conditions. During photostability testing, only a slight change in colour was observed, but no change in impurity profile leading to the conclusion that the active substance is not sensitive to light.

2.2.3. Finished Medicinal Product

Pharmaceutical Development
The objective of the product development was to obtain an immediate release oral dosage form with rapid disintegration and dissolution, preferably as a film-coated tablet formulation.

Linagliptin is a highly soluble active substance. It is considered to be a Class 3 drug substance (high solubility, poor permeability) according to the Biopharmaceutical Classification System (BCS) due to its incomplete oral systemic bioavailability (about 30% compared to intravenous administration) and the moderate permeability observed in Caco-2 cells.

Due to the low active substance content in the final formulation, the active substance is milled to ensure an adequate content uniformity. Several particle size ranges were investigated and a change in the active substance particle size distribution within the investigated range has no relevant influence on in-vitro dissolution while the content uniformity of the tablets is acceptable.

The excipients chosen for the formulation development are commonly used in oral pharmaceutical dosage forms and comply with PhEur requirements. All components are inert showing no interactions with drug release.

A standard aqueous wet granulation process was chosen to manufacture the product. All critical process parameters have been identified and controlled by appropriate in process controls.

The manufacturing process of the pivotal studies of phase II and III were identical. There are only some marginal differences regarding the pigment of the film-coating between the formulation used for the phase III studies and the commercial product.

Adventitious agents
None of the excipients used for Trajenta are of animal or human origin

Manufacture of the Product
The manufacturing process is a standard process for these kinds of formulations such as: blending, wet granulation, compression and coating. The manufacturing process has been adequately validated according to the relevant European guidelines. Process validation data were presented and demonstrate that the process is reproducible and provides a drug product that complies with the in-process and finished product specifications.

Product Specification
The product specification includes tests for description (visual), identification (UV spectrum, HPLC), loss on drying (weighing), dissolution (HPLC), uniformity of dosage units (HPLC or NIR), assay (HPLC), and degradation products (HPLC). The release and shelf life limits differ with regard to the fact that identification and uniformity of dosage units is only tested at release. The other acceptance criteria do not differ between release and shelf life.

The analytical methods used for release and shelf life testing have been adequately described and validated.

Batch analysis data from adequate number of batches at full scale and smaller batches have been provided to demonstrate compliance with the proposed release specifications.

Stability of the Product
Stability studies were carried out according to the ICH requirements. Samples were stored at 25°C/60 % RH for up to 24 months and in 40°C/75 % RH for 6 months.

The parameters tested were description, loss on drying, dissolution, degradation products, assay, and microbial limits. The analytical procedures used are identical to those proposed for routine testing of the commercial product and are stability indicating. Validated pharmacopoeial methods are applied for microbial testing.

In addition, a stress stability study investigating the effects of elevated temperature, humidity, and light was conducted accoring to ICH and analytical data found to be within the shelf life specifications. On the basis of the provided stability data, the assigned shelf life as defined in the Summary of Product Characteristics (SmPC) is well supported. The product does not require any specific storage conditions.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of Trajenta is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

The active substance is well characterised and documented. It simultaneously exists in two polymorphic forms, which however do not differ with regard to relevant physicochemical properties.

The excipients are commonly used in these types of formulations and comply with Ph. Eur. requirements. The packaging material is commonly used and well documented. The manufacturing process of the finished product is a standard process that has been adequately described. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

Quality Development

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

To support the clinical evaluation of linagliptin a number of non-clinical pharmacology and toxicity studies were conducted prior to and in parallel with the clinical program. These studies included a battery of both *in vitro* and *in vivo* genotoxicity studies, safety pharmacology studies, acute and repeated dose oral studies, rodent carcinogenicity studies, developmental and reproductive toxicity studies.

All pivotal non-clinical toxicity studies were conducted in line with ICH Non-clinical Testing Guidelines and in compliance with the Good Laboratory Practice (GLP) requirements.

CHMP Scientific advice concerning non-clinical studies was not sought.

2.3.2. Pharmacology

Linagliptin is a potent, selective, orally active, competitive, reversible and long-acting inhibitor of dipeptidyl-peptidase-4 (DPP-4). This membrane bound protease is expressed in many tissues including kidneys, liver, intestine, lymphocytes and vascular endothelial cells. A significant level of DPP-4 activity is also observed in plasma. By inhibiting DPP-4, linagliptin prolongs and enhances activity of the incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), resulting in increased glucose-dependent insulin secretion, suppression of glucagon secretion and delay of gastric emptying and thereby to the maintenance of post-meal glycemic control.

Primary pharmacodynamic studies

In vitro, linagliptin potently and selectively inhibited DPP-4 activity, whereas its main metabolite, CD1790, was pharmacologically inactive.

In both normal and diabetic mice and rats, the results of the studies showed that oral administration of linagliptin significantly inhibits plasma DPP-4 activity accompanied by improvements in glucose homeostasis and glucose tolerance. In diabetic rats, linagliptin also significantly increased glucose-induced elevations of GLP-1 and insulin. Although efficacious in diabetic animals, the magnitude of decreasing blood glucose is dependent on the severity of insulin resistance in these animals. In Zucker Diabetic Fatty rats, which suffer from defects in insulin secretion and severe insulin resistance, linagliptin less significantly reduced blood glucose levels than in normal animals.

In Rhesus monkeys and Beagle dogs, linagliptin also inhibited DPP-4 activity >70% within 30 min and was maintained for at least 7 hours. However, no blood glucose levels were measured to strengthen the results. The IC50 values of 0.23 nM for cynomolgus DPP4 and 0.20 nM for the human DPP-4 show that potency is comparable in both species and lies in the subnanomolar range. This shows the suitability of cynomolgus monkeys as selected species.

Long duration of action in terms of both inhibition of DPP-4 and glycaemic control was, however, demonstrated in mice and rats orally dosed with linagliptin. The results of these studies suggest that a once daily dosing frequency is adequate to maintain an appropriate degree of DPP-4 inhibition that exerts therapeutic effects on glucose.

Long-term treatment of diabetic mice reduced fed plasma glucose and glycated hemoglobin (HbA1c) after 14 and 28 days. This improved hyperglycaemia could not be explained by improved insulin sensitivity by linagliptin.

Secondary pharmacodynamic studies

Secondary pharmacodynamic studies (non-GLP) were performed to investigate the potential of linagliptin to induce neurological, cardiovascular, pulmonary, gastrointestinal and renal effects.

In vitro, linagliptin inhibited the human muscarinic receptors M1, M2 and M3, but the matching IC50 values were significantly higher than the IC50 value by which linagliptin inhibits DPP-4. *In vivo*, administration of 30 mg/kg linagliptin to conscious rats significantly increased protein and fat metabolism and probably led to hepatocellular stress. Although no toxicokinetic measurements were obtained in these studies, administration of 5 mg/kg linagliptin to male rats in a single dose toxicity study resulted in a Cmax of 547 nM, compared to the clinical Cmax of 11.1 nM. Overall, linagliptin appears not to have potential off-target activity when administered at therapeutic concentrations.

Although inhibition of DPP-4 may result in decreased gastric emptying, this effect was not observed in the secondary pharmacodynamic study evaluating the effect of linagliptin on gastrointestinal function in rats.

Safety pharmacology programme

Safety pharmacology studies were performed to examine the potential effects of linagliptin on cardiovascular, respiratory and central nervous systems.

Although *in vitro* cardiovascular safety studies indicated a low pro-arrhythmic potential for linagliptin, this potential was not confirmed by the results of the *in vivo* cardiovascular safety studies. Moreover, administration of supratherapeutic concentrations of linagliptin did not significantly affect respiratory and central nervous system function in rats.

Overall, data from the safety pharmacology supports the clinical development of linagliptin.

Pharmacodynamic drug interactions

In a diabetic mouse model, the administration of a combination of metformin (an anti-diabetic drug that improves hyperglycaemia by suppressing hepatic gluconeogenesis) and linagliptin had a superior and additive effect on glycaemic control compared to the respective monotherapies.

2.3.3. Pharmacokinetics

Absorption

Oral bioavailability of linagliptin appeared to be moderate in mice (18-44%), rats (51-55%) and monkeys (41-69%). The volume of distribution at steady state is high in all species (>4 l/kg), which suggests extensive tissue distribution. The clearance differs between species, varying from 16 (monkey) to 77 ml/min/kg (mouse). The terminal half-lives were long in all species (>10 h), except for the DPP-4 knockout mice and DPP-4 deficient rats, that showed short terminal half-lives of approximately 2-4h. After oral administration of 5 or 15 mg/kg linagliptin in mice, $AUC_{0-\infty}$ and C_{max} increased more than proportionally with dose. This indicates non-linear mechanisms in the pharmacokinetics of linagliptin in mice in this dose range. Non-linear pharmacokinetic behaviour of linagliptin was also observed in rats and rabbits, which may be due to a concentration dependency of linagliptin plasma protein binding due to DPP-4 binding saturation. Toxicokinetic studies showed some plasma accumulation of linagliptin in rat and dog plasma after repeated dosing.

Distribution

The binding of linagliptin to plasma proteins is high at concentrations of about 1 nM (>99%). The plasma protein binding is concentration dependent, since the binding is lower (70-85%) when concentrations are about 30 nM or higher. This observed concentration-dependency was shown to be due to saturation of binding to DPP-4. The blood-plasma ratio at 300 nM [^{14}C]linagliptin was ~1 in rats and ~0.6 in dogs, monkeys and humans. After administration of 1 nM [^{14}C]linagliptin, the blood-plasma ratio was much lower (~0.09 in rats and ~0.05 in monkeys). This concentration dependency is probably due to the binding to plasma DPP-4. Linagliptin is mainly located in plasma, especially at therapeutic plasma levels, giving no cause to expect extensive binding to erythrocytes. [^{14}C]linagliptin-related radioactivity was extensively distributed in rats and was present in all organs examined, except in the brain and spinal cord. The PK of linagliptin was markedly dependent on binding to DPP4. Accordingly, linagliptin showed a remarkably slow off-kinetics of linagliptin from DPP4 *in vitro*.

Linagliptin-related material does not cross the blood-brain barrier. Maximum concentrations were seen 30 minutes post-dose for all tissues, with highest concentrations in liver and kidneys. Measurable concentrations were found 168 hours post-dose in liver, spleen, thymus, Harder´s gland, lung, salivary gland, epididymis, adrenal, skin and bone marrow. In the kidney, a significant retention of radioactivity was observed for the cortex region and especially for the *zona intermedia*. During chronic use of linagliptin, steady state in tissue will be achieved quickly once DPP-4 is saturated. Therefore, only limited accumulation in tissue is expected to occur. Linagliptin crosses the placenta barrier in rats and rabbits. Fetal exposure in rats reached about 50% of the maternal exposure, whereas 2-5% was found in foetuses of rabbits.

Metabolism

Linagliptin was metabolised by CYP3A4. The *in vitro* metabolism of linagliptin was very low in human liver microsomes and human hepatocytes. Of the seven metabolites, two were formed at quantifiable amount, namely oxidation in the quinazoline moiety and CD1790. Cynomolgus monkey showed the highest extent of metabolism, followed by the female rabbit, the mouse and the rat. In humans after oral administration, metabolic clearance pathways of linagliptin only contributed to a minor extent to its overall disposition and elimination. Overall, the *in vivo* metabolism of linagliptin showed that qualitative metabolite profiles across the non-clinical species did not differ substantially and that only the relative proportions of the minor metabolites did vary. However, the metabolism in humans was slightly different from that in the pre-clinical species. The human metabolite M650(1) was not observed in animal plasma but in bile and faeces of the Cynomolgus monkey. The human metabolite M665(8) was not observed in the animal species. The peak of M665(8) and M650(1) was present for 5.5% in human plasma, but the contribution of the separate metabolites was not investigated by the applicant. Furthermore, metabolite m4 was observed in human plasma and in mouse and rat only in the faeces and not in plasma. In addition metabolite M515(1) was observed as single peak in human metabolism studies, but only as co-elution with M476(1) in the pre-clinical species studies. The peak of the M531(2), M490(1) and M506(1) and the peak of M665(8) and M650(1) was observed in humans, but this specific peak combination was not observed in the pre-clinical species. Adequate exposure of animal species of safety testing to the major human metabolite CD1790 was shown. Therefore, potential effects of general toxicity, carcinogenicity and teratogenicity that may be caused by the presence of CD1790 as a human circulating metabolite were covered by non-clinical safety testing.

Humans obviously produce many conjugated metabolites whereas in monkey unconjugated ones are frequent. So it is conceivable that the human metabolites are conjugates of the monkey metabolites. M650(1) was indeed identified as glucuronic acid conjugate of CD1790, the major human metabolite. M665(8) was characterized as glucuronic acid conjugate of the oxidation products of linagliptin

M489(1-5) in animals. Thus, both are conjugation products of metabolites and are not expected to be toxic. M4 could not directly be characterized with respect to chemical structures due to very low concentrations in the sample material with high matrix burden and ionization suppression effects. However, HPLC retention time data allowed a correlation to corresponding animal metabolites and can be considered sufficient. The absolute concentration of m4 after a dose of 10 mg linagliptin in pooled plasma samples was very low (0.7 nM). Based on these findings a toxic effect of m4 at these low concentrations is very unlikely.

Excretion

The predominant route of elimination of radioactivity in mice, rat, rabbit and monkey following oral and IV administration was via faeces with a minor contribution eliminated in urine (<30%). A considerable fraction of the faecally excreted radioactivity can be assigned to biliary excretion (up to 46% of dose within 6 h in mice, 38-43% of dose within 6 h in rats, 5% of dose within 4 h in rabbits and 27% of dose within 6 h in monkeys). The applicant claimed that linagliptin becomes secreted into the gut as parent drug, but does not undergo entero-hepatic recirculation to a major extent. As a reason it was suggested inhibition of linagliptin absorption by bile components. If so, it could be expected that a fat-rich meal also impairs bio-availability of linagliptin but this was not observed. The studies performed on biliary secretion of linagliptin employed a test system that was too artificial to discriminate between these possibilities. However, since knowing the exact mechanism would have no consequences for therapeutic use of linagliptin no further studies are required.

[^{14}C]linagliptin-derived material was excreted in milk, the concentration in milk was about 4-fold higher than in maternal plasma 1 h after administration. About 90-95% of the radioactivity was accounted to the parent compound. The remaining radioactivity (5-10%) excreted via milk was distributed over 7 minor metabolites.

Pharmacokinetic drug interactions

Linagliptin was a competitive inhibitor of monoamine oxidase B (MAO-B). In addition, linagliptin is a weak inhibitor of CYP3A4/3A5. Clinical relevance of the MAO-B and CYP3A4/3A5 inhibition is unlikely, because the therapeutic plasma levels of linagliptin are in the low nanomolar range and the IC_{50} value is in the micromolar range. The inactive metabolite, CD1790, is a competitive inhibitor of CYP2C9 and a mechanism-based inhibitor of CYP3A4 in human liver microsomes. However, it is considered unlikely that inhibition of CYP isozymes under *in vivo* human conditions would occur, because the therapeutic plasma levels of linagliptin are in the low nanomolar range and the IC50 value is in the micromolar range. Linagliptin is not an inducer of hepatic CYP. The CYP induction potential of CD1790 was not investigated, but *in vivo* study in rats administered linagliptin did not show biologically relevant changes of CYP activity. Therefore, it is unlikely that the major human metabolite is a CYP inducer. Linagliptin is an inhibitor of the drug transporters P-glycoprotein, OATP2, OATP8, OCTN1, OCT1 and OATP2. Given the micromolar concentrations of linagliptin that are needed for inhibition a relevant drug-drug interaction is very unlikely under clinical use of linagliptin in humans.

Linagliptin hardly penetrated into the brain, obviously mainly due to the action of P-gp. This would imply that in case of P-gp inhibition by concomitantly administered drugs penetration of linagliptin into the brain is conceivable. Based on the discussion and literature provided by the applicant, only very low concentrations of around 1 nM at steady state levels in humans will be reached in brain interstitial fluid. Taking into account the high concentrations needed to inhibit CNS receptors *in vitro*, no adverse reactions at a CNS level are expected.

2.3.4. Toxicology

Single dose toxicity

Oral acute toxicity studies in mice and rats were repeated with a different batch of linagliptin due to differences in the impurity profile between the batches used in early toxicological investigations and the one produced for an early clinical study.

The acute toxicity of linagliptin in mice and rats was low as indicated by a maximum non-lethal dose of ≤1000 mg/kg.

Repeated dose toxicity

Liver, kidneys and gastrointestinal tract were identified as the principal target organs of toxicity in mice and rats at high doses of linagliptin at repeat doses (≥100 mg/kg/day, >300x Maximum Recommended Human Dose (MRHD) based on AUC). In rats also effects on reproductive organs, thyroid and the lymphoid organs were seen (≥60 mg/kg/day, >150x MRHD). No relevant and consistent gender differences were observed.

Strong pseudo-allergic reactions were observed in dogs at medium doses (≥15 mg/kg/day, 450x clinical C_{max}), secondarily causing cardiovascular changes, which were considered dog-specific. Therefore, no further repeat-dose testing has been performed with dogs.

At high doses of linagliptin (>1000x MRHD, based on AUC) liver, kidneys, stomach, reproductive organs, thymus, spleen, and lymph nodes were target organs of toxicity in Cynomolgus monkeys. At medium dose (>100x MRHD) irritation of the stomach is the major finding. No important gender difference is observed. Necrotic skin lesions, which were observed after administration of other DPP-4 inhibitors, were not seen. The NOAEL of the longer oral toxicity studies in Cynomolgus monkeys is 10 mg/kg/day (40-66x MRHD).

Intravenous administration of linagliptin to Cynomolgus monkeys at high dose (40 mg/kg/day), was associated with first degree atrioventricular block and signs indicative of pseudo-allergy. Because there was no relationship between the signs of pseudo-allergy and histamine plasma concentrations, this effect was not as clear as in dogs. Also this route of administration will not be used in human therapy; therefore, these findings will not be relevant for human use.

Genotoxicity

Linagliptin did not show a genotoxic potential up to toxic concentration or dosage levels when tested in bacterial and mammalian systems.

The potential genotoxicity of the main metabolite CD 1790 of linagliptin was also assessed in the Ames test and in the chromosome aberration assay in human lymphocytes. In these *in vitro* assays the racemate CD 1750, which contains 50% of the S-enantiomer CD 1790 and 50% of the R-enantiomer, was used.

No specific *in vivo* test with CD 1790 was performed as this metabolite is present in all animal species used for toxicological testing. In the rat the plasma levels of CD 1790 was about 3-5% compared to the parent compound linagliptin based on AUC. In the rat bone marrow micronucleus test (U04-1827), in which dosages of up to 600 mg/kg/day of linagliptin were administered, an exposure of approximately 20000 nM.h CD 1790 (corresponding to 1000-fold clinical exposure of CD 1790) was calculated. It can therefore be concluded that CD 1790 is also negative in the rat bone marrow micronucleus assay.

Carcinogenicity

Long-term studies

In the 2-year carcinogenic mouse study, linagliptin did not induce carcinogenic effects, except for a significant increase in malignant lymphomas in females. This was attributed to a high background of lymphomas in mice. Because linagliptin is not genotoxic and lymphoid hyperplasia in spleen and thymus was not increased in female mice, it was concluded that this finding is not relevant for humans.

Oral administration of linagliptin up to 60 mg/kg/day to Wistar rats for 2 years revealed no evidence of a carcinogenic potential. A dosage of 60 mg/kg/day corresponds to 418-times clinical exposure for linagliptin and 185-times clinical exposure for the main metabolite CD 1790 at MRHD.

Short or medium-term studies

No short-term studies were performed. Dose selection was based on the results of the repeated-dose toxicity studies.

The CHMP considered this appropriate.

Reproduction Toxicity

Fertility and early embryonic development

The NOAEL in rats for fertility and early embryonic development is found at 240 mg/kg/day (943x MRHD, based on AUC value of study U06-1637).

Embryo-fœtal development

No teratogenic effects occurred in Wistar rats up to and including the high dose of 240 mg/kg/day linagliptin (943x MRHD). The NOAEL for both maternal toxicity and embryo-foetal toxicity was 30 mg/kg/day (49x MRHD).

No teratogenic effects were observed in Himalayan rabbits up to and including the high dose of 150 mg/kg/day (1943x MRHD). A NOAEL of 25 mg/kg/day (78x MRHD) was derived for embryo-foetal toxicity. For maternal toxicity the NOAEL was 4 mg/kg/day (2.1x MRHD).

Prenatal and postnatal development, including maternal function

Linagliptin produced maternal toxicity in rats at 300 mg/kg/day (1506x MRHD). At this dosage, there was also an influence of linagliptin on body weight and body weight development of the offspring. The offspring's fertility however was not changed. The NOAEL if linagliptin in rats for both maternal and offspring toxicity, was considered to be 30 mg/kg/day (49x MRHD).

In conclusion, the results from the reproductive toxicity studies do not indicate a reproductive risk to the foetus, suckling neonate or to adults at doses of linagliptin with very high safety margins and well above maternal toxicity levels. Therefore, it is considered that linagliptin is unlikely to affect reproduction at therapeutic exposures in humans.

Local tolerance

To evaluate the tolerance for linagliptin as an injection solution, several studies were performed. Injectable solutions (0.5 mg/mL) of linagliptin were well tolerated after a single paravenous, intra-arterial, intravenous, or intramuscular injection. Linagliptin was also well tolerated subsequent to

topical application on rabbit skin. In an *ex vivo* study, injectable solutions (0.5 mg/mL) of linagliptin induced no relevant hemolysis in human blood.

Other toxicity studies

Antigenicity

No antigenicity studies have been performed. This was considered acceptable.

Toxicity in juvenile animals

No studies on juvenile toxicity have been performed, because the product is not intended for < 18 year old humans.

The CHMP considered this to be acceptable.

Immunotoxicity

The applicant did not perform additional immunotoxicity studies, because changes in immune related tissues like thymus, bone marrow, spleen and lymph nodes occurred only at very high dosages and are considered secondary to other toxicity and not due to a direct effect of linagliptin on the immune system. The absence of an immunotoxic potential of linagliptin is further demonstrated by the chronic toxicity studies and carcinogenicity studies.

Impurities

Impurities were present in varying amounts, ranging from < 0.05 to 0.68%. All impurities were in sufficient excess of the human exposure in the toxicity tests, resulting in acceptable safety factors (>100x MRHD). All impurities were properly tested and no safety concern is evident.

Photosafety

Linagliptin has a second absorption maximum at a wavelength of greater than 290 nm (U09-1738). Therefore, the phototoxic potential of linagliptin was evaluated in clinical setting. This was considered acceptable.

Pseudo-allergy

The most prominent finding in the toxicity studies in dogs was drug-induced hypersensitivity. This finding was classified as a pseudo-allergic reaction as it became apparent without prior sensitization. The reaction was associated with significantly increased plasma histamine levels and was clearly dose-related. In the 2-week dose range finding study in the dog (U04-2187), pseudo-allergy was seen at dosages of 15 mg/kg/day or higher. In the 4-week dog study (U05-1944) a dosage of 9 mg/kg/day was derived as no effect level. The exposure was 210-fold above clinically relevant plasma levels. A high amount of impurities did not alter the pseudo-allergic reaction. Neither clinical signs of pseudo-allergy nor increased plasma histamine concentration were observed in Cynomolgus monkeys at oral dosages up to 300 mg/kg/day and in Rhesus monkeys up to 150 mg/kg.

Studies results indicate that pseudo-allergy by linagliptin is of no relevance for humans.

2.3.5. Ecotoxicity/environmental risk assessment

A $PEC_{surfacewater}$ of 0.025 µg/L was calculated using the default Fpen of 0.01. Since the $PEC_{surfacewater}$ exceeded the threshold value of 0.01 µg/L, a phase II ERA was performed.

The outcome of the phase II assessment shows that the PEC/PNEC ratios for all three compartments are clearly below the trigger values of 1 and 0.1, respectively (see table 7).

PEC and PNEC values for linagliptin

Compartment	PEC	PNEC	PEC/PNEC ratio	Trigger for Tier B
Surface water	0.025 µg/L	320 µg/L	7.8×10^{-5}	1
Microorgansisms (STP)	0.025 µg/L	21000 µg/L	1.2×10^{-6}	0.1
Groundwater	0.006 µg/L	320 µg/L	7.8×10^{-5}	1
Sediment	1.57 µg/kg	125000 µg/kg	1.3×10^{-5}	1

Therefore, the use of linagliptin as active ingredient with the use pattern as given above can be considered to result in insignificant environmental risk for the three aquatic compartments (surface water, groundwater and sediment). Thus, an extended environmental fate and effects analysis for the three compartments in Tier B is considered to be not necessary.

Since the log K_{ow} of the undissociated compound was determined to be below 3 (1.7), linagliptin is considered to have a no potential to bioaccumulate. Therefore, bioconcentration does not have to be considered in Tier B.

The OECD 106 adsorption study was conducted with three different soils and two sewage sludges. The study shows that the normalisation to the organic carbon (OC) content of the soils/sludges is not feasible due to the lack of direct correlation between adsorption of the substance and the OC content of the soils/sludges. Therefore, a Kd-trigger for sludge of 3700 L/kg (corresponding to the Koc-trigger of 10000 L/kg assuming a default OC content in sludge) is considered to be more reasonable than the Koc-trigger as proposed in the EMEA guideline.

For the sludges, the OECD 106 adsorption study resulted in a Kd of 190 L/kg. Since this is below the trigger of 3700 L/kg, a terrestrial risk assessment was not considered in Tier B.

The criterion for significant shifting to the sediment (10% of the substance at any time point after or at 14 days is present in sediment) is exceeded for linagliptin. Therefore, effects on sediment organisms were considered in Tier B and a toxicity study on chironomids was conducted. Since the PEC/PNEC ratio is below the trigger of 1, it can be concluded that the use of linagliptin as active ingredient with the use pattern as given above can be considered to result in insignificant environmental risk for the compartment sediment.

No adverse environmental effects resulting from the excipients of the product are expected, taking into account the expected maximum release to the environment resulting from the intended application of Trajenta.

Summary of main study results

PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD122	log P_{ow} = 1.7 (undissociated compound)	Potential PBT: No
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	log P_{ow} = 1.7 (undissociated compound)	not B

	BCF	-			not B
Persistence	DT50 or ready biodegradability	Not readily biodegradable			P/not P
Toxicity	NOEC or CMR	3.2 mg/L			T/not T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default	0.025	µg/L			> 0.01 threshold
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Mean of 3 soils: Koc = 19234 Kd = 286 Mean of 2 sludges: Koc = 726 Kd = 190			
Ready Biodegradability Test	OECD 301A	Not ready biodegradable (0% in 28 days)			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 0.8d (r), 1.1d (p) $DT_{50, sediment}$ = 110d (r), 42.2d (p) $DT_{50, whole\ system}$ = 5.2d (r), 1.6d (p) Shifting to sediment = 50.9% (r), 72.4% (p) at day 100			r = river p = pond
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test (*Pseudokirchneriella subcapitata*)	OECD 201	NOEC EC50 NOEC EC50	4.1 16 4.1 49	mg/L mg/L mg/L mg/L	Based on yield Based on yield Based on growth rate Based on growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	3.2	mg/L	
Fish, Early Life Stage Toxicity Test/*Brachydanio rerio*	OECD 210	NOEC	12.0	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50 NOEC	792 210	mg/L mg/L	
Phase IIb Studies					
Sediment dwelling organism (*Chironomus riparius*)	OECD 218	NOEC	125	mg/kg	

Considering the above data, linagliptin is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

To support the development and marketing authorization the applicant has used a variety of animal species, i.e. mice, diabetic/obese mice, rats, diabetic rats, rabbits, minipigs, dogs and monkeys. In in vitro data the sensitivity to linagliptin was similar in all species. The applicant scientifically justified this variety of animal species which was used to support the development and marketing authorization of linagliptin. The applicant explained that the healthy rodents could have been adequate, but the intended use of linagliptin in Type 2 diabetes patients led to the use of diabetic rodents models. The applicant also clarified why there was a change from dog to monkey in the chronic toxicological

studies, because of the pseudo-allergy observed in dogs. The applicant underlined the adequacy of the monkeys because of the skin lesions observed with other gliptins. The applicant is aware of the importance of the 3R's (Replace, Refine and Reduce) in developing a compound, although from a hindsight view other choices could have been made.

In several animal tissues and in human plasma, traces of covalently bound material has been found. Also N-acetyl-cystein conjugate (mercapturate) has been found in mice, monkeys and humans. These data indicate that linagliptin may be converted into a reactive intermediate, which can bind covalently to proteins, resulting in a hapten. Thus, an idiosyncratic reaction will be possible. As idiosyncratic reactions, the applicant has proposed the medical concepts of drug induced liver injury, acute renal failure and blood dyscrasia. Search in clinical trials did not reveal any drug induced liver injury or renal failure. There were other explanations for the patients with agranulocytose (1), bone marrow failure (1), leukopenia (2). There were two patients with platelet count decrease; in one of these the platelet count was already low at baseline, and there were no further AEs with a close time proximity. There were no AEs affecting two different haematological cell lines. Furthermore, safety laboratory parameters did no show an effect of linagliptin towards a reduction of red blood cells, white blood cells, or platelets. Although the CHMP agreed with the applicant that the data do not provide evidence that treatment with linagliptin contributes to an increased risk of drug-induced liver injury, acute renal failure, or blood dyscrasia, it was concerned that the experience is too small to detect this type of adverse effects. Therefore "Idiosyncratic adverse reactions" were included in the Risk Management Plan.

The single- and repeated-dose toxicology studies on general toxicity revealed that linagliptin is well tolerated up to high doses. At very high doses toxicity towards several different organs becomes obvious with no clear underlying mechanism. This is in line with the findings on other DPP-4 inhibitors and could be related to loss of DPP-4 selectivity at high doses. Some DPP-4 inhibitors caused skin lesions in monkeys which may be attributed to off-target DPP-8/DPP-9 inhibition. No skin lesions were observed with linagliptin, suggesting that linagliptin did not inhibit DPP-8/DPP-9 in *in vitro* assays.

A slight but consistent elongation of the heart-rate corrected QT interval of the ECG was found in the repeated-dose studies in high-dose male dogs (around 36-time human therapeutic exposure). Effects on heart rate and blood pressure were seen at around 5-time human therapeutic exposure, the underlying mechanism being unclear. Toxicity of linagliptin could be enhanced by co-administration of a P-gp inhibitor due to the fact that part of the absorbed drug becomes immediately secreted back in the gut lumen by P-gp (see Pharmacokinetic section). This effect is not related to DPP-4 inhibitors and was not observed with other DPP-4 inhibitors.

All studies on genotoxicity with linagliptin and its main metabolite CD 1790 (tested in the racemate CD 1750) were negative. Linapliptin is therefore considered to be devoid of any relevant genotoxic potential. All specified and identified potential impurities have been sufficiently qualified for their genotoxic potential. According to the applicant identified genotoxic impurities are well below TTC based on the evaluation of the synthesis process.

Considering the available data, linagliptin is not expected to pose a risk to the environment.

2.3.7. Conclusion on the non-clinical aspects

The non-clinical studies show that linagliptin has appropriate pharmacology and toxicology for the intended clinical use.

2.4. Clinical aspects

2.4.1. Introduction

The linagliptin clinical development program comprised a total of 24 phase I trials, 4 phase II trials and 9 phase III trials (with treatment periods between 12 and 78 weeks). In total, 4,687 patients with type 2 diabetes mellitus and 453 healthy volunteers received treatment with linagliptin. Of these, 3,692 patients were treated for at least 24 weeks, 2,474 patients for at least 52 weeks, and 536 patients for more than 78 weeks. Overall, 44.3% of patients were recruited in Europe, 40.2% in Asia, 9.3% in North America, and 6.2% in South America.

An overview of phase I, II and III trials is given in the following two tables.

Overview of Phase I and Phase II trials

Study number	Type of study	SRD/MRD	Lina (N)	Comparator (N)	Healthy subjects (HS) or diagnosis of patients
Phase I studies in healthy subjects					
1218.1	PK/PD	SRD	48	Placebo:16	HS
1218.8	BA	powder and tablets	24	-	HS
1218.10	PK/PD	SRD iv	0.5-10mg iv: 28	Placebo: 8	HS
1218.7	PK	^{14}C Human ADME iv/oral	5-10 mg iv: 12	-	HS
1218.25	BA	tablet formulations	24	-	HS
1218.33	BA	tablet strenghts	12	-	HS
1218.34	BA	food	32	-	HS
1218.45	PK/PD	1x5mg vs 2x2.5mg	16	-	HS
Phase I studies in patients with T2DM					
1218.2	PK/PD	2 week multiple rising dose (MRD)	1-10mg: 36	Placebo: 12	T2DM
1218.3	PK/PD	4 week MRD	2.5-10mg: 61	Placebo: 16	T2DM
Phase I/II studies in special population					
1218.26	PK/PD	renal impairment	5mg: 51	-	HS, RI, T2DM
1218.27	PK/PD	hepatic impairment	5mg: 33	-	HS, HI
1218.11	PK/PD	SRD& 2 week MRD	1-10mg: 42	Placebo: 14	HS (Japan)
1218.12	PK/PD	4 week MRD	0.5-10mg: 55	Placebo: 18	T2DM (Japan)
1218.58	PK	SD, MD	5mg: 12	-	HS (China)
Phase I drug-drug interaction trials					
1218.31	PK	DDI-ritonavir, CO	5mg: 12	Rit 400mg	HS
1218.67	PK	DDI-rifampicin	5mg: 16	Rif 600mg	HS
1218.4	PK	DDI-metformin, CO	10mg: 16	Met 2550mg	HS
1218.13	PK	DDI-pioglitazone, CO	10mg: 20	Pio 45mg	HS
1218.30	PK	DDI-glyburide, CO	5mg: 20	Glyb 1.75mg	HS
1218.9	PK	DDI-simvastatin	10mg: 20	Sim 40mg	HS
1218.28	PK/PD	DDI-warfarin	5mg: 18	War 10mg	HS
1218.29	PK	DDI-digoxin, CO	5mg: 20	Digox 0.25mg	HS
1218.44	PK	DDI-oral contraceptive	5mg: 18	Microgynon	HS
Phase I thorough QT study					
1218.32	PK/PD	QT-interval	5mg-	Moxifloxacin	HS

			100mg: 44	400mg	
Phase II studies					
1218.5	Eff/Safety	3 lina doses vs pla vs met	0.5-5mg:170	Pla: 67 Met 2000mg: 65	T2DM
1218.6	Eff/Safety	lina vs pla vs glim	1mg-10mg: 197	Pla: 71 Glim 1-3mg: 65	T2DM
1218.37	Eff/Safety	lina vs sita vs pla	5mg: 40	Sita 100mg: 41 Pla: 40	T2DM

PK: pharmacokinetics, PD: pharmacodynamics; BA: bioavalability; SRD: single rising dose; SD: single dose; MRD: multiple rising dose; MD: multiple dose; HS: healthy subjects; RI: renal impairment; HI: hepatic impairment; CO: cross-over

Overview of Phase III trials

Characteristics, duration (Study grouping)	Study number	Treatments	Total randomised	Placebo	Linagliptin 5 mg	Active comparator
Pivotal double-blind placebo-controlled efficacy studies, 24 weeks (EFF-1)	1218.15	Lina + Pio vs. Pio	389 (100.0)	130 (33.4)	259 (66.6)	0 (0.0)
	1218.16	Lina vs. PBO	503 (100.0)	167 (33.2)	336 (66.8)	0 (0.0)
	1218.17	Lina + Met vs. Met	701 (100.0)	177 (25.2)	524 (74.8)	0 (0.0)
	1218.18	Lina + Met + SU vs. Met + SU	1058 (100.0)	265 (25.0)	793 (75.0)	0 (0.0)
Double-blind active-controlled efficacy study, 52 weeks (EFF-2)	1218.20	Lina+ Met vs. glimepiride+Met	1560 (100.0)	0 (0.0)	779 (49.9)	781 (50.1)
Additional double-blind placebo-controlled efficacy studies, 18 weeks	1218.35	Lina + SU vs. SU	245 (100.0)	84 (34.3)	161 (65.7)	0 (0.0)
	1218.50	Lina vs. PBO (in metformin-intolerant patients)	227 (100.0)	76 (33.5)	151 (66.5)	0 (0.0)
Double-blind efficacy studies with more than one linagliptin dose level (EFF-10)	1218.5 1218.6 1218.23[c]	Lina vs. PBO vs. Met*	302 (100.0)	67 (22.2)	55 (18.2)[f] 66 (19.8)[g]	65 (21.5)[a]
		Lina vs. PBO vs. SU*	333 (100.0)	71 (21.3)	159 (28.3)[h]	65 (19.5)[b]
		Lina vs. PBO vs. Vog	561 (100.0)	80 (14.3)		162 (28.9)
Open-label long-term extension study, 78 weeks (EFF-11)	1218.40[d]	Lina + various antidiabetic medications	2122 (100.0)	0 (0.0)	2122 (100.0)[e]	0 (0.0)
Overall total			5879 (100.0)	1117 (19.0)	3872 (65.9)	1073 (18.3)

Lina = linagliptin, Pio = pioglitazone, PBO = placebo, Met = metformin, SU = sulfonylurea, Vog = voglibose

a Metformin open-label arm for sensitivity analyses b Glimepiride open-label arm for sensitivity analyses
c Patients initially randomised to placebo were randomised to linagliptin 5 mg or 10 mg after 12 weeks of treatment; patients initially randomised to active comparator (voglibose) were randomised to linagliptin 5 mg or 10 mg after 26 weeks of treatment. Therefore, the total number of patients in study 1218.23 is smaller than the sum of patients in the individual treatment groups.
d Extension of the pivotal placebo-controlled studies (1218.15, 1218.16, 1218.17, 1218.18). Thus, the total number of patients who participated in study 1218.40 is not included in the overall total.

e A total of 1533 patients in study 1218.40 had received linagliptin already in the pivotal placebo-controlled studies and they are therefore not included in the overall total.
f Since various linagliptin dose levels were tested, overall 170 patients received linagliptin (any dose)
g Since various linagliptin dose levels were tested, overall 197 patients received linagliptin (any dose)
h Since both 5 mg and 10 mg linagliptin doses were tested, overall 319 patients received linagliptin

Initial scientific advice was sought from the CHMP on 16 May 2007 (EMEA/CHMP/SAWP/ 385760/2007). Subsequently, the clinical program was revised and a follow-up Scientific Advice was sought on 23 April 2008 (EMEA/CHMP/ SAWP/311988/2008). The emphasis of the advice was on the design features of the phase III trials, particularly dosing, the adequacy of the safety database, and the non-inferiority margin in the active-controlled 1218.20 trial. The suggestions of the CHMP were subsequently addressed and the clinical development program was adjusted to a certain extent.

For linagliptin, the CHMP "Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus" is applicable. In general, the applicant has followed this guideline.

The claimed indication for Trajenta was:

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

- when diet and exercise alone do not provide adequate glycaemic control and when metformin is inappropriate.
- in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- in combination with a sulphonylurea when diet and exercise plus a sulphonylurea alone do not provide adequate glycaemic control and when metformin is inappropriate .
- in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycaemic control.
- in combination with a thiazolidinedione, when the thiazolidinedione alone with diet and exercise, does not provide adequate glycaemic control in patients for whom use of a thiazolidinedione is considered appropriate."

The approved indication and posology are the following:

"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."

"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, a lower dose of the sulphonylurea may be considered to reduce the risk of hypoglycaemia (see section 4.4)

Special populations

Renal impairment

For patients with renal impairment, no dose adjustment for Trajenta is required.

Hepatic impairment

Pharmacokinetic studies suggest that no dose adjustment is required for patients with hepatic impairment but clinical experience in such patients is lacking.

Elderly

No dose adjustment is necessary based on age.

However, clinical experience in patients > 75 years of age is limited.

Paediatric population

The safety and efficacy of linagliptin in children and adolescents has not yet been established. No data are available."

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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

2.4.2. Pharmacokinetics

Absorption

After oral administration of a 5 mg dose, linagliptin is rapidly absorbed, with peak plasma concentrations occurring 1.5 to 2.5 hours post dose (median t_{max}), suggesting pre-dominant absorption in the upper intestine.

Linagliptin has an oral systemic bioavailability of 30% and a moderate permeability. Additionally, linagliptin is a highly soluble drug. Therefore, linagliptin can be considered a Class 3 drug substance according to the Biopharmaceutical Classification System (BCS).

Food-interaction studies

The effect of a high fat, high caloric meal on the pharmacokinetics of a 5 mg single dose of linagliptin administered as a tablet was investigated in study 1218.34.

Intake of food prolonged the time to reach maximum plasma concentrations by 2 hours and lowered the Cmax by 15%. No influence on the AUC_{0-72} was observed. The other pharmacokinetic parameters of linagliptin were comparable under fasted and fed conditions. The decrease of the Cmax of linagliptin has no clinical relevance as the pharmacodynamic targets were reached at these plasma levels. Therefore, it was concluded that linagliptin can be administered with and without food.

Distribution

Plasma protein binding of linagliptin in human plasma is concentration-dependent, decreasing from 98.8% at 2 nM to 83% at 20 nM. Consequently the protein unbound fraction of linagliptin in plasma increases with increasing total plasma concentrations. This is probably reflecting the saturation of binding to DPP-4 with increasing concentrations of linagliptin. As a result, linagliptin shows non-linear distribution kinetics both after oral and intravenous administration. After single oral administration of 5 mg linagliptin the apparent volume of distribution, Vz/F was approximately 12700 L.

Elimination

After an oral dose of 5 mg linagliptin, plasma concentrations decline in at least a bi-phasic manner with a long terminal half-life. The initial rapid decline mainly represents the distribution of the drug into a large peripheral compartment and the fast elimination of non-DPP-4 bound linagliptin. Once concentrations drop to a magnitude within the range of plasma DPP-4 concentrations, a long terminal phase (terminal half-life for linagliptin up to 200 hours) is observed. This is assumed to be related to the tight binding of linagliptin to DPP-4 and the slow dissociation of the linagliptin-DPP-4 complex. Thus it is expected that the terminal half life does not contribute to the accumulation of the drug. The accumulation half-life of linagliptin, as determined from accumulation after oral administration of multiple doses of 5 mg linagliptin, is 11.4 hours. Linagliptin shows a dose–dependent apparent total clearance at steady-state. After repeated oral administration of a 5 mg dose CL/F,ss is 1120 mL/min and renal clearance was 70 mL/min.

The parent compound was excreted unchanged in urine and faeces with 76% (61% out of 81%) of excreted radioactivity after intravenous dosing and with 90% (78% out of 87%) of excreted radioactivity after oral dosing. All metabolites contributed to less than 10 % of the excreted radioactivity. In plasma, CD 1790 was identified as major metabolite with 16.9% of sample radioactivity in pooled samples after oral administration. Other metabolites found in humans showed exposure levels well below 10% of linagliptin plasma exposure. Linagliptin is metabolised mainly by CYP3A4.

Dose proportionality and time dependencies

Linagliptin AUC_{ss} and $C_{max,ss}$ increased less than proportionally with dose after multiple dose administration of single tablets with dose strengths of 1 mg, 2.5 mg, and 5 mg. This is of minor importance as only the 5 mg tablet will be marketed.

Intra-individual variability was not specifically determined.

No specific studies were performed investigating time dependency.

Special populations

Impaired renal function

The pharmacokinetics, pharmacodynamics, safety and tolerability of single and multiple 5 mg doses of linagliptin tablets in patients with different degrees of renal impairment (RI) in comparison to subjects with normal renal function was investigated in an open, parallel-group, phase I trial (1218.26). All patients received 5 mg single or multiple dose once daily under fasting conditions.

The influence of RI is only moderate for the parent compound as well as for the main metabolite. The increase in exposure in severe renal impairment is less than 2 -fold and the exposure in T2DM patients with severe renal impairment is comparable with “healthy” impaired patients.

Therefore, the CHMP endorsed the recommendation included in the SmPC that no dose adjustment in these patients is considered necessary.

Impaired hepatic function

The influence of impaired hepatic functions was investigated in study 1218.27. The pharmacokinetics of linagliptin was only slightly influenced by reduction of the hepatic functions. Only exposure to the

main metabolite was significantly reduced, however, as the elimination of linagliptin by metabolism is small (less than 13%), this reduction in exposure is of no clinical relevancy.

The CHMP endorsed the proposed text in the SmPC that no dose reduction is considered necessary in patients with hepatic impairment.

Gender/weight

In the population pharmacokinetic analysis, in which 459 patients were involved, the influence of gender and weight was considered of no clinical relevancy. The difference in exposure was not more than 9% higher in female than in male subjects. The influence of weight was less than 20%, and therefore not clinical relevant.

Race

As linagliptin is mainly excreted unchanged in the faeces, large difference between races are not expected based on differences in expression of enzymes. Differences may occur due to variability in the volume of distribution as this is rather high for linagliptin. This may explain the 30% higher Cmax in Japanese subjects.

Age

The influence of age on the pharmacokinetics of linagliptin is only investigated in the population pharmacokinetic analysis. In this analysis 459 patients were involved. The mean age in this analysis was 60 years. Clinically there was an increase in adverse events with increased age observed. This increase in adverse events can not be explained by an increase in exposure in this group of patients. A special pharmacokinetic study on the influence of age is considered not necessary.

The CHMP endorsed the proposed text in the SmPC that no dose adjustment is necessary for the elderly population.

No PK is available in children; however PK studies in this population are foreseen as part of the PIP for this product.

Pharmacokinetic interaction studies

In vitro data indicate that linagliptin is a substrate for CYP3A4 and P-gp, OATP8-, OCT2-, OAT4-, OCTN1- and OCTN2. No relevant inhibition of CYPs or transporter proteins at clinically plausible concentrations of linagliptin or its major metabolite CD1790 was found. Furthermore, no hints on enzyme induction (CYP 1A2, 2B6 and 3A4) were found in human hepatocytes.

Effects of other medicinal products on linagliptin pharmacokinetics

Co-administration of linagliptin with ritonavir, strong P-gp/CYP3A4 inhibitor, resulted in 2-fold increase in exposure and 3-fold increase in Cmax. This was explained by an increase in bioavailability due to inhibition of P-gp, while there was a small effect of ritonavir on the elimination of linagliptin. Due to the wide safety margin of linagliptin, up to 2-fold increases in exposure in total concentrations of linagliptin with concomitant use of P-gp/CYP3A4 inhibitors is considered acceptable, particularly if the increased exposure is only transient. However, the unbound concentrations, which are usually less than 1% at the therapeutic dose of linagliptin, were increased 4-5-fold after co-administration with ritanovir. These changes in linagliptin pharmacokinetics were not considered to be clinically relevant. Therefore, clinically relevant interactions would not be expected with other P-glycoprotein/CYP3A4 inhibitors.

Co-treatment with rifampicin, a potent P-gp/CYP3A4 inducer, resulted in a decrease of 40% in linagliptin exposure and a decrease in relative exposure of the CYP3A4 formed metabolite CD 1790, which is explained by induction of P-gp. The reduction in linagliptin exposure is time dependent suggesting that full efficacy of linagliptin in combination with strong P-gp inducers might not be achieved, particularly if these are administed long-term. Co-administration with other potent inducers of P-glycoprotein and CYP3A4, such as carbamazepine, phenobarbital and phenytoin has not been studied. This has been adequately reflected in the SmPC.

Effects of linagliptin on other medicinal products

In vitro data indicate no risk for interactions due to inhibition of CYP450 or drug transporter proteins by linagliptin. This was confirmed by clinical studies, where linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glyburide, pioglitazone, warfarin, simvastatin, digoxin or oral contraceptives.

Pharmacokinetics using human biomaterials

Linagliptin was found to be a weak competitor inhibitor and a weak to moderate mechanism based inhibitor of CYP3A4. Considering the therapeutic plasma concentrations of linagliptin, a clinical relevance of this finding is unlikely. There was no inhibition *in vitro* of any of the other CYP isoenzymes under investigation by linagliptin (i.e., CYP 1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 4A11).

The major metabolite, CD 1790, was found to be a competitive inhibitor of CYP2C9 and a mechanism-based inhibitor of CYP3A4. Considering maximum plasma concentrations of CD 1790, a clinically relevant CYP2C9 and CYP3A4 mediated interaction is unlikely.

Finally, no hints on enzyme induction (CYP 1A2, 2B6 and 3A4) were found in human hepatocytes. Therefore, linagliptin is not an inducer of hepatic cytochrome P450.

2.4.3. Pharmacodynamics

Pharmacodynamics were studied in 11 phase I/II trials, including healthy volunteers, subjects with T2DM and special populations (renally or hepatically impaired patients, Japanese subjects).

Mechanism of action

Mechanism of action is DPP-4 inhibition. Nutrient intake stimulates the secretion of the gastrointestinal incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), both of which exert glucose-dependent insulinotropic effects and assist pancreatic insulin and glucagon in maintaining glucose homeostasis. GLP-1 lowers blood glucose levels by augmenting the glucose-stimulated insulin release. Moreover, GLP-1 inhibits glucagon secretion, slows gastric emptying, and induces satiety. The plasma half-life of GLP-1 is limited to a few minutes because of rapid proteolytic degradation by the enzyme DPP-4. Inhibition of DPP-4 prolongs the half-life of active GLP-1 and thereby increases plasma insulin levels and lowers plasma glucose levels. Since GLP-1 activity ceases when the glucose concentration falls below 55 mg/dL, prolongation of the half-life of GLP-1 by DPP-4 inhibitors bears little risk of hypoglycaemia.

Primary and Secondary pharmacology

Inhibition of DPP-4 was considered the most relevant biomarker for the effectiveness of linagliptin. A median DPP-4 inhibition of 80% at trough was assumed as a threshold based on published data. Plasma glucose and active GLP-1 were other markers for effectiveness. Exploratory biomarkers

included glucagon, C-peptide, insulin, fructosamine, 1,5-Anhydroglucitol and glycated haemoglobin (HbA1c).

DPP-4 inhibition was measured in 10 of the PD-studies, after multiple dosing of linagliptin (1 mg, 2.5 mg, 5 mg and 10 mg) to T2DM patients and healthy volunteers. Trough median DPP-4 inhibition was >80% in patients receiving 5 mg linagliptin once daily. Doses of 1 mg and 2.5 mg were less effective, whereas higher doses did not result in a considerable larger median DPP-4 inhibition. A consistent DPP-4 inhibition of >80% at trough with 5 mg linagliptin was also seen in Japanese, as well as in Caucasian and Japanese healthy volunteers. On basis of these results 5 mg was chosen as therapeutic dose.

The magnitude of steady-state DPP-4 inhibition was not altered by concomitant dosing of metformin, or renal or hepatic impairment. However, concomitant treatment with rifampicin resulted in a decrease of DPP-4 inhibition, with trough levels of 53% inhibition. This is in line with pharmacokinetic data, which showed a reduction in AUC and Cmax of linagliptin when combined with rifampicin. Therefore, a decrease in efficacy of linagliptin can be expected when patients are treated with rifampicin concomitantly or more generally with a potent P-gp inducer. This is expressed in the SmPC.

Generally linagliptin plasma concentrations correlated well with DPP-4 activity/inhibition.

Results on secondary parameters as active GLP-1, glucose, insulin and glucagon were consistent with the primary parameter. However, there was no clear difference in effect between 2.5 mg and 5 mg dose.

Fructosamine was measured in some early linagliptin trials (studies 1218.2 and 1218.3). However, fructosamine was generally highly variable, and measurements of fructosamine were not included in studies of longer duration. Instead, 1,5-Anhydroglucitol was measured, as it was regarded to be a better marker of glucose control over an intermediate (up to 2 weeks) time period. In study 1218.37, treatment with 5 mg linagliptin over 4 weeks resulted in a statistical significant increase of 1,5-AG concentrations of 1.8 µg/mL ($p<0.0001$) compared to placebo (1.0 µg/mL vs. -0.8 µg/mL) and thus indicate that glucose excursions during linagliptin treatment are reduced. The concentration of 10 mcg/dL at week 4 also indicates that nearly no glucose excursions above 180 mg/dL occurred, as this was found to be the reference value in optimally controlled patients with type 2 diabetes.

Additionally, a thorough QTc study (1218.32) evaluated the effect of 5 mg linagliptin, 100 mg linagliptin, placebo and positive control (moxifloxacin 400 mg) on QT prolongation. There was no clinically relevant increase in the QTcI interval following administration of 5 mg and 100 mg linagliptin compared with placebo.

2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Generally, linagliptin plasma concentrations correlated well with DPP-4 activity/inhibition. This relationship was comparable in Caucasian and in Japanese subjects and was not relevantly influenced by renal or hepatic impairment, or by concomitant administration of metformin. Ritonavir, a potent P-gp/CYP3A4 inhibitor increased linagliptin exposure 2-fold. Due to the wide safety margin of linagliptin, up to 2-fold increases in exposure in total concentrations of linagliptin with concomitant use of P-gp/CYP3A4 inhibitors is considered acceptable, particularly if the increased exposure is only transient. Although, the unbound concentrations were increased 4-5-fold after co-administration with ritanovir, it was considered not be a safety concern.

Rifampicin, as a potent P-gp inducer, decreased linagliptin steady-state AUC by 40% and DPP-4 inhibition by 30%. Therefore, co-administration of linagliptin and a potent P-gp inducer might result in lower efficacy of linagliptin. This has been adequately reflected in the SmPC.

Pharmacodynamics of linagliptin were studied in 11 Phase I/II trials. DPP-4 inhibition >80% over 24h was achieved with multiple dosing of 5 mg linagliptin. Lower doses were less effective, whereas higher doses did not result in a considerable larger median DPP-4 inhibition. On basis of these results 5 mg was chosen as therapeutic dose. Results on secondary parameters as active GLP-1, glucose, insulin and glucagon were consistent with the primary parameter. However, there was no clear difference in effect between 2.5 mg and 5 mg dose.

Although age has been investigated as covariate, the number of very elderly subjects > 75 yrs in all clinical studies was small, and pharmacodynamics have not been studied in very elderly patients apart from a population pharmacokinetic/pharmacodynamic analysis.

In a thorough QT study, single doses of 5 mg or 100 mg linagliptin did not prolong QT interval of the ECG.

2.4.5. Conclusions on clinical pharmacology

Pharmacokinetics and pharmacodynamics of linagliptin have been studied extensively, and the choice of 5 mg as therapeutic dose appears to be reasonable from a pharmacodynamic point of view.

Linagliptin did not prolong QT interval of the ECG.

2.5. Clinical efficacy

Eleven phase II/III studies with different trial designs, different durations of treatment, and different antidiabetic background medications were used for the evaluation of efficacy and safety of linagliptin. In these 11 studies, 4278 patients were assigned to linagliptin (any dose), and 3872 to linagliptin 5 mg. A total of 1117 patients received placebo and 1073 patients an active comparator.

The Phase III program for linagliptin examined the efficacy of linagliptin in monotherapy use and in combination use with 3 important antihyperglycaemic medications: metformin, sulfonylurea (SU) and a PPARγ agonist (pioglitazone). These combinations were expected to be clinically valuable given potentially complementary mechanisms of action—adding agents that target in insulin resistance and/or excessive hepatic glucose production (a PPARγ agonist or metformin)—with linagliptin, an agent that targets enhancing insulin secretion and lowering glucagon concentrations.

Efficacy and safety of linagliptin was examined
- as monotherapy in two studies: 1218.16 and 1218.23
- as initial combination with pioglitazone : 1218.15
- as add-on to an SU: 1218.35
- as add-on to metformin: 1218.17, 1218.20
- as add-on to metformin and a SU: 1218.18

2.5.1. Dose response studies

Three of the four provided phase II studies were dose response studies (1218.5, 1218.6 and 1218.12) which examined linagliptin in doses from 0.5 to 10 mg given once daily. Studies 1218.5 and 1218.6 are the main dose finding studies, whereas Study 1218.12 was a short-term supportive phase II study.

In addition to the change from baseline in HbA1c, DPP-4 inhibition was used as parameter for selecting the optimum linagliptin dose for Phase III clinical development. DPP-4 inhibition is a well recognized biomarker for efficacy, as predicted by the mode of action. For other DPP-4 inhibitors, non-clinical studies showed that DPP-4 inhibition of 80% or more over 24 h was related to maximum effects in incretin response and glucose reduction.

Study 1218.5 compared linagliptin doses of 0.5 mg, 2.5 mg, and 5 mg once daily as monotherapy with placebo. Median DPP-4 inhibition was 38.5%, 74.5%, and 81% for the 0.5 mg, 2.5 mg, and 5 mg doses, respectively. Thus, DPP-4 inhibition of 80% or more was reached only with the 5 mg dose, but not with the 2 lower doses. The differences between linagliptin and placebo in the adjusted mean changes from baseline in HbA1c were -0.14% (0.5 mg), -0.41% (2.5 mg), and -0.46% (5 mg) for the different doses of linagliptin. Superiority over placebo was shown for the 2.5 mg and 5 mg doses of linagliptin, but not for the 0.5 mg dose.

In study 1218.6, which was performed in patients using metformin background therapy, the efficacy of linagliptin 1 mg, 5 mg, and 10 mg once daily versus placebo was assessed. It was shown that both the linagliptin 5 mg and 10 mg doses provided median DPP-4 inhibition of more than 80% (85.0% and 90.0%), whereas the 1 mg dose did not reach this target (63.0%). The treatment differences in the adjusted mean HbA1c changes from baseline were -0.40% (1 mg), -0.72% (5 mg), and -0.67% (10 mg) for the different linagliptin doses; all 3 doses were shown to be superior to placebo. The HbA1c reductions observed in study 1218.6 were generally more pronounced than in study 1218.5.

Overall, these results support the 5 mg dose as optimal dose to be taken forward to phase III.

2.5.2. Main studies

Four pivotal efficacy studies were submitted in this application (1218.15, 1218.16, 1218.17 and 1218.18). These studies were randomized, multinational, double-blind, placebo-controlled, 24 week efficacy studies**.** Randomisation was stratified by HbA1c (<8.5% versus ≥8.5%) and number of previous antidiabetic treatments.

Below are described aspects that were common to all pivotal efficacy studies.

Methods

- **Study Participants**

Main inclusion criteria
- Adult male and non-pregnant female patients with T2DM either on previous or no previous antidiabetic agent and pre-defined HbA1c values at screening and randomisation, (depending on previous AHA, for details see individual studies),
- Age ≥18 to ≤80 years of age,
- BMI ≤40 kg/$m^{2,}$.

Main exclusion criteria
- Treatment with insulin, GLP-1 analogues/agonists, or anti-obesity drugs within past 3 months;
- diabetic ketoacidosis within past 6 months;
- heart failure NHYHA class III or IV (1218.15 only); CV event within the past 6 months,
- impaired hepatic function (ALT, AST, ALP above 3 ULN),
- FPG > 240 mg/dl(> 13.3 mmol/L),
- limitation in the degree of renal impairment in studies 1218.17 and 1218.18,
- current treatment with systemic steroids or change in dosage of thyroid hormones within 6 weeks.

- **Objectives**

The primary objective was testing the superiority hypothesis of linagliptin versus placebo (as monotherapy or add-on) or the non-inferiority of linagliptin versus active control in decreasing HbA1c.

- **Outcomes/endpoints**

The primary efficacy endpoint in all the studies was HbA1c change from baseline to the last on-treatment visit.

Secondary glycaemic endpoints included: FPG, proportion of patients reaching HbA1c < 7.0% or <6.5 % or HbA1c reduction of at least 0.5%. Some studies included a meal tolerance test (MTT, in study 1218.16, 1218.17).

Other relevant endpoints included: Use of rescue therapy, change from baseline in body weight after 24 weeks treatment (presented in safety part), change from baseline in waist circumference after 24 weeks of treatment (presented in safety part) and change from baseline in lipid parameters after 24 weeks of treatment (presented in safety section).

- **Randomisation**

Randomisation was stratified by the HbA1c value at the beginning of the placebo run-in period (<8.5% versus ≥8.5%). Randomisation was also stratified by the number of oral antidiabetic drugs at the time of enrolment in most of the trials, except for study 1218.18.

- **Blinding (masking)**

Access to the randomisation code was restricted to dedicated randomisation personnel. Neither the patient nor the investigator was aware of the identity of a patient's treatment.

- **Statistical methods**

The primary statistical analysis in all pivotal studies analyzed the change from baseline in HbA1c after 24 weeks of treatment using an ANCOVA model with 'treatment' as well as 'prior use of antidiabetic agents' as categorical covariates and 'baseline HbA1c' as continuous covariate. The primary analysis was conducted at the 2-sided 5% level of significance and based on the FAS data set. Missing data were imputed using LOCF and additional sensitivity analyses were performed.

Statistical methods employed are generally considered appropriate.

Below are described aspects that were study specific:

Study 1218.15

This was a study in patients with T2DM to evaluate the efficacy and safety of linagliptin 5 mg as initial combination with pioglitazone 30 mg in comparison with placebo as initial combination with pioglitazone 30 mg.

Patients were treated in 43 centers in Europe and Asia: Japan (24.9%), Spain (23.1%), Hungary (21.9%), Romania (18.8%), Greece (6.4%), Austria (4.4%), Portugal (0.5%).

Study period was from 15 April 2008 to 19 June 2009.

Methods

- **Design**

Multinational, randomized, double-blind, placebo-controlled, parallel group study, consisting of an open-label, 2-week placebo run-in, followed by a 24-week double-blind treatment period and a 1-week follow-up after termination of study medication.

- **Study participants**

Patients with T2DM, either drug-naive or pre-treated with any antidiabetic agent as monotherapy or combination therapy.

HbA_{1c} at screening: 7.5% to 11.0% in treatment naïve patients and 7.0% to 9.5% in pretreated patients. HbA1c at start of run-in: between 7.5% and 11.0%.

(For other inclusion and exclusion criteria see general method aspects section above).

- **Treatments**

Patients eligible after the run-in period were randomised in a 2:1 ratio to 24 weeks of treatment with either 5 mg linagliptin or placebo as initial combination with 30 mg pioglitazone (linagliptin+pioglitazone and placebo+pioglitazone, respectively).

Results

- **Participant flow**

A total of 707 patients were enrolled and 389 were randomized (see table below). The most common reason for not being randomized was the HbA1c results before randomisation (42.5 %).

Disposition of randomised patients –Screened set

	Pbo+pio N (%)	Lina+pio N (%)	Total N (%)
Enrolled			707
Randomised	130	259	389
Treated[1]	130 (100.0)	259 (100.0)	389 (100.0)
Not prematurely discontinued trial medication	111 (85.4)	244 (94.2)	355 (91.3)
Prematurely discontinued trial medication	19 (14.6)	15 (5.8)	34 (8.7)
Adverse event	6 (4.6)	4 (1.5)	10 (2.6)
Study disease worsening	1 (0.8)	1 (0.4)	2 (0.5)
Other disease worsening	2 (1.5)	0 (0.0)	2 (0.5)
Other AE	3 (2.3)	3 (1.2)	6 (1.5)
Lack of efficacy [2]	1 (0.8)	1 (0.4)	2 (0.5)
Non-compliance to protocol	2 (1.5)	3 (1.2)	5 (1.3)
Lost to follow-up	3 (2.3)	2 (0.8)	5 (1.3)
Refused to continue trial medication	4 (3.1)	4 (1.5)	8 (2.1)
Other reason	3 (2.3)	1 (0.4)	4 (1.0)

[1] In all tables 'treated' refers to treatment with randomised study drug
[2] Includes patients who discontinued due to hyperglycaemia

- **Conduct of the study**

There were three global and two local protocol amendments to the original clinical trial protocol. These amendments were considered not influencing the study results.

No interim analysis was planned or performed for this study.

- **Baseline data**

At study start, main demographic characteristics were as follows [mean (range)]

Age: 57.5 y (25-79), 25.4 % of patients were ≥ 65,

BMI: 29.0 kg/m^2 (16.8- 39.7), 42.2 % had a BMI ≥ 30,

Diabetes duration: 25.5 % had duration of diabetes up to 1 year, 42.4% >5 years.

A total of 31.8% of the patients had taken one antidiabetic agent and 18.4% had taken ≥ 2 antidiabetic agents. Pre-treated patients were mainly on metformin monotherapy (22.1%) or SU monotherapy (7.9%) or the combination of both (9.5%).

Overall, 60.9% of patients were male, 74.6% were Caucasian and 24.9% Asian.

- **Numbers analyzed**

In both groups, over 97.0% of patients were included in the primary FAS analysis and over 95% in the PPS analysis (see Table below).

Number of patients by analysis set –Randomized set

	Pbo+pio N (%)	Lina+pio N (%)	Total N (%)
Randomised set	130 (100.0)	259 (100.0)	389 (100.0)
Treated set	130 (100.0)	259 (100.0)	389 (100.0)
FAS	128 (98.5)	252 (97.3)	380 (97.7)
FAS-completers*	106 (82.8)	236 (93.7)	342 (90.0)
PPS	123 (96.1)	246 (97.6)	369 (97.1)

* Completers were patients with a minimum treatment duration of 149 days and without premature discontinuation of study drug and had an HbA_{1c} measurement after 24 weeks of treatment.

- **Outcomes and estimation**

Primary endpoint

Treatment with 5 mg once daily linagliptin + pioglitazone was superior to treatment with placebo + pioglitazone in lowering **HbA1c** with a statistically significant difference of −0.51%.

The unadjusted mean change from baseline in HbA1c showed similar results.

Adjusted means for the change in HbA1c (%) from baseline at Week 24 – FAS (LOCF)

	Pbo+pio	Lina+pio
Number of patients	128	252
Number of patients with baseline and on-treatment results	128	252
Baseline		
Mean (SE)	8.58 (0.08)	8.60 (0.05)
Change from baseline		
Mean (SE)	−0.75 (0.11)	−1.25 (0.07)
Adjusted[1] mean (SE)	−0.56 (0.09)	−1.06 (0.06)
Comparison vs. pbo+pio (difference lina+pio – pbo+pio)		
Adjusted[1] mean (SE)		−0.51 (0.10)
95% Confidence interval		(−0.71, −0.30)
p-value		<0.0001

[1] Model includes continuous baseline HbA_{1c}, number of prior antidiabetic drugs, and treatment
SE = Standard error

In both treatment groups, HbA1c levels decreased until week 18 and remained stable thereafter.

The secondary analysis PPS supports the results of the primary analysis, although the placebo adjusted treatment effect was smaller (mean difference [95%CI]: -0.48 [-0.69; -0.28] for HbA1c.

The FAS-completers showed an even smaller placebo adjusted treatment effect (mean difference [95%CI]: -0.35 [-0.56; -0.14] for HbA1c.

Adjusted mean HbA1c changes from baseline were similar between Asian and European populations (-0.96 % vs. -1.09%, respectively), whereas placebo-adjusted changes were not (-0.91% vs. -0.37%, respectively).

Secondary endpoints:

The addition of 5 mg qd linagliptin to pioglitazone was superior to placebo in addition to pioglitazone in lowering **FPG** resulting in a treatment difference of -14.2 mg/dL (3.5 mmol/L). The results were confirmed by the secondary FAS-completer analysis.

A larger proportion of patients in the linagliptin + pioglitazone group achieved HbA1c levels <7% or <6.5% or an HbA1c reduction of at least 0.5%.

Number of patients with categorical HbA1c change from baseline at Week 24 – FAS (LOCF)

	Pbo+pio			Lina+pio		
	n[1]	(%)	N[2]	n[1]	(%)	N[2]
Response criterion						
HbA_{1c}<7.0%	39	(30.5)	128	108	(42.9)	252
Among patients with baseline HbA_{1c} ≥7.0%	39	(30.5)	128	108	(42.9)	252
HbA_{1c}<6.5%	18	(14.1)	128	44	(17.5)	252
Among patients with baseline HbA_{1c} ≥7.0%	18	(14.1)	128	44	(17.5)	252
Among patients with baseline HbA_{1c} ≥6.5%	18	(14.1)	128	44	(17.5)	252
HbA_{1c} reduction from baseline ≥0.5%	65	(50.8)	128	189	(75.0)	252

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

The proportion of patients requiring **rescue therapy** was 7.9% in the linagliptin + pioglitazone group and 14.1% in the placebo + pioglitazone group. The odds ratio obtained from the accompanying logistic regression was 0.446 (p<0.05). In addition, linagliptin + pioglitazone patients required rescue therapy later than placebo + pioglitazone patients.

Other endpoints

By week 24, both treatment groups had an increase in mean weight, with an adjusted mean change from baseline that was greater in the linagliptin + pioglitazone group (2.3 kg) than in the placebo + pioglitazone group (1.2 kg). This translated to a statistically significant treatment difference in mean change from baseline of 1.10 kg (p<0.05).

Discussion of the study results

Overall, superiority of linagliptin + pioglitazone over placebo + pioglitazone was demonstrated in the present study by the primary endpoint change in HbA1c from baseline after 24 weeks of treatment. However, the placebo adjusted effect of linagliptin (-0.51%) was rather modest and of borderline clinical relevance. The PPS analysis showed an even smaller effect (-0.48%). Clinically relevant effects on HbA1c were also not reached in patients on combination therapy prior to study.

Due to differences in placebo response, the placebo-adjusted treatment effect was larger in Asian patients (-0.91%) than in European patients (-0.37%). The treatment effect observed in the European population is not considered clinically relevant.

Linagliptin aggravated the pioglitazone-induced weight gain by a yet unknown mechanism (see safety section of this AR), which is clearly undesirable.

Overall, the placebo-adjusted glucose-lowering effect of linagliptin in this study was modest and of borderline clinical relevance. European patients, the relevant population for this application, did not have a relevant placebo-adjusted improvement in glycaemic control. Considering these efficacy results and the observed weight gain, the combination therapy of linagliptin + pioglitazone appears unfavourable.

Study 1218.16

This was a study in patients with type 2 diabetes to evaluate the efficacy and safety of linagliptin 5 mg as monotherapy in comparison to placebo. Patients were treated in 66 centers in in Asia 50.1 % (with the highest proportion of 26.8 % in India and of 14.3 % in Malaysia) and Europe 49.9% (with the highest proportion of 17.7% in Ukraine and of 12.3% Slovakia).

Study period was 15 February 2008 to 06 May 2009

Methods

- **Design**

Multinational, randomized, double-blind, placebo-controlled, parallel group study, consisting of an open-label, 2-week placebo run-in, followed by a 24-week double-blind treatment period and a 1-week follow-up after termination of study medication.

- **Study participants**

Patients with T2DM, either drug-naive or pre-treated with not more than one antidiabetic agent (except for PPARγ agonist) with a stable dose for 10 weeks prior study.
HbA_{1c} at screening: 7.0% to 10.0% in treatment naïve patients and 6.5% to 9.0% in pretreated patients. HbA1c at start of run-in: between 7.0% and 10.0%.
There were no limitations in the degree of renal impairment in this study.
(For other inclusion and exclusion criteria see general method aspects section above).

- **Treatments**

Patients eligible at start of the run-in period were randomised in a 2:1 ratio to either 5 mg linagliptin or placebo.

- **Outcomes/endpoints**

For primary and secondary endpoints see general method section above.
In addition, PK/PD of linagliptin (plasma concentrations at trough after 12 and 24 weeks of treatment);

To support the analysis of renal function during the trial, estimated Glomerular Filtration Rate (eGFR) was categorised according to the Modification of Diet in Renal Disease (MDRD) staging, and the frequency of patients with shifts in renal impairment stage was investigated. In addition, renal function was categorised based on the estimated creatinine clearance (eCcr) values calculated using the Cockcroft-Gault formula. The stages of renal function are specified in the table below.

Staging of renal function based on eGFR values (MDRD) and eCcr values (Cockcroft-Gault)

Stage	eGFR [mL/min]	eCcr [mL/min]	Description
1	≥90	>80	Normal renal function
2	60 to 89	50 to 80	Mild renal impairment
3	30 to 59	30 to <50	Moderate renal impairment
4	<30	<30	Severe renal impairment

Results

- **Participant flow**

A total of 935 patients were enrolled and 503 were randomized. The most common reason for not being randomized was the HbA1c at screening and before randomisation (38.2%).

The discontinuation rates were higher in the placebo group (9%) compared with the linagliptin group (5.4%) without a striking difference in any specific cause.

Disposition of randomised patients –Screened set

	Placebo N (%)	Linagliptin N (%)	Total N (%)
Enrolled			935
Randomised	167	336	503
Treated[1]	167 (100.0)	336 (100.0)	503 (100.0)
Not prematurely discontinued trial medication	152 (91.0)	318 (94.6)	470 (93.4)
Prematurely discontinued trial medication	15 (9.0)	18 (5.4)	33 (6.6)
Adverse event	4 (2.4)	5 (1.5)	9 (1.8)
Other disease worsening	0 (0.0)	1 (0.3)	1 (0.2)
Other AE	4 (2.4)	4 (1.2)	8 (1.6)
Lack of efficacy [2]	2 (1.2)	0 (0.0)	2 (0.4)
Lost to follow-up	1 (0.6)	2 (0.6)	3 (0.6)
Refused to continue trial medication	4 (2.4)	6 (1.8)	10 (2.0)
Other reason	4 (2.4)	5 (1.5)	9 (1.8)

[1] 'treated' refers to treatment with randomised study drug
[2] Includes patients who discontinued due to hyperglycaemia

- **Conduct of the study**

There were three global and two local protocol amendments to the original clinical trial protocol. These amendments were considered not influencing the study results.

No interim analysis was planned or performed for this study.

- **Baseline data**

At study start, main demographic characteristics were as follows [mean (range)]

Age: 55.7 y (24-79), 20.9 % of patients were ≥ 65 y,

BMI: 29.5 kg/m^2 (16.0- 41.2), 40.0 % had a BMI ≥ 30,

Diabetes duration: 36.1% had duration of diabetes up to 1 year, 25.2% >5 years.

A total of 56.5% of the patients had not previously taken an antidiabetic agent, 43.5% had taken one antidiabetic agent. Pre-treated patients were mainly on metformin monotherapy (32.3%) or SU monotherapy (10.9%).

Overall, 48.3% of patients were male, 53.7% were Caucasian and 46.1% Asian.

eGFR (MDRD staging): 43.1% of patients had an eGFR of ≥ 90 mL/min, 3.6% had 30 to <60 mL/min.

There were no relevant differences in the mean baseline characteristics between the treatment groups.

- **Numbers analysed**

In both groups, over 97.0% of patients were included in the primary FAS analysis, over 93% in the PPS analysis and over 90% in the FAS-completers analysis.

Number of patients by analysis set

	Placebo N (%)	Linagliptin N (%)	Total N (%)
Randomised set	167 (100.0)	336 (100.0)	503 (100.0)
Treated set	167 (100.0)	336 (100.0)	503 (100.0)
FAS	163 (97.6)	333 (99.1)	496 (98.6)
FAS-completers	148 (90.8)	312 (93.7)	460 (92.7)
PPS	152 (93.3)	314 (94.3)	466 (94.0)
MTT-set	29 (17.8)	73 (21.9)	102 (20.6)

- **Outcomes and estimations**

Primary endpoint

Treatment with 5 mg qd linagliptin was superior to treatment with placebo in lowering **HbA1c** with a statistically significant difference of −0.69% ($p<0.0001$). The unadjusted mean change from baseline in HbA1c showed similar results.

Adjusted means for the change in HbA1c (%) from baseline at Week 24 – FAS (LOCF)

	Placebo	Linagliptin
Number of patients	163	333
Number of patients with baseline and on-treatment results	163	333
Baseline		
Mean (SE)	8.00 (0.07)	8.00 (0.05)
Change from baseline		
Mean (SE)	0.22 (0.08)	-0.46 (0.05)
Adjusted[1] mean (SE)	0.25 (0.07)	-0.44 (0.05)
Comparison vs. placebo (difference linagliptin - placebo)		
Adjusted[1] mean (SE)		-0.69 (0.08)
95% Confidence interval		-0.85, -0.53
p-value		<0.0001

[1] Model includes continuous baseline HbA_{1c}, number of prior antidiabetic drugs, and treatment
SE = Standard error

In the linagliptin group, HbA1c levels decreased until week 12 and remained relatively stable thereafter. In the placebo group, HbA1c levels increased slightly over time.

The secondary analysis PPS supports the results of the primary analysis, the placebo adjusted treatment effect was (mean difference [95%CI]: -0.69 [-0.86; -0.53] for HbA1c. The FAS-completers showed a smaller placebo adjusted treatment effect [95%CI]: -0.56 [-0.73; -39] for HbA1c.

Whereas the mean absolute change from baseline in HbA1c was similar for Asian and Caucasian patients (-0.45% vs. -0.42%, respectively) the placebo-adjusted change was not (-0.91% vs. -0.52%).

Secondary endpoints

The treatment of 5 mg QD linagliptin was superior to placebo in lowering **FPG** resulting in a mean treatment difference of -23.3 (3.6) mg/dL at week 24. The results were confirmed by the secondary FAS-completer analysis.

A larger proportion of patients in the linagliptin compared to the placebo group achieved HbA1c levels < 7% or < 6.5% or HbA1c reduction ≥0.5%.

Number of patients with categorical HbA1c change from baseline at Week 24 – FAS (LOCF)

	Placebo			Linagliptin		
	n[1]	(%)	N[2]	n[1]	(%)	N[2]
Response criterion						
HbA_{1c} <7.0%	25	(15.3)	163	94	(28.2)	333
Among patients with baseline HbA_{1c} ≥7.0%	17	(11.6)	25	77	(25.2)	94
HbA_{1c} <6.5%	8	(4.9)	163	36	(10.8)	333
Among patients with baseline HbA_{1c} ≥7.0%	6	(12.8)	8	26	(20.1)	36
Among patients with baseline HbA_{1c} ≥6.5%	8	(4.9)	8	35	(10.6)	36
HbA_{1c} reduction from baseline HbA_{1c} ≥0.5%	31	(19.0)	163	157	(47.1)	333

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

Of the MTT parameters, difference in the adjusted mean change from baseline in total glucose AUC at 24 weeks between the two treatment groups was -3.26 mmol h/L with a statistically significant p-value of 0.0026, further supporting the results of the primary and secondary endpoints.

The proportion of patients requiring **rescue therapy** was 20.9 % in the placebo group versus 10.2% in the linagliptin group. Based on the regression result, the odds of requiring rescue therapy was about 3 times lower for patients treated with linagliptin compared to those taking placebo (odds ratio = 0.316, $p < 0.05$).

Other endpoints

In patients receiving linagliptin, the median **DPP-4 inhibition** at trough was greater than 80% with 84.18% at week 12 and 82.81% at week 24 and thus constant over time.

No meaningful change in the body weight was observed in either group. The difference in the adjusted means of change from baseline to 24 weeks in body weight between treatment groups was 0.28 kg.

Pharmacokinetic results

Analysis of linagliptin plasma concentrations at trough was performed on the data with original results (OR). The geometric mean (gMean) plasma concentrations of linagliptin at trough remained constant over time.

Mean linagliptin trough levels over time were comparable between patients with normal, mildly or moderately impaired renal function.

Geometric mean trough plasma concentrations of linagliptin - FAS (OR)

	Visit 5		Visit 7	
	N	gMean [nmol/L]	N	gMean [nmol/L]
MDRD				
no renal impairment	123	6.55	114	6.23
mild renal impairment	142	6.30	114	6.82
moderate renal impairment	14	6.30	11	6.32
eCcr				
no renal impairment	200	6.33	176	6.34
mild renal impairment	73	6.77	59	6.99
moderate renal impairment	6	5.15	4	7.31

Discussion of the study results

In the present study linagliptin at dose of 5 mg QD provided statistically significant and clinically relevant improvement in glycaemic control in patients with T2DM not sufficiently controlled on monotherapy (PPARγ agonists excluded) and in treatment naïve patients. Due to differences in placebo response, the placebo-adjusted treatment effect was larger in Asian patients (-0.91%) than in Caucasian patients (-0.52%). The results on HbA1c were supported by the results on the secondary endpoints.

The data of pharmacokinetic properties in patients with mild to moderate degrees of renal insufficiency confirm that dose adjustment in these patients is not necessary.

Study 1218.17

This was a study in patients with type 2 diabetes to evaluate the efficacy and safety of linagliptin 5 mg as add-on therapy to metformin in comparison to placebo. Patients were recruited in Asia (39.5%), Europe (26.1%), North America (which included Australia and New Zealand, 18.7%) and South America (15.7%).

Study period was 31 January 2008 to 18 May 2009.

Methods

- **Design**

Multinational, randomized, double-blind, placebo-controlled, parallel group study, consisting of an open-label, 2-week placebo run-in, followed by a 24-week double-blind treatment period and a 1-week follow-up after termination of study medication.

- **Study participants**

Patients with T2DM, pre-treated with either metformin alone or metformin in combination with one other antidiabetic agent (except pioglitazone, rosiglitazone, insulin) unchanged for at least 10 weeks prior to study. A dose of ≥1500 mg/day metformin was required for inclusion into the trial. Minimal required dose of metformin was 1500 mg per day unless the investigator documented patients to be on their maximum tolerated dose.

HbA1c at screening: 7.0% to 10.0% in patients pre-treated on metformin alone and 6.5% to 9.0% in patients pre-treated on metformin in combination with one other antidiabetic agent.

HbA1c at start of run-in: between 7.0% and 10.0%.

- **Treatments**

Patients eligible after the run-in period were randomised in 3:1 to either 5 mg linagliptin or placebo.

- **Outcome/endpoints**

For primary and secondary endpoints see general method section above.

In addition further endpoints were:

- MTT: change from baseline for 2-h post-prandial glucose (2hPPG), glucose AUC, insulin AUC, C-peptide AUC, and insulin AUC to glucose AUC ratio.

Results

- **Participant flow**

A total of 1268 patients were enrolled and 701 were randomized. The most common reason for not being randomized was not meeting the HbA1c criteria (36.0%).

The premature discontinuation rates were 7.9% in the placebo group and 7.5% in the linagliptin group. The main reason for premature discontinuation was in both groups, refused to continue trial medication.

Disposition of randomised patients –Screened set

	Placebo N (%)	Linagliptin N (%)	Total N (%)
Enrolled			1268
Started wash-out			297
Started placebo run-in			808
Not randomised			567
Randomised	177	524	701
Not treated	0	1	1
Treated *	177 (100.0)	523 (100.0)	700 (100.0)
Not prematurely discontinued trial medication	163 (92.1)	484 (92.5)	647 (92.4)
Prematurely discontinued trial medication	14 (7.9)	39 (7.5)	53 (7.6)
Adverse events	3 (1.7)	9 (1.7)	12 (1.7)
AE study dis. worse	1 (0.6)	1 (0.2)	2 (0.3)
AE other dis. worse	0 (0.0)	3 (0.6)	3 (0.4)
AE other	2 (1.1)	5 (1.0)	7 (1.0)
Lack of efficacy #	0 (0.0)	1 (0.2)	1 (0.1)
Non compl. protocol	3 (1.7)	2 (0.4)	5 (0.7)
Lost to follow-up	2 (1.1)	6 (1.1)	8 (1.1)
Refused cont. medic.	4 (2.3)	13 (2.5)	17 (2.4)
Other	2 (1.1)	8 (1.5)	10 (1.4)

* In all tables 'treated' refers to treatment with randomised study drug
# Includes patients discontinued due to hyperglycaemia

- **Conduct of the study**

There were three global and two local protocol amendments to the original clinical trial protocol. These amendments are considered not influencing the study results.

No interim analysis was planned or performed for this study.

- **Baseline data**

At study start, main demographic characteristics were as follows [mean (range)]:

Age: 56.5 y (21-79), 22.0% of patients were ≥ 65 y,

BMI: 29.9 kg/m^2 (19.1-52.3), 43.9 % had a BMI ≥ 30,

Diabetes duration: 34.0% had duration of diabetes > 1 to 5 years, 54.9% >5 years.

Overall, 54.1% of patients were male, 76.1% were Caucasian and 20.9% were Asian. In both treatment groups, around 20% of the patients were of Hispanic/Latino origin.

Pre-treated patients were mainly on metformin monotherapy (68.6%) or on combination of metformin plus sulfonylurea (26.9%).

eGFR: (MDRD staging) 59.1% of patients had an eGFR of ≥ 90 mL/min, 37.6% had 60 to < 90 mL/min and 3.3% had 30 to <60 mL/min.

There were no relevant differences in baseline efficacy variables.

The study population adequately represents the intended target population of patients with T2DM, patients on metformin alone or in combination with one other oral antidiabetic agent with insufficient glycaemic control. The age group 65 to 74 years (19.8% in the placebo group and 18.7% in the linagliptin group) was rather small to reflect the real proportion of T2DM and the group of ≥ 75 years (3.4% placebo and 2.9% linagliptin) was not sufficiently considered.

- **Numbers analysed**

In both treatment groups, more than 97% of patients were included in the primary FAS analysis and more than 89% in the secondary FAS-completers and PPS analysis. Treatment compliance was 97.7% in the placebo and 96.8% and thus similar between both treatment groups

Number of patients by analysis set

		Placebo N (%)	Linagliptin N (%)	Total N (%)
Randomised set		177 (100.0)	524 (100.0)	701 (100.0)
Treated set	N (% of randomised set)	177 (100.0)	523 (99.8)	700 (99.9)
FAS	N (% of randomised set)	175 (98.9)	513 (97.9)	688 (98.1)
FAS-completers	N (% of FAS)	156 (89.1)	468 (91.2)	624 (90.7)
PPS	N (% of FAS)	156 (89.1)	460 (89.7)	616 (89.5)
MTT-set	N (% of FAS)	26 (14.9)	85 (16.6)	111 (16.1)

- **Outcomes and estimations**

Primary endpoint

The add-on of 5 mg QD linagliptin to metformin was superior to add-on of placebo to metformin in lowering **HbA1c** with an adjusted mean treatment difference of -0.64% (p< 0.0001). The unadjusted mean change from baseline in HbA1c showed similar results.

Adjusted means for the change in HbA1c (%) from baseline at Week 24 – FAS (LOCF)

	Placebo	Linagliptin
Number of patients with baseline and on-treatment results	175	513
Baseline		
Mean (SE)	8.02 (0.07)	8.09 (0.04)
Change from baseline		
Mean (SE)	0.10 (0.08)	−0.56 (0.04)
Adjusted* mean (SE)	0.15 (0.06)	−0.49 (0.04)
Comparison vs. Placebo (diff. Linagliptin - Placebo)		
Adjusted* mean (SE)		−0.64 (0.07)
95% confidence interval		(−0.78, −0.50)
p-value		<0.0001

* Model includes continuous baseline HbA1c, prior use of antidiabetic agents, and treatment
SE = Standard error

In the linagliptin group, HbA1c levels decreased until week 12 and remained relatively stable thereafter. In the placebo group, HbA1c levels increased minimally over time.

The secondary analysis PPS supports the results of the primary analysis, the placebo adjusted treatment effect was (mean difference [95%CI]: -0.68 [-0.84; -0.53] p<.0001 for HbA1c. The FAS-completers showed a smaller placebo adjusted treatment effect [95%CI]: -0.57 [-0.72; -42] for HbA1c.

Whereas the adjusted mean HbA1c change from baseline was slightly smaller for Asian than for European patients (-0.49% vs. -0.57%, respectively), contrasting results were obtained for the placebo-adjusted changes (-0.73% vs. -0.51%).

Secondary endpoints

The add-on of 5 mg QD linagliptin to metformin was superior to add-on of placebo to metformin in lowering **FPG** with an adjusted mean treatment difference of -21.1 mg/dL (3.1 mmol/L).

More patients on linagliptin compared to placebo achieved **HbA1c values of <7% or <6.5%** or an **HbA1c reduction of ≥0.5%**.

Number of patients with categorical HbA1c change from baseline at Week 24 – FAS (LOCF)

	Placebo			Linagliptin		
	n[1]	(%)	N[2]	n[1]	(%)	N[2]
Response criterion						
HbA_{1c}<7.0%	20	(11.4)	175	145	(28.3)	513
Among patients with baseline HbA1c ≥7.0%	15	(9.2)	163	127	(26.2)	485
HbA_{1c}<6.5%	6	(3.4)	175	55	(10.7)	513
Among patients with baseline HbA1c ≥7.0%	4	(2.5)	163	47	(9.7)	485
Among patients with baseline HbA1c ≥6.5%	4	(2.3)	171	53	(10.4)	511
HbA_{1c} reduction from baseline ≥0.5%	38	(21.7)	175	255	(49.7)	513

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

In the MTT subpopulation the treatment difference in adjusted mean change from baseline at week 24 was -67.13 mg/dL ($p<0.05$) for 2hPPG and -5.35 mmol h/L ($p<0.05$) for glucose AUC in favour of linagliptin.

The proportion of patients requiring the use of rescue medication was 18.9% in the placebo group and 7.8% in the linagliptin group (odds ratio 0.276, $p < 0.05$). In addition linagliptin patients required rescue therapy later than placebo patients.

Other endpoints

The treatment difference in the adjusted means of change from baseline to 24 weeks in body weight was estimated to be 0.04 kg.

Discussion of the study results

The results of this study showed statistically significant and clinically relevant (albeit moderate) superior efficacy of linagliptin 5 mg as add-on in comparison to placebo add-on in patients with T2DM with insufficient glycaemic control on metformin. Results of primary and secondary analyses were consistent.

Due to differences in placebo response, the placebo-adjusted treatment effect was larger in Asian patients (-0.73%) than in European patients (-0.51%).

Study 1218.18

This was a study in patients with T2DM to evaluate the efficacy and safety of linagliptin 5 mg as add-on to metformin in combination with a SU in comparison to placebo. Patients were treated in the following countries: Argentina, Belgium, Canada, China, Germany, Korea, Philippines, Russia, Taiwan, Turkey, and the United Kingdom.

Study period was from 25 February 2008 to 21 May 2009

- **Design**

Multinational, randomized, double-blind, placebo-controlled, parallel group study, consisting of an open-label, 2-week placebo run-in, followed by a 24-week double-blind treatment period and a 1-week follow-up after termination of study medication.

- **Study participants**

Patients with T2DM, pre-treated only with a stable daily dose of ≥ 1500 mg per day (or documented maximally tolerated dose) of metformin and a maximally tolerated dose of a SU both unchanged for at least 10 weeks prior to study.

HbA1c at screening and after the placebo run-in period had to be between 7.0% and 10.0%.

- **Treatments**

Patients eligible after the run-in period were randomised in a 3:1 ratio to either 5 mg linagliptin or placebo.

Results

- **Participant flow**

A total of 1598 patients were enrolled and 1058 were randomized. The most common reason for not being randomized was not fulfilling HbA1c criteria (26 %).

The highest percentage of randomized study participants were from Asia (50.6%), whereas only 18.7% were from Europe and the lowest percentage from North America (8.7%).

The discontinuation rates were 8.0% in the placebo group and 7.3% in the linagliptin group. The main reasons for premature discontinuation were refused to continue trial medication (3%) in the placebo group and adverse events (2.9%) in the linagliptin group.

Disposition of randomised patients

	Placebo N (%)	Linagliptin N (%)	Total N (%)
Enrolled			1598
Started placebo run-in			1136
Not randomised			540
Randomised	265	793	1058
Not treated	2	1	3
Treated *	263 (100.0)	792 (100.0)	1055 (100.0)
Not prematurely discontinued trial medication	242 (92.0)	734 (92.7)	976 (92.5)
Prematurely discontinued trial medication	21 (8.0)	58 (7.3)	79 (7.5)
Adverse events	5 (1.9)	23 (2.9)	28 (2.7)
AE study dis. worse	1 (0.4)	3 (0.4)	4 (0.4)
AE other dis. worse	1 (0.4)	4 (0.5)	5 (0.5)
AE other	3 (1.1)	16 (2.0)	19 (1.8)
Lack of efficacy #	4 (1.5)	2 (0.3)	6 (0.6)
Non compl. protocol	4 (1.5)	19 (2.4)	23 (2.2)
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)
Refused cont. medic.	8 (3.0)	14 (1.8)	22 (2.1)
Other	0 (0.0)	0 (0.0)	0 (0.0)

* Treated refers to treatment with randomised study drug
# Includes patients discontinued due to hyperglycemia

- **Conduct of the study**

There were three global and six local protocol amendments to the original clinical trial protocol. These amendments performed during the study are considered not influencing the study results.

No interim analysis was planned or performed for this study.

- **Baseline data**

At study start, main demographic characteristics were as follows [mean (range)]:

Age: 58.1 y (23-79), 27.3% of patients were ≥ 65 y,

BMI: 28.33 kg/m^2 (15.75-39.97), 32% had a BMI ≥ 30,

Diabetes duration: 23.9% had duration of diabetes > 1 to 5 years, 73.3% >5 years.

Overall, 47.2% of patients were male, 46.6% were Caucasian and 51.7% were Asian. In both treatment groups, around 22% of the patients were of Hispanic/Latino origin.

eGFR: (MDRD staging, mL/min): 57.0% had an eGFR ≥90 and 5% an eGFR 30 to <60 mL/min

There were no relevant differences in mean values of baseline characteristics including efficacy variables.

The study population adequately represents the intended target population of patients with T2DM with an insufficient glycaemic control despite a background therapy of metformin and a SU. However, the very elderly subgroup of T2DM of ≥ 75 years (3.0% placebo and 4.8% linagliptin) was not sufficiently considered.

- **Numbers analysed**

In both groups, over 98% of patients were included in the primary FAS analysis, over 93% in the PPS analysis and over 90% in the FAS-completers analysis (see Table below). Treatment compliance was 96.5% in the placebo and 97.8% in the linagliptin group.

Number of patients by analysis set

	Placebo N (%)	Linagliptin N (%)	Total N (%)
Randomised	265 (100.0)	793 (100.0)	1058 (100.0)
Treated	263 (99.2)	792 (99.9)	1055 (99.7)
FAS	262 (98.9)	778 (98.1)	1040 (98.3)
FAS-completers	236 (90.1)	725 (93.2)	961 (92.4)
PPS	246 (93.9)	733 (94.2)	979 (94.1)

- **Outcomes and estimations**

Primary endpoint

The add-on of 5 mg QD linagliptin to metformin and a SU was superior to add-on of placebo in lowering **HbA1c** resulting in mean adjusted mean treatment difference of -0.62%.

Adjusted means for the change in HbA1c (%) from baseline at Week 24 – FAS (LOCF)

	Placebo	Linagliptin
Number of patients	262 (100.0)	778 (100.0)
Number of patients with baseline and on-treatment results	262 (100.0)	778 (100.0)
Baseline		
Mean (SE)	8.14 (0.05)	8.15 (0.03)
Change from baseline		
Mean (SE)	−0.10 (0.05)	−0.72 (0.03)
Adjusted[1] mean (SE)	−0.10 (0.05)	−0.72 (0.03)
Comparison vs. placebo (difference linagliptin – placebo)		
Adjusted[1] mean (SE)		−0.62 (0.06)
95% Confidence interval		(−0.73, −0.50)
p-value		<0.0001

[1] Model includes continuous baseline HbA_{1c} and treatment
SE = Standard error

The secondary PPS analysis supports the results of the primary analysis, the placebo adjusted treatment effect was (mean difference [95%CI]: -0.61 [-0.73; -0.49] p<.0001) for HbA1c.

The FAS-completers showed a smaller placebo adjusted treatment effect [95%CI]: -0.54 [-0.66; -0.42] p<.0001 for HbA1c.

HbA1c results were similar in patients on metformin doses ≥ 1500 mg and <1500 mg.

Whereas the adjusted mean HbA1c change from baseline was similar for Asian and European patients (-0.69% vs. -0.63%, respectively), placebo-adjusted changes were not (-0.69% vs. -0.47%, respectively).

No significant effect of the baseline metformin dose was observed on HbA1c in this trial.

Secondary endpoints:
The add-on of 5 mg QD linagliptin to metformin and a SU was superior to the add-on of placebo in lowering **FPG** resulting with an adjusted mean treatment difference of -12.7 mg/dL (2.8 mmol/L). The results were confirmed by the secondary FAS-completer analysis.

A larger proportion of patients in the linagliptin compared to the placebo group achieved **HbA1c levels < 7% or < 6.5%** or **HbA1c reduction ≥0.5%** (see Table below).

Number of patients with categorical HbA1c change from baseline at Week 24 – (NCF) – FAS

	Placebo			Linagliptin		
	n[1]	(%)	N[2]	n[1]	(%)	N[2]
Response criterion						
HbA_{1c}<7.0%	24	(9.2)	262	243	(31.2)	778
Among patients with baseline HbA_{1c} ≥7.0%	20	(8.1)	247	217	(29.2)	742
HbA_{1c}<6.5%	11	(4.2)	262	102	(13.1)	778
Among patients with baseline HbA_{1c} ≥7.0%	8	(3.2)	247	85	(11.5)	742
Among patients with baseline HbA_{1c} ≥6.5%	11	(4.2)	262	102	(13.1)	777
HbA_{1c} reduction from baseline ≥0.5%	79	(30.2)	262	453	(58.2)	778

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

The number of patients requiring **rescue therapy** was 34 (13.0%) in the placebo group and 42 (5.4%) in the linagliptin group (odds ratio: 0.361, p<0.0001). The median time to start of rescue therapy was shorter (119 days) for patients under placebo than for patients under linagliptin treatment (132 days).

Other endpoints
No meaningful change in **body weight** was noted in both treatment groups.

Discussion of the study results
In the present study, linagliptin add-on at a dose of 5 mg q.d. provided statistically significant and clinically relevant (albeit modest) improvement in glycaemic control compared to placebo add-on in patients with T2DM not sufficiently controlled on metformin and a sulfonylurea. The superiority was reflected in all glycaemic parameters evaluated and the proportion of patients requiring rescue therapy.

Due to differences in placebo response, the placebo-adjusted treatment effect, again, was larger in Asian patients (-0.69%) than in European patients (-0.47%).

Summary of Main Efficacy Results

The following tables summarise the efficacy results from the main studies supporting the approved indications for the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of Efficacy for trial 1218.16

Title: A randomised, double-blind, placebo-controlled parallel group efficacy and safety study of linagliptin (5 mg administered orally once daily) over 24 weeks, in drug naïve or previously treated (6 weeks washout) type 2 diabetic patients with insufficient glycaemic control			
Study identifier	1218.16		
Design	Randomised, double-blind, placebo-controlled, parallel-group comparison		
	Duration of main phase:		24-week treatment period with linagliptin 5 mg or placebo as monotherapy
	Duration of Run-in phase:		6-week washout including a 2-week open-label placebo run-in (patients pre-treated with an OAD) or 2-week open-label placebo run-in (patients not pre-treated with an OAD)
	Duration of Extension phase:		not applicable
Hypothesis	Superiority of treatment with linagliptin over placebo in regard to the adjusted mean change in HbA_{1c} from baseline to Week 24		
Treatment groups	Linagliptin		Linagliptin 5 mg tablet QD for 24 weeks, 336 patients randomised
	Placebo		Placebo tablet for 24 weeks, 167 patients randomised
Endpoints and definitions	Primary endpoint	Confirmatory	HbA_{1c} change from baseline after 24 weeks of treatment
	Secondary endpoint	Exploratory	FPG change from baseline after 24 weeks of treatment
	Other endpoint	Exploratory	Body weight change from baseline after 24 weeks of treatment
Database lock	17 June 2009		

Results and Analysis

Analysis description	**Primary Analysis:** after 24 weeks of treatment an analysis of covariance (ANCOVA) was performed to compare the change from baseline in HbA_{1c}. The model included 'treatment' and 'prior use of antidiabetic agents' as fixed effects and 'baseline HbA_{1c}' as covariate. The primary analysis was conducted at the 2-sided 5% level of significance.		
Analysis population and time point description	Full analysis set (FAS): the FAS consisted of all randomised patients who were treated with at least one dose of study medication, had a baseline HbA_{1c} measurement, and had at least one on-treatment HbA_{1c} measurement.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Linagliptin
	Number of patients	163	333
	Adjusted mean change in HbA_{1c} from baseline after 24 weeks [%]	0.25	-0.44
	SE	0.07	0.05
Effect estimate per comparison	HbA_{1c} change from baseline after 24 weeks [%]	Comparison groups	Treatment difference (linagliptin - placebo)
		Adjusted mean	-0.69
		SE	0.08
		P-value	<0.0001
Notes			
Analysis description	**Secondary endpoint:** the change from baseline in FPG was analysed in a similar way as the HbA_{1c} percent change, but in an exploratory way.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Linagliptin
	Number of patients	149	318
	Adjusted mean change in FPG from baseline after 24 weeks [mg/dL]	14.8	-8.5
	SE	3.0	2.0
Effect estimate per comparison	FPG change from baseline after 24 weeks [mg/dL]	Comparison groups	Treatment difference (linagliptin - placebo)
		Adjusted mean	-23.3
		SE	3.6
		P-value	<0.0001
Analysis description	**Other endpoint:** the change from baseline in Body weight was analysed in a similar way as the HbA_{1c} percent change, but in an exploratory way.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Linagliptin
	Number of patients	124	288
	Adjusted mean change in weight from baseline after 24 weeks [kg]	-0.29	-0.00

	SE	0.19	0.13
Effect estimate per comparison	Body weight change from baseline after 24 weeks [kg]	Comparison groups	Treatment difference (linagliptin - placebo)
		Adjusted mean	0.28
		SE	0.23
		P-value	0.2122

Summary of Efficacy for trial 1218.17

Title: A 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 patients with insufficient glycaemic control despite metformin therapy			
Study identifier	1218.17 [U09-2533]		
Design	Randomised, double-blind, placebo-controlled, parallel-group comparison		
	Duration of main phase:		24-week treatment period with linagliptin 5 mg or placebo as add-on therapy to metformin
	Duration of Run-in phase:		6-week washout including a 2-week open-label placebo run-in (patients pre-treated with metformin and an additional OAD) or 2-week open-label placebo run-in (patients pre-treated with metformin only)
	Duration of Extension phase:		not applicable
Hypothesis	Superiority of treatment with linagliptin over placebo in regard to the adjusted mean change in HbA_{1c} from baseline to Week 24		
Treatment groups	Linagliptin		Linagliptin 5 mg tablet QD for 24 weeks as add-on to metformin, 524 patients randomised
	Placebo		Placebo tablet for 24 weeks as add-on to metformin, 177 patients randomised
Endpoints and definitions	Primary endpoint	Confirmatory	HbA_{1c} change from baseline after 24 weeks of treatment
	Secondary endpoint	Exploratory	FPG change from baseline after 24 weeks of treatment
	Other endpoint	Exploratory	Body weight change from baseline after 24 weeks of treatment
Database lock	16 July 2009		

Results and Analysis

Analysis description	**Primary Analysis:** After 24 weeks of treatment an analysis of covariance (ANCOVA) was performed to compare the change from baseline in HbA_{1c}. The model included 'treatment' and 'prior use of antidiabetic agents' as fixed effects and 'baseline HbA_{1c}' as covariate. The primary analysis was conducted at the 2-sided 5% level of significance.		
Analysis population and time point description	Full analysis set (FAS): the FAS consisted of all randomised patients who were treated with at least one dose of study medication, had a baseline HbA_{1c} measurement, and had at least one on-treatment HbA_{1c} measurement.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Linagliptin
	Number of patients	175	513
	Adjusted mean change in HbA_{1c} from baseline after 24 weeks [%]	0.15	-0.49
	SE	0.06	0.04
Effect estimate per comparison	HbA_{1c} change from baseline after 24 weeks [%]	Comparison groups	Treatment difference (linagliptin - placebo)
		Adjusted mean	-0.64
		SE	0.07
		P-value	<0.0001
Notes			
Analysis description	**Secondary endpoint:** the change from baseline in FPG was analysed in a similar way as the HbA_{1c} percent change, but in an exploratory way.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Linagliptin
	Number of patients	159	495
	Adjusted mean change in FPG from baseline after 24 weeks [mg/dL]	10.5	-10.7
	SE	2.8	1.7
Effect estimate per comparison	FPG change from baseline after 24 weeks [mg/dL]	Comparison groups	Treatment difference (linagliptin - placebo)
		Adjusted mean	-21.1
		SE	3.1
		P-value	<0.0001
Analysis description	**Other endpoint:** the change from baseline in Body weight was analysed in a similar way as the HbA_{1c} percent change, but in an exploratory way.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Linagliptin
	Number of patients	133	452
	Adjusted mean change in weight from baseline after 24 weeks [kg]	-0.44	-0.41

	SE	0.30	0.17
Effect estimate per comparison	Body weight change from baseline after 24 weeks [kg]	Comparison groups	Treatment difference (linagliptin - placebo)
		Adjusted mean	0.04
		SE	0.23
		P-value	0.909

Summary of Efficacy for trial 1218.18

Title: A 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 patients with insufficient glycaemic control despite a therapy of metformin in combination with a sulphonylurea			
Study identifier	1218.18 [U09-2458]		
Design	Randomised, double-blind, placebo-controlled, parallel-group comparison		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24-week treatment period with linagliptin 5 mg or placebo as add-on therapy to metformin in combination with a sulphonylurea (SU) 2-week open-label placebo run-in not applicable
Hypothesis	Superiority of treatment with linagliptin over placebo in regard to the adjusted mean change in HbA_{1c} from baseline to Week 24		
Treatment groups	Linagliptin		Linagliptin 5 mg tablet qd for 24 weeks as add-on to metformin and an SU, 793 patients randomised
	Placebo		Placebo tablet for 24 weeks as add-on to metformin and an SU, 265 patients randomised
Endpoints and definitions	Primary endpoint	Confirmatory	HbA_{1c} change from baseline after 24 weeks of treatment
	Secondary endpoint	Exploratory	FPG change from baseline after 24 weeks of treatment
	Other endpoint	Exploratory	Body weight change from baseline after 24 weeks of treatment
Database lock	19 August 2009		

Results and Analysis

Analysis description	**Primary Analysis:** after 24 weeks of treatment an analysis of covariance (ANCOVA) was performed to compare the change from baseline in HbA_{1c}. The model included 'treatment' as fixed effect and 'baseline HbA_{1c}' as covariate. The primary analysis was conducted at the 2-sided 5% level of significance.		
Analysis population and time point description	Full analysis set (FAS): the FAS consisted of all randomised patients who were treated with at least one dose of study medication, had a baseline HbA_{1c} measurement, and had at least one on-treatment HbA_{1c} measurement.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Linagliptin
	Number of patients	262	778
	Adjusted mean change in HbA_{1c} from baseline after 24 weeks [%]	-0.10	-0.72
	SE	0.05	0.03
Effect estimate per comparison	HbA_{1c} change from baseline after 24 weeks [%]	Comparison groups	Treatment difference (linagliptin - placebo)
		Adjusted mean	-0.62
		SE	0.06
		P-value	<0.0001
Notes			
Analysis description	**Secondary endpoint:** the change from baseline in FPG was analysed in a similar way as the HbA_{1c} percent change, but in an exploratory way.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Linagliptin
	Number of patients	248	739
	Adjusted mean change in FPG from baseline after 24 weeks [mg/dL]	8.1	-4.6
	SE	2.4	1.4
Effect estimate per comparison	FPG change from baseline after 24 weeks [mg/dL]	Comparison groups	Treatment difference (linagliptin - placebo)
		Adjusted mean	-12.7
		SE	2.8
		P-value	<0.0001
Analysis description	**Other endpoint:** the change from baseline in Body weight was analysed in a similar way as the HbA_{1c} percent change, but in an exploratory way.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Linagliptin
	Number of patients	222	714
	Adjusted mean change in weight from baseline after 24 weeks [kg]	-0.06	0.27

	SE	0.17	0.09
Effect estimate per comparison	Body weight change from baseline after 24 weeks [kg]	Comparison groups	Treatment difference (linagliptin - placebo)
		Adjusted mean	0.33
		SE	0.19
		P-value	0.0803

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

Pooled analysis across trials was performed for the 4 large placebo-controlled pivotal Phase III-trials (1218.15, 1218.16, 1218.17, and 1218.18, with different background medication).

The baseline characteristics of patients in the 4 individual studies were similar in the linagliptin and placebo groups. Some imbalances between the linagliptin and placebo were seen with regards to pre-treatment with oral antidiabetic agents: the percentage of patients without prior use of OADs was 16.5% for linagliptin and 21.7% for placebo, and 52.7% (linagliptin) and 46.6% (placebo) of patients took 2 or more prior OADs.

The pooled analysis across the 4 placebo-controlled pivotal trials showed that age, gender, BMI, diabetes duration, previous antidiabetic medication, renal impairment or insulin resistance did not relevantly affect treatment response to linagliptin but demonstrated a highly significant influence of race /geographical region on placebo-adjusted HbA1c decreases, the reasons of which are unclear. The overall treatment effect in European/Caucasian patients is smaller than in Asian patients and of borderline clinical relevance. Below there is a detailed description of the pooled analysis.

- **Age**

The adjusted mean treatment differences in HbA1c were very similar across age categories except for the patients aged 75 years or older, for whom the difference in adjusted means was numerically higher (-0.83%). However, the number of patients in this age category was small.

Change from baseline HbA1c [%] after 24 weeks in EFF-1 pool by age – FAS (LOCF)

Age group/ treatment group	Number of patients	Baseline HbA_{1c}, mean (SD)	Change from baseline in HbA_{1c}		Difference from placebo		
			Mean (SD)	Adjusted mean (SE) [a]	Adjusted mean (SE) [a]	95% CI	p-value
≤50 years/							
Placebo	194	8.21 (0.89)	-0.07 (1.22)	0.02 (0.06)			
Linagliptin	442	8.20 (0.88)	-0.60 (0.93)	-0.54 (0.04)	-0.56 (0.07)	(-0.71, -0.42)	<0.0001
51 to 64 years/							
Placebo	363	8.16 (0.89)	-0.10 (1.02)	-0.02 (0.05)			
Linagliptin	970	8.20 (0.85)	-0.73 (0.91)	-0.66 (0.03)	-0.64 (0.05)	(-0.74, -0.54)	<0.0001
65 to 74 years/							
Placebo	152	8.09 (0.87)	-0.13 (0.96)	-0.09 (0.07)			
Linagliptin	398	8.08 (0.82)	-0.72 (0.86)	-0.69 (0.04)	-0.60 (0.08)	(-0.76, -0.44)	<0.0001
≥75 years/							
Placebo	19	8.06 (0.78)	0.05 (1.04)	0.03 (0.20)			
Linagliptin	66	8.01 (0.79)	-0.77 (0.96)	-0.80 (0.11)	-0.83 (0.22)	(-1.27, -0.39)	0.0002

a Model includes baseline HbA_{1c}, washout, treatment, study, BMI, subgroup, and treatment-by-subgroup interaction

- **Gender**

Demographic characteristics of both genders were well balanced between linagliptin and placebo. Change in HbA1c from baseline was independent of gender.

- **Race**

When demographics were compared between Caucasian and Asian patients, lower mean age (54.4 vs. 59.0 y) and mean BMI (26.05 kg/m2 vs. 30.91 kg/m2) were observed for Asian patients. The number of Black patients was small (linagliptin: 12 patients; placebo: 4 patients).

For Asian patients treated with linagliptin, a similar adjusted mean change from baseline after 24 weeks was observed as for Caucasian patients (Asian: -0.60%; Caucasian: -0.65%). However, an increase in mean HbA1c after 24 weeks was seen in Asian patients receiving placebo (0.20%). Thus, the adjusted mean difference between linagliptin and placebo was greater for Asian patients (-0.80%) than for Caucasian patients (-0.50%). The low p-value for the treatment-by-race interaction term (p = 0.0003) indicated that race may have had an influence on the treatment effect of linagliptin.

Change from baseline HbA1c [%] after 24 weeks in different races – FAS (LOCF)

Race/ treatment group	Number of patients	Baseline HbA_{1c}, mean (SD)	Change from baseline in HbA_{1c}		Difference from placebo		
			Mean (SD)	Adjusted mean (SE) [a]	Adjusted mean (SE) [a]	95% CI	p-value
White/							
Placebo	438	8.16 (0.88)	-0.22 (1.02)	-0.16 (0.04)			
Linagliptin	1121	8.14 (0.82)	-0.70 (0.90)	-0.65 (0.03)	-0.50 (0.05)	(-0.59, -0.40)	<0.0001
Black or African American/							
Placebo	4	7.75 (0.53)	0.18 (0.33)	0.13 (0.43)			
Linagliptin	12	8.55 (1.03)	-1.06 (0.99)	-1.01 (0.25)	-1.15 (0.49)	(-2.11, -0.18)	0.0197
Asian/							
Placebo	286	8.16 (0.89)	0.10 (1.11)	0.20 (0.05)			
Linagliptin	743	8.20 (0.88)	-0.69 (0.92)	-0.60 (0.03)	-0.80 (0.06)	(-0.91, -0.68)	<0.0001

a Model includes baseline HbA_{1c}, washout, treatment, study, subgroup, and treatment-by-subgroup interaction

On request by the CHMP, data on DPP-4 inhibition across races were presented. The level of DPP-4 inhibition in the linagliptin Phase III-trials was calculated by race, based on the pooled studies 1218.16, 1218.20, and 1218.23. The analysis of DPP-4 inhibition at Week 24 to 28 showed that linagliptin 5 mg reached a sufficient median DPP-4 inhibition of 84% and 82% in Caucasian and Asian patients, respectively (mean ± SD: 78 ±27% and 80 ± 14% in Caucasian and Asian patients, respectively) and similar DPP-4 inhibition across regions.

- **Geographical region**

The absolute HbA1c reductions from baseline were not markedly different across regions. Differences in placebo-adjusted effect sizes were, however, larger between regions, the reasons of which are unknown. The overall placebo-adjusted treatment effect in European patients was small (-0.44% in HbA1c) and of questionable clinical relevance. This finding is also in line with the result from the related analysis regarding race indicating that Caucasian patients had a smaller placebo-adjusted HbA1c reduction (-0.5%) than Asian paitents (-0.8%).

A limitation of the studies was that a large proportion of the European patients were recruited from Russia and the Ukraine, where lifestyle and diabetes care may be different from patients in the EU potentially contributing to a larger placebo effect. A new subgroup analysis as requested by the CHMP demonstrated that the treatment difference of linagliptin in comparison to placebo was -0.57% in HbA1c in pooled data from patients from EU countries (studies 1218.16, 1218.17, 1218.18, 1218.35 and 1218.50).

- **Baseline body mass index**

The placebo-adjusted treatment differences in mean change in HbA1c was comparable between the 2 BMI categories (BMI <30 kg/m2: -0.64%; BMI ≥30 kg/m2: - 0.59). There was no striking difference in placebo response in obese (-0.15%) vs. non-obese (-0.06%) patients.

- **Baseline HbA1c**

The absolute and placebo-adjusted mean difference in the HbA1c change from baseline between linagliptin and placebo increased with increasing baseline HbA1c.

Change from baseline HbA1c [%] after 24 weeks in different baseline HbA1c subgroups – FAS (LOCF)

Baseline HbA_{1c}/ treatment group	Number of patients	Baseline HbA_{1c}, mean (SD)	Change from baseline in HbA_{1c}		Difference from placebo		
			Mean (SD)	Adjusted mean (SE) [a]	Adjusted mean (SE) [a]	95% CI	p-value
<7.0%/							
Placebo	43	6.76 (0.24)	0.25 (0.83)	0.21 (0.13)			
Linagliptin	91	6.75 (0.25)	-0.10 (0.64)	-0.13 (0.09)	-0.33 (0.16)	(-0.65, -0.02)	0.0371
7.0% to <8.0%/							
Placebo	292	7.48 (0.28)	0.09 (0.91)	0.12 (0.05)			
Linagliptin	749	7.49 (0.26)	-0.45 (0.70)	-0.43 (0.03)	-0.55 (0.06)	(-0.66, -0.43)	<0.0001
8.0% to <9.0%/							
Placebo	251	8.44 (0.29)	-0.15 (1.05)	-0.06 (0.06)			
Linagliptin	671	8.41 (0.28)	-0.81 (0.89)	-0.74 (0.04)	-0.68 (0.06)	(-0.80, -0.55)	<0.0001
≥9.0%/							
Placebo	142	9.48 (0.45)	-0.48 (1.30)	-0.33 (0.07)			
Linagliptin	365	9.46 (0.41)	-1.16 (1.10)	-1.07 (0.05)	-0.74 (0.09)	(-0.91, -0.57)	<0.0001

a Model includes categorical baseline HbA_{1c}, washout, treatment, study, subgroup, and treatment-by-subgroup interaction

- **Time since diagnosis of diabetes**

Overall, treatment effect of linagliptin was independent of the time since diagnosis of diabetes although placebo-adjusted HbA1c changes were somewhat lower in patients with diabetes duration < 1year (-0.49%) than in those diagnosed for 1 to 5 years (-0.62%) and those diagnosed for more than 5 years (-0.66%).

- **Washout of previous antidiabetic medication**

The key demographic parameters were overall balanced between linagliptin and placebo. As to race distribution, 73.4% of the patients who washed out previous OADs were Caucasian, but only 55.6% of those who did not wash out prior OADs. Correspondingly, 26.0% of the patients who performed a washout were Asian, compared with 43.8% of those who did not wash out prior OADs.

Even though the treatment difference was numerically higher for those patients who washed out prior OADs than for those who did not (-0.72% vs. -0.59%), there was no significant treatment-by-washout interaction (p = 0.1392) indicating that the washout of previous antidiabetic medication before randomisation did not relevantly influence on the treatment effect of linagliptin.

- **Renal impairment**

Most of the patients had none or mild renal impairment. As expected, patients with lower renal function were on average older and had a longer duration of diabetes. Nevertheless, treatment responses were similar among MDRD groups.

- **Baseline HOMA IR**

The results do not suggest an influence of insulin resistance on the treatment effect of linagliptin.

Clinical studies in special populations

Patients with mild to severe renal insufficiency were investigated in the PK/PD study 1218.26 (see Pharmacokinetics section above). Patients with mild to moderate renal insufficiency could regularly be

enrolled in phase III trials but severe renal impairment was an exclusion criterion. In the four pivotal trials, a total of 987 (linagliptin, N=715) patients with mild renal impairment and 109 (linagliptin, N=80) patients with moderate renal impairment were enrolled. The treatment effect of linagliptin in terms of adjusted mean differences to placebo in HbA1c was similar in patients with normal renal function (-0.61%), and patients with mild (-0.63%) or moderate (-0.57%) renal impairment. Efficacy of linagliptin was also demonstrated in a separate trial in patients with severe renal insufficiency (study 1218.43). In this trial the adjusted mean difference to placebo in HbA1c after 52 weeks was -0.72%. The results from both phase I and phase III results showed that dose adjustment for linagliptin is not necessary in patients with renal impairment.

Patients with hepatic impairment were investigated in the PK/PD study 1218.27 but were excluded in phase III trials. However, DPP-4 inhibition in all hepatically impaired subjects in study 1218.27 was generally greater or equal 80% over the whole steady state dosing interval (full efficacy of DPP-4 inhibitors is normally reached with >/= 80% DPP-4 inhibition). Therefore, the CHMP agreed that the observed differences in linagliptin exposure are considered to be not clinically relevant and thus, no dose adjustment is considered necessary in all severity types of hepatic dysfunction.

In the clinical studies, the number of patients aged 75 years or above was very low (in the combined four pivotal placebo-controlled studies: 19 and 66 patients for placebo and linagliptin, respectively).

Supportive studies

Long-term efficacy and safety were examined in studies: 1218.20, 1218.23 and 1218.40.

Other supportive studies submitted with this application are studies 1218.35 and 1218.50.

During the registration process, (interim) results of several supportive trials were presented. Results were submitted of a study with linagliptin monotherapy in patients with severe renal insufficiency (study 1218.43). In this study, 133 patients were randomised to receive placebo (65 patients) or 5 mg linagliptin once daily (68 patients). In addition, results were presented of a recent Phase IIb trial (1218.62) with linagliptin dual combination therapy. This trial investigated the efficacy of linagliptin 2.5 mg twice daily (bid) and linagliptin 5 mg once daily versus placebo as add-on to metformin over 12 weeks.

Study 1218.20 was a multinational, randomised, double-blind, active-controlled study to evaluate efficacy and safety of linagliptin 5 mg compared to glimepiride over two years, in T2DM patients with insufficient glycaemic control despite metformin therapy. After 52 weeks, lnagliptin was associated with a decrease in HbA1c of -0.38%, and glimepiride was associated with a decrease of -0.60% in the full analysis set (FAS). According to the pre-defined non-inferiority margin of 0.35% for HbA1c, non-inferior efficacy of linagliptin vs. glimepiride could be shown in the primary FAS analysis at 52 weeks (treatment difference 0.22%). The PPS analysis showed a slightly higher treatment difference with a mean value of 0.26%. After 104 weeks, linagliptin was associated with a decrease in HbA1c of -0.16%, and glimepiride was associated with a decrease of -0.36% in the full analysis set (FAS) with a mean treatment difference of 0.20%. The PPS (LOCF) analysis again showed a larger treatment difference of 0.28% in HbA1C.

Study 1218.23 was a placebo and active-controlled study using voglibose. Voglibose is not approved in the EU and, therefore, the comparison with voglibose is not considered relevant for this application.

Study 1218.40 was an open-label extension trial without a control group in patients who completed one of the 4 pivotal placebo-controlled trials (1218.15, 1218.16, 1218.17, or 1218.18). The objective was primarily to evaluate safety of 5 mg linagliptin during long-term treatment as monotherapy or in combination with metformin, pioglitazone, or metformin in addition to a sulphonylurea drug.

Furthermore, the objective was to assess efficacy in a descriptive exploratory way. All patients received 5 mg linagliptin.

Patients were analysed according to their previous exposure to linagliptin. In the group of patients who had received linagliptin in the previous studies, the HbA1c levels achieved during the 24 weeks of treatment in the previous trials were maintained in this extension study until week 42. Thereafter, HbA1c appeared to increase slightly but patient numbers were small.

In the group of patients who had been randomised to placebo in the previous studies, the maximum effect of linagliptin on HbA1c was observed at Week 18 of this extension study (mean change from baseline: -0.68%). From Week 30 to Week 42, no further reductions in mean HbA1c values were observable. Subsequently, HbA1c levels started to slightly increase again but patient number became smaller.

Study 1218.35 was a multinational, 18-week study investigating efficacy and safety of 5 mg linagliptin in combination with a SU.

Linagliptin was superior in reducing HbA1c compared to placebo with a mean treatment difference of -0.47% (95% CI -0.7, -0.24) at week 18 week. However, the clinical relevance of this effect is considered questionable. Subgroup analysis confirmed that gender did not influence the treatment response.

Asian patients had a larger mean change from baseline in HbA1c (-0.76%) than European (-0.40%) patients.

The placebo-adjusted effect on HbA1c in European patients was -0.29%.

Study 1218.50 investigated efficacy and safety of linagliptin 5 mg compared to placebo (part 1, 18 weeks) and to glimepiride (part 2, 34 weeks) in patients intolerant to metformin therapy. 93% of study population did not tolerate metformin due to gastrointestinal intolerance.

At week 18 linagliptin was superior to placebo in reducing HbA1c with a mean treatment difference of -0.57%. Secondary results were consistent. The mean HbA1c change from baseline was small and similar in Asian (-0.35%) and European (-0.37%) patients. However, the placebo-adjusted treatment mean change in HbA1c was larger in Asian patients (-0.80%) than in Caucasian patients (-0.45%).

The results of part 2 of the study (double-blind extension period, where placebo patients switched to glimepiride) were provided during the evaluation of this application. The results showed a fall in the mean HbA1c change from baseline in the control group (glimepiride) from Week 18 to Week 30 and thereafter the mean was fairly constant. The mean HbA1c change from baseline remained constant for linagliptin from Week 18 throughout the remainder of the trial. There were differences in mean HbA1c from baseline between linagliptin and glimepiride from Week 30 onwards, with glimepiride having a larger decrease from baseline compared with linagliptin. The treatment with glimepiride induced a decrease in HbA1c of 0.82%, whereas linagliptin was associated with a decrease of 0.44%.

2.5.3. Discussion on clinical efficacy

Efficacy and safety of linagliptin were studied in 11 phase II/III studies, comparing the effects of linagliptin with placebo as monotherapy in general, as monotherapy in patients intolerant for metformin, as add-on to metformin or sulphonylurea or pioglitazone, and as triple therapy with sulphonylurea and metformin.

Overall, treatment with 5 mg linagliptin once daily resulted in a decrease in HbA1c of approximately 0.6%. For Asian patients treated with linagliptin, a similar adjusted mean change from baseline in HbA1c was observed as for Caucasian patients (Asian: -0.60%; Caucasian: -0.65%). However, the

placebo-adjusted mean treatment difference was greater for Asian patients (-0.80%) than for Caucasian patients (-0.50%). The relatively small effect size in European patients (per se and in comparison with Asian patients) was more or less observed in all studies. In PK studies, peak and total exposure were about 30% higher in Japanese and Chinese subjects than in Caucasian subjects. However, the median and mean level of DPP-4 inhibition was similar in the different races and geographical regions. Potential differences in diet and diabetes care may have explained the differences between Asian and Caucasian patients. Since the majority of European patients were recruited from countries outside the EU, a new subgroup analysis on EU patients was requested by the CHMP. This analysis demonstrated that the treatment difference of linagliptin in comparison to placebo was -0.57% in pooled data from patients from EU countries (studies 1218.16, 1218.17, 1218.18, 1218.35, 1218.50), providing reassurance that linagliptin is effective in the EU population. The placebo effect was rather high in the non-EU countries compared to EU countries which may be due to differences in pre-study diabetes care. The pooled analyses including the 4 pivotal placebo-controlled trials suggest that age, gender, BMI, diabetes duration, previous antidiabetic medication, renal impairment or insulin resistance did not relevantly affect treatment response.

No active-controlled trial investigating linagliptin monotherapy has been submitted. The applicant did not apply for an unrestricted monotherapy indication, but only for an indication in patients for whom metformin is inappropriate due to intolerance, or is contraindicated due to renal impairment. Linagliptin showed acceptable efficacy in European patients in the pivotal study 1218.16 (placebo-adjusted effect -0.52%). In the supportive study 1218.50, the effect in the European population was small (placebo-adjusted difference was -0.15%); however, the effect in the Caucasian population was similar to results in study 1218.16 (placebo-adjusted difference: -0.43%). Considering the fact that in 93% of the patients in study 1218.50 metformin was inappropriate due to gastrointestinal intolerance, an indication in those patients is acceptable. The number of patients in this study with contraindications for metformin due to severe renal insufficiency or hepatic insufficiency was low. However, in a dedicated study in patients with severe renal impairment, linagliptined proved to be effective. Taken the available data in patients with moderate to severe renal impairment together, linagliptin appears to be a relevant treatment option in this population for whom metformin is contraindicated. Thus, the currently proposed restricted monotherapy indication (for patients for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment) is considered acceptable.

Linagliptin was investigated in initial combination with pioglitazone. However, this study was performed in patients that were pretreated with a variety of oral antidiabetic drugs: 50% of subjects had not received any glucose lowering drugs before the study, 30% was on one drug and 18% on two or more. Therefore, at least half of the patients can not be considered as insufficiently controlled on pioglitazone, and therefore efficacy in the claimed indication (in combination with a thiazolidinedione, when the thiazolidinedione alone with diet and exercise, does not provide adequate glycaemic control) has not been adequately demonstrated. In addition, the treatment effect in European patients was relatively weak (-0.37%).

In dual combination therapy with metformin, a relevant decrease in HbA1c was found (-0.51%) in European patients of study 1218.17, supported by a change of –0.73% in the dose-finding study 1218.6. The supportive study 1218.62 investigated the efficacy of linagliptin 2.5 mg twice daily and linagliptin 5 mg once daily versus placebo as add-on to metformin over 12 weeks. In Caucasian patients, the placebo adjusted treatment effect of linagliptin was -0.69 (2.5 mg bid) and -0.66 (5 mg qd) suggesting that linagliptin has similar glucose-lowering effects with both treatment regimens.

The claim of non-inferior efficacy of linagliptin compared to glimepiride (study 1218.20) is not appropriately supported by data. The pre-defined non-inferiority margin was too wide considering the treatment effects observed for linagliptin as well as glimepiride. In addition, approximately 50% of the patients did not receive the maximum dose of 4 mg of glimepiride. Moreover, despite relatively low

baseline HbA1c values, more patients in the linagliptin group than in the glimepiride group needed rescue medication (24.7% linagliptin; 21.5% glimepiride) or discontinued the trial due to lack of efficacy (5.8% linagliptin; 1.9% glimepiride). Interestingly, data from the second part of study 1218.50 showed that the treatment with glimepiride induced a mean decrease in HbA1c of 0.82%, whereas linagliptin was associated with a decrease of 0.44% further supporting the impression that efficacy of the two agents is not similar.

The CHMP was of the view that the indication of linagliptin in dual therapy with SU is not approvable because the placebo-adjusted effect on HbA1c in European patients was only -0.29%.

Triple therapy was investigated in one trial in which linagliptin was compared to placebo in patients treated with a combination of metformin and a sulphonylurea (1218.18). The treatment effect of linagliptin was -0.62%. However, the placebo-adjusted mean change in HbA1c was, larger in Asian patients (-0.69%) than in European patients (-0.47%),

The treatment effect of linagliptin in terms of adjusted mean differences to placebo in HbA1c was similar in patients with normal renal function (-0.61%), and patients with mild (-0.63%) or moderate (-0.57%) renal impairment. In the dedicated trial in patients with severe renal insufficiency (1218.43) the adjusted mean difference to placebo in HbA1c after 52 weeks was also similar (-0.72%). Efficacy of linagliptin in patients with various degrees of renal impairment appears reasonably established.

The number of patients with hepatic impairment (n = 34) was very small.

In the clinical studies, the number of patients aged 75 years or above was very low (in the combined 4 pivotal placebo-controlled studies: 19 and 66 patients for placebo and linagliptin, respectively). It is difficult to estimate the effect of linagliptin on HbA1c in very elderly patients and the same applies to safety (see below). This has been adequately reflected in the SmPC. Further data in these patients are needed. A new trial in elderly patients is now ongoing (as described in the RMP).

Only 1 randomized trial with a study duration longer than 24 weeks (glimepiride-controlled trial study 1218.20) was performed. Based on results of this trial, treatment effect of linagliptin appears largely maintained over one year of treatment. In both the linagliptin and glimepiride groups, maximum HbA1c reduction was achieved around week 16 with a more pronounced reduction observed for glimepiride. After this time point, mean HbA1c levels remained stable in the linagliptin group, whereas in the glimepiride group they increased continuously. Therefore, the treatment difference became smaller over time but was still present at week 52 (the time point of the primary analysis). During the second year, the HbA1c levels of both the glimepiride and the linagliptin group increased (at week 104: linagliptin change in HbA1c of -0.16%; glimepiride change in HbA1c of -0.36% in the full analysis set (FAS)). Evidence for long term efficacy is therefore limited, but follow up data of the studies do not indicate loss of efficacy (ongoing extension trial 1218.40). So far, HbA1c values in this trial appear rather stable over about one year. In the absence of a comparator, the overall rate of rescue therapy cannot be assessed.

2.5.4. Conclusions on the clinical efficacy

Overall, treatment with 5 mg linagliptin once daily resulted in a modest effect on the primary efficacy endpoint (HbA1c) with statistically significant reductions in HbA1c, fasting plasma glucose and postprandial glucose. No direct comparison is made with other gliptins. A problem of this dossier is the inclusion of only a small percentage of patients from the EU or from North America in the clinical studies, especially when considering the observed differences in placebo-adjusted HbA1c reductions across races (Asians vs. Caucasians) and geographical regions. The subgroup analysis on pooled data on EU patients provides reassurance that linagliptin is efficacious in the population applied for.

In conclusion, linagliptin has been shown to be effective as monotherapy in patients with intolerance or contraindications due to renal impairment to metformin, and as add-on treatment with metformin or with metformin and SU. Efficacy of linagliptin has not sufficiently been demonstrated in European patients as add-on to SU or add-on to pioglitazone.

2.6. Clinical safety

This application is supported by safety data from 37 studies, including 9 phase III trials, 4 phase II trials, and 24 phase I studies. Of the phase I studies, 20 were performed in healthy subjects, 2 studies in patients with type 2 diabetes, 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 8 study groupings, SAF-1 to SAF-8, with the aim to group trials of similar designs, durations, and patient/subject populations.

SAF-1 is the largest set and comprises all trials conducted in patients with type 2 diabetes. This set was used to determine the frequency of rare adverse events and events of special interest. SAF-2 (all placebo-controlled trials) and SAF-3 (pivotal trials) are of particular interest because they allow the profiling of linagliptin against placebo. These 3 safety groupings overlap substantially: SAF-2 (all placebo-controlled trials) comprises about 80% of the patients in SAF-1 (all trials in patients) and SAF-3 (pivotal trials) includes about 71% of patients of SAF-2. Since SAF-2 is the largest and most comprehensive placebo-controlled grouping, the subgroup analyses were based on this set. The different study groupings are summarized below in Table 8.

During the registration process, results of the study with linagliptin monotherapy in patients with severe renal insufficiency (study 1218.43) were added.

Grouping of studies for the analysis of safety

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 (linagliptin 5 mg vs. linagliptin all doses)	12 days to 104 weeks	.2, .3, .5, .6, .12, .15, .16, .17, .18, .20, .23, .35, .37, .40, .50 (pooled analysis)	n=4687
SAF-2	All 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, .37, .50 (pooled analysis)	n=3749
SAF-3	Pivotal placebo-controlled trials with linagliptin 5 mg in patients (Placebo vs. linagliptin 5 mg)	24 weeks	.15, .16, .17, .18 (pooled analysis)	n=2647
SAF-4	Long-term safety in an active-controlled trial in patients (linagliptin 5 mg vs. glimepiride)	≥52 weeks	.20 (by-study analysis)	n=1559
SAF-5	Long-term safety in controlled and uncontrolled trials in patients (linagliptin 5 mg)	52 to ≤102 weeks	.20, .23, .40 (pooled analysis)	n=3436
SAF-6	Placebo-controlled trials with more than one linagliptin dose level in patients (Placebo, linagliptin ≤2.5 mg, 5 mg, 10 mg)	12 days to 52 weeks	.2, .3, .5, .6, .12, .23 (pooled analysis)	n=1100
SAF-7	Phase I trials in healthy subjects (linagliptin total)	1 to 21 days	.1, .4, .7, .8, .9, .10, .11, .13, .25, .28, .29, .30, .31, .32, .33, .34, .44, .45, .58, .67 (pooled analysis)	n=453
SAF-8	Trials in patients with renal and hepatic impairment (renal: without vs. mild vs. moderate vs. severe vs. ESRD; hepatic: without vs. mild vs. moderate vs. severe)	1 to 10 days	.26, .27 (by-study analysis)	n=84

* Numbers are based on the treated set

Patient exposure

SAF-1 (all trials in patients with type 2 diabetes) comprised 6198 patients in total. Of these 4687 patients were treated with linagliptin (any dose) and 4040 patients received linagliptin 5 mg once daily. In addition, 21 patients were treated with linagliptin 5 mg in the 1218.26 (phase I study in patients with renal impairment). Therefore the overall number of patients with type 2 diabetes who received treatment with linagliptin 5 mg was 4061.

Of the patients treated with linagliptin 5 mg, 3430 patients were exposed for 6 months or longer, 2390 patients for 12 months or longer and 536 patients for 18 months or longer. In the pool of placebo-controlled trials (SAF-2), overall exposure in patient years was higher in the linagliptin group than in the placebo group due to the weighted allocation ratios in most trials.

In the trial with patients with severe renal failure, 68 patients were randomised to receive 5 mg linagliptin.

Adverse events

The overall percentages of patients with adverse events in SAF-2 were comparable between treatments (placebo 53.8% vs. linagliptin 55.0%). The proportions of patients with adverse events of mild (36.8% vs. 37.6% in the placebo and linagliptin group, respectively), moderate (15.6% vs. 15.6%), or severe (1.4% vs. 1.8%) intensity were similar. Drug-related adverse events were slightly more frequent in the linagliptin group than with placebo (8.5% vs. 10.4%). The most frequent drug-

related adverse events were hypoglycaemia with a higher incidence in the linagliptin group (2.4% vs. 5.0%, in the placebo and linagliptin group, respectively, occurring predominantly in a background of metformin+SU), and hyperglycaemia with a higher incidence in the placebo group (1.5% vs. 0.5%). The frequency of premature discontinuations of study drug was higher in the placebo group than in the linagliptin group (3.6% vs. 2.3%). The difference was mainly due to higher incidences of hyperglycaemia (0.9% vs. 0.2%) and blood glucose increased (0.4% vs. 0.1%) in the placebo group. The incidence of serious adverse events was low in both treatment groups (2.5% vs. 2.7%). In SAF-2, there were 2 fatal serious adverse events in the linagliptin group and none in the placebo group. A summary of the adverse events by category is provided in the following table.

Summary of adverse events for SAF-2 (all placebo-controlled trials) - TS

	Placebo N (%)	Linagliptin 5 mg N (%)
Number of patients	1183 (100.0)	2566 (100.0)
Patient years of exposure	433.8	1041.4
Patients with any adverse event	636 (53.8)	1412 (55.0)
Patients with adverse events of severe intensity	16 (1.4)	45 (1.8)
Patients with investigator-defined drug-related adverse events	101 (8.5)	268 (10.4)
Patients with adverse events of special interest [a]	10 (0.8)	16 (0.6)
Patients with adverse events leading to discontinuation	43 (3.6)	58 (2.3)
Patients with serious adverse events	29 (2.5)	69 (2.7)

[a] Hypersensitivity reactions, renal events, and hepatic events (based on investigator-reporting, excluding severe cutaneous adverse reactions and pancreatitis).

Generally, on the level of system organ classes, there were only small differences between the treatment groups. However, on the level of preferred terms some clear differences were observed. As expected, hyperglycaemia occurred with a higher frequency in the placebo/background group than in the linagliptin group (10.6% vs. 5.0%). Conversely, hypoglycaemia was less frequent in the placebo group (4.1%) than in the linagliptin group (7.6%). Overall, infections and infestations were the most frequent adverse events. Musculoskeletal and connective tissue disorders; respiratory, thoracic and mediastinal disorders, and vascular disorders occurred with a higher incidence in the linagliptin group, however the difference never exceeded 2%. In addition, higher frequencies in the linagliptin group were also observed for skin and subcutaneous tissue disorders (2.6% vs. 4.0%); where no preferred term reached an overall incidence of 1% or above and no single preferred term showed a clear increase. The individual study reports describe 2 patients with photosensitivity with linagliptin. Linagliptin was not associated with a decrease in absolute lymphocyte count.

Frequency of patients with adverse events occurring in more than 1% in either treatment group on the preferred term level, sorted by frequency in system organ class for the SAF-2 (all placebo controlled trials

System organ class Preferred term	Placebo N (%)	Linagliptin 5 mg N (%)
Number of patients	1183 (100.0)	2566 (100.0)
Patient years of exposure	433.8	1041.4
Patients with any adverse event	636 (53.8)	1412 (55.0)
Infections and infestations	244 (20.6)	491 (19.1)
Nasopharyngitis	65 (5.5)	150 (5.8)
Upper respiratory tract infection	53 (4.5)	84 (3.3)
Urinary tract infection	28 (2.4)	56 (2.2)
Influenza	16 (1.4)	37 (1.4)
Gastrointestinal disorders	127 (10.7)	269 (10.5)
Diarrhoea	27 (2.3)	53 (2.1)
Constipation	21 (1.8)	40 (1.6)
Nausea	14 (1.2)	28 (1.1)
Abdominal pain upper	15 (1.3)	18 (0.7)
General disorders and administration site conditions	61 (5.2)	124 (4.8)
Asthenia	9 (0.8)	28 (1.1)
Fatigue	17 (1.4)	13 (0.5)
Investigations	49 (4.1)	102 (4.0)
Blood glucose increased	16 (1.4)	16 (0.6)
Metabolism and nutrition disorders	208 (17.6)	408 (15.9)
Dyslipidaemia	13 (1.1)	31 (1.2)
Hyperglycaemia	125 (10.6)	128 (5.0)
Hypoglycaemia	49 (4.1)	195 (7.6)
Musculoskeletal and connective tissue disorders	102 (8.6)	264 (10.3)
Arthralgia	21 (1.8)	47 (1.8)
Back pain	30 (2.5)	50 (1.9)
Pain in extremity	11 (0.9)	34 (1.3)
Nervous system disorders	81 (6.8)	183 (7.1)
Dizziness	21 (1.8)	51 (2.0)
Headache	41 (3.5)	76 (3.0)
Respiratory, thoracic and mediastinal disorders	26 (2.2)	102 (4.0)
Cough	10 (0.8)	47 (1.8)
Vascular disorders	28 (2.4)	92 (3.6)
Hypertension	22 (1.9)	58 (2.3)

The overall incidences of adverse events (any adverse event) were similar in the placebo and linagliptin groups across background medications. The incidences of adverse events in the placebo arms ranged from 42.9% to 59.7% and in the linagliptin arms from 42.2% to 66.1%. For both treatment groups, the lowest incidences were observed with SU as background, however this may also be due to the shorter exposure of only 18 weeks in this trial. The highest incidences of adverse events were observed with a metformin plus SU background in both treatment groups. The incidence of adverse events was particularly high with the triple combination of linagliptin plus metformin plus SU (66.1%). This was almost entirely due to an increased incidence of hypoglycaemia (14.8% vs. 22.8%). A similar pattern was observed for drug-related adverse events where also the metformin+SU combination showed higher incidences in both treatment groups, again this was due to higher incidences of hypoglycaemia (7.6% vs. 14.5%). The frequencies of adverse events that led to discontinuation of treatment were slightly higher in the placebo groups with all background medications with the exception of metformin+SU. The combination of linagliptin, metformin, and SU led to high incidences of metabolism disorders with substantially higher frequencies in the linagliptin

group. The differences in the system organ class were predominantly due to different incidences of hypoglycaemia. The frequency of hypoglycaemia events was 16.0% (placebo) and 23.7% (linagliptin). An analysis by age (<65, 65-74, ≥75 years) showed a substantial increase with older age, in the placebo group from 12.0% to 37.5% and in the linagliptin group from 22.8% to 44.7%. In SAF-2 (the largest placebo-controlled safety grouping of patients with T2DM treated with linagliptin 5 mg compared to placebo), the overall incidences of adverse events were higher in the group of patients with moderate renal impairment (50.0% placebo and 65.2% linagliptin 5 mg). However, these adverse events were relatively mild. Therefore, linagliptin could be considered as a possible alternative for metformin in patients with moderate renal insufficiency. In the study with patients with severe renal impairment, the rate of AEs was higher than in the other trials, which was obviously due to the worse condition of these patients. No major difference in AE incidence between the linagliptin and the placebo group was observed in general (94.1% vs. 92.3%, respectively). All AEs of "renal impairment" (meaning worsening of renal function in these patients) were more frequent in the linagliptin (16.2% vs. 6.2%, respectively), but the absolute numbers were small. On average, renal function measured as eGFR was not influenced by linagliptin.

Serious adverse event/deaths/other significant events

Deaths

Overall there were 12 deaths in this clinical trial program: 7 patients died under treatment with linagliptin (SAF-1) and 3 patients died under treatment with glimepiride (SAF-4); 2 patients died after treatment with linagliptin during the post-treatment period in SAF-1. Of the patients who had received linagliptin (n=9), 8 patients died of cardiac conditions and 1 patient due to pulmonary embolism. None of the events were considered to be related to the study medication. After adjustment for exposure years, estimates of death incidence rates (per 1000 patient years exposure) indicated comparable death rates for linagliptin and comparators. However, the incidence rate with placebo was 0.0.

Estimates of death incidence rates per 1000 patient years exposure during controlled Phase III studies and uncontrolled extension trial (BI trial 1218.40)

BI trials	Treatment	Number of patients	Exposure [years]	Number of patients with fatal AE	Time at risk [years]	Incidence rate [per 1000 years at risk]
Controlled Phase III trials[a]	Linagliptin 5 mg	3319	2059.6	4	2072.9	1.9
	Combined comparator	1920	1372.2	3	1378.7	2.2
	Placebo	977	421.8	0	427.1	0.0
	Active comparator	943	950.3	3	951.6	3.2
Uncontrolled extension trial[b]	Linagliptin 5 mg	2121	1887.1	3	not determined	≤1.6

[a] BI trials 1218.15, 1218.16, 1218.17, 1218.18, 1218.20, 1218.23, 1218.35, and 1218.50
[b] BI trial 1218.40

Other Serious Adverse Events

In SAF-2, the frequency of serious adverse events was low and comparable between treatment groups (placebo 2.5% vs. linagliptin 2.7%). In the post-treatment period 2 patients who had been randomised to placebo and 5 patients who had received linagliptin had serious adverse events. In the system organ classes, cardiac disorders (0.3% vs. 0.5%), skin and subcutaneous tissue disorders (0% vs. 0.1%), and vascular disorders (0.1% vs. 0.4%) slightly higher frequencies were observed in the linagliptin group than in the placebo group. Myocardial infarction (n=4), myocardial ischemia (n=1) and myocarditis (n=1) were only observed in the linagliptin group. For vascular disorders, the different

incidences were mainly due to higher frequencies of hypertension (0.1%) and hypertensive crisis (0.1%) in the linagliptin group. On average, no increase in blood pressure or heart rate was observed in SAF-2.

Adverse events of special interest

Based on scientific considerations and regulatory advice the safety data base was searched for events of special interest which were hypersensitivity reactions, renal events, hepatic events, severe cutaneous adverse reactions, and pancreatitis. The incidences of the adverse events of special interest were low and comparable between treatments.

Using the largest set (SAF-1), in total 11 patients (8 patients under treatment with any dose of linagliptin and 3 patients in the post-treatment period) with pancreatitis were identified who had received linagliptin. In data set SAF-2 (controlled trials), pancreatitis was reported by 0 patients in the placebo group and 1 patient in the linagliptin 5 mg group. A very narrow definition for pancreatitis was used so that the low incidence prevents further conclusions. During the registration process, the applicant used a set of terms that is rather broad but clearly related to pancreatitis to take into consideration all conditions which could identify adverse action of linagliptin towards pancreas, e.g. worsening of an existing pancreatitis or acute exacerbation of an existing chronic pancreatitis. The Applicant selected relevant terms to cover potentially drug-induced events and exclude most likely not drug-induced events. Thus, 2 out of 2566 patients developed acute pancreatitis (or acute exacerbation of a chronic pancreatitis), i.e. slightly less than 1 in 1000. This is a rough estimate since the absolute number of events is low, leading to a high uncertainty, but it appears reasonable to designate pancreatitis as "rare". Amylase elevations were more frequently observed under linagliptin than under placebo.

In SAF-2, hypersensitivity reactions were seen in 0.5% (placebo) and 0.7% (linagliptin) of patients. Among these were 2 patients with angioedema; one patient had a serious adverse event and in one patient it led to discontinuation. Renal events were reported by 2 patients (0.2%) in the placebo group and 3 patients (0.1%) in the linagliptin 5 mg group. Hepatic events were reported by 14 patients (1.2%) in the placebo group and 25 patients (1.0%) in the linagliptin 5 mg group. Skin exfoliation (n=5) and exfoliative dermatitis (n=1) were observed only in the linagliptin group. Of the 5 patients with skin exfoliation, 1 patient discontinued treatment. However, 4 patients had the highest severity grade of mild and for 1 patient the highest severity was moderate. Furthermore, 1 patient experienced exfoliative dermatitis of moderate intensity.

A total of 5239 patients with type 2 diabetes mellitus were included in a cardiovascular meta-analysis. The primary endpoint 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. In total, 11 primary events were observed in the linagliptin group and a total of 23 primary events occurred in the comparator group (with 3 primary events in the placebo group, 20 primary events in the glimepiride group, and none in the voglibose group), resulting in incidence event rates (per 1000 patient years of exposure) for the primary endpoint of 5.3 for linagliptin and 16.8 for the comparators. Linagliptin treatment was not associated with an increase in cardiovascular risk, and the primary endpoint for linagliptin was significantly lower than for the total comparators. As most of the primary events (58%) occurred in the group receiving glimepiride an analysis against the pooled placebo-group confirmed that linagliptin was not associated with increased CV risk.

Laboratory findings

No clinically relevant findings or differences between the treatment groups were observed for any of the measured parameters (haematology and differential counts, electrolytes, enzymes, substrates, urine analysis and sediment).

Safety in special populations

PK studies in hepatically and renally impaired patients were performed indicating no relevant changes of PK in these patient populations. Animal studies revealed liver and kidney toxicity only at high, clinically irrelevant doses. For patients with moderate renal impairment in the placebo controlled trials, a higher overall incidence of adverse events was observed in the linagliptin group (50.0% vs. 65.2%). Study 1218.43 has been conducted to investigate the efficacy and safety of linagliptin in patients with T2DM with severe chronic renal impairment. No major difference in AE incidence between the linagliptin and the placebo group was observed in general. The number of patients with hepatic impairment being treated with linagliptin was too low to yield any relevant information in a subgroup analysis.

Safety related to drug-drug interactions and other interactions

Absorption and distribution of linagliptin are dependent on P-gp action. P-gp limits oral bio-availability of linagliptin. The P-gp inhibitor Ritonavir doubled oral bioavailability of linagliptin. However, in clinical studies phase II/III, linagliptin was found to be safe in combination with CYP3A4/P-gp inhibitors. In addition, linagliptin was shown to have a large safety window in phase I studies. Maximum total concentrations and maximum total AUC observed after administration of a single 600 mg dose were 161 and 134-fold higher than after the administration of 5 mg linagliptin in combination with ritonavir. The effect of P-gp inhibition on the bioavailablity of metformin is adequately mentioned in the SmPC.

Discontinuation due to adverse events

The discontinuation rate was in general lower in the linagliptin groups than in the placebo groups. Lack of efficacy was often the reason for discontinuation. No new safety concerns became obvious when regarding the discontinuation rates.

Post-marketing experience

There is currently no post-marketing experience with the use of this product.

2.6.1. Discussion on clinical safety

Overall, in the phase III studies with linagliptin the incidence of adverse events, drug-related adverse events, adverse events of severe intensity, adverse events leading to discontinuation, and serious adverse events were very similar across studies, with no major differences compared to placebo and active comparator groups. In general, the safety profile appears comparable with other DPP-4 inhibitors.

The safety database is considered large enough and the observation period long enough to sufficiently characterize the AE profile of linagliptin. However, the European diabetes guideline under revision ("Guideline on clinical investigation of medicinal products in the treatment of diabetes mellitus", CPMP/EWP/1080/00 Rev. 1) suggests to include an adequate number of high risk patients to represent as much as possible the general population of diabetic patients with regard to comorbidities, e.g. CV

risk factors, and concomitant drugs. From the baseline data it appears that only few such high risk patients were included, especially not patients with high cardiovascular risk.

Linagliptin appears to be tolerated relatively well in terms of gastrointestinal complaints.

The adverse events clearly and consistently associated with linagliptin included an increased incidence of hypoglycaemia. This effect was most pronounced when linagliptin was added to a background treatment of metformin and sulfonylurea, in particular in elderly patients: in very elderly patients, the incidence of investigator-defined-hypoglycaemic events was approximately 45% with linagliptin. However, in this age group, the incidence of hypoglycaemic events with placebo in combination with metformin and sulfonylurea was also relatively high (37.5%) and when causality is taken into account numbers were smaller. Also, medical assistance was only required in very small percentage of patients. Other gliptins have also been associated with this problem when combined with SU derivatives as also indicated in their SmPCs. Similarly, this problem is sufficiently addressed in the SmPC of linagliptin.

Experience in very elderly patients is limited. Study 1218.63, where only patients of at least 70 years of age are included, is currently being conducted. This study will provide important information on the use of linagliptin in elderly patients. The SmPC adequately reflects that experience in elderly patients is limited.

A numerical increase in AE frequency related to vascular disorders was consistently observed in all large controlled studies. The severity of the AEs was mainly mild or moderate; only a small number of severe AEs was observed, and linagliptin did not exceed placebo level in respect to severe AEs.

The nature of the cardiovascular AEs with increased incidence under linagliptin was consistently related to blood pressure and heart rate. An increase of heart rate and biphasic reaction of blood pressure in response to linagliptin was also observed in non-clinical safety pharmacology studies. Blood pressure and heart rate were regularly measured before and during the clinical trials. On average, no increase in blood pressure or heart rate was observed in SAF-2. However, taking into consideration the rather low incidence of hypertension cases including hypertensive crisis (around 3%), it is well conceivable that these cases could not noticeably alter the average blood pressure. The reasons for linagliptin's potential effects on heart rate and blood pressure are not known. In the long run even small increases of blood pressure may accelerate the progression of CV disease. Effects of linagliptin on blood pressure, heart rate/rhythm and long-term cardiovascular effects will be investigated in a randomized follow-up trial. This trial has already been started.

The results of a dedicated meta-analysis of cardiovascular events based on independent adjudication suggest that treatment with linagliptin does not increase cardiovascular risk. In comparison with placebo, linagliptin was not associated with an increased CV risk. In comparison with placebo and active comparators (voglibose, glimepiride) combined, CV risk of linagliptin was estimated to be significantly lower. The current information on CV risk is very limited but, in line with other DPP-4 inhibitors there is no suspicion of a detrimental effect.

Long-term cardiovascular effects will be investigated in the above mentioned randomized follow-up trial.

Death rate with linagliptin was higher in comparison to placebo but numbers were very small and after adjustment for exposure years, estimates of death incidence rates indicated comparable death rates for linagliptin and active comparators. None of the events were considered to be related to the study medication. Also, the number of patients on placebo was much lower than on linagliptin.

Linagliptin enhanced the pioglitazone-induced weight gain (study 1218.15). However, the effect was small, and it may be a class effect of DPP4 inhibitors. As described above, the combination of linagliptin and TZDs is not considered approvable.

Diabetic complications summarised under "microvascular disease", including diabetic retinopathy, diabetic nephropathy, and diabetic neuropathy, were represented to a reasonable percentage (around 20-25%) of patients. For patients with moderate renal impairment in the placebo controlled trials, a higher overall incidence of adverse events was observed in the linagliptin group (50.0% vs. 65.2%). Therefore, linagliptin should be used with care in these patients. Study 1218.43 has been conducted to investigate the efficacy and safety of linagliptin in patients with T2DM with severe chronic renal impairment. No major difference in AE incidence between the linagliptin and the placebo group was observed in general. All AEs belonging to the term "renal impairment" were more frequent in the linagliptin, but the absolute numbers were small. On average, renal function measured as eGFR was not influenced by linagliptin. The use of linagliptin in patients with severe renal insufficiency is considered acceptable. The number of patients with hepatic impairment being treated with linagliptin was too low to yield any relevant information in a subgroup analysis. Its use cannot be recommended.

The higher frequency of skin and subcutaneous tissue disorders in the linagliptin group is a concern, as DPP-4 inhibitors have been associated with skin reactions during preclinical studies in animals. Skin exfoliation and exfoliative dermatitis were observed only in the linagliptin group. This is in line with the serious skin reactions during treatment with other DPP-4 inhibitors and is addressed in the RMP. Phototoxicity did not occur during treatment with linagliptin, but the individual study reports describe 4 patients with photosensitivity with linagliptin. The identification of these 4 patients was due to spontaneous reports from the patients. The complaints were mild to moderate. Active enquiries with regard to photosensitivity will be performed in future studies.

Two patients developed angioedema; one patient had a serious adverse event and in one patient the adverse event led to discontinuation. It is uncertain whether these reactions were due to linagliptin as they may have been influenced by co-medication.

A higher incidence of infections has been described with other DPP-4 inhibitors. The DPP-4 inhibitors may be relatively specific for GLP-1, but the long-term consequences of DPP-4 inhibition and its effects on other DPP-4 substrates, particularly with respect to immune function, are unknown. Although linagliptin was not associated with an increased risk of infections (19.1% vs. 20.6%) or a decrease in absolute lymphocyte count, it is important to realize that these observations were done in relatively short term trials, and potential long term effects remain a concern. This should be monitored closely post marketing, an issue that is addressed in the RMP.

Similar to other GLP-1 based therapies, linagliptin may be associated with an increased risk of pancreatitis, but the number of cases was not excessively high. 2 out of 2566 patients developed acute pancreatitis (or acute exacerbation of a chronic pancreatitis). This is a rough estimate since the absolute number of events is low, leading to a high uncertainty, but it appears reasonable to designate pancreatitis as "rare". No consistent increase in serum amylase was detected throughout the large controlled studies. A slightly higher percentage of serum amylase increase was observed in linagliptin-treated patients than in placebo patients of data set SAF-2. This issue also needs to be monitored further, as indicated in the RMP.

Data indicate that the incidence of linagliptin-dependent AEs could be further increased by the presence of inhibitors of P-gp or CYP3A4. However, overall in clinical studies phase II/III, linagliptin was found to be safe in combination with CYP3A4/P-gp inhibitors. In addition, linagliptin was shown to have a large safety window in phase I studies. Maximum total concentrations and maximum total AUC observed after administration of a single 600 mg dose were higher than after the administration of 5 mg linagliptin in combination with ritonavir. The effect of P-gp inhibition on the bioavailablity of metformin has been adequately reflected in the SmPC.

2.6.2. Conclusions on the clinical safety

In the phase III studies the overall incidence of adverse events was very similar across studies, with linagliptin being mostly comparable to placebo and active comparator groups. In general, the safety profile appears comparable with other DPP-4 inhibitors. Several issues, including hypertension, heart rate, pancreatitis, angioedema, photosensitivity and hypoglycaemia are appropriately labelled in the SmPC as potential adverse events. Long-term cardiovascular effects will be investigated in a randomized follow-up trial, as described in the Risk Management Plan. In patients with renal failure, no major difference in AE incidence between the linagliptin and the placebo group was observed in general. It cannot be excluded that linagliptin increases the incidence of infections and causes worsening of renal function under certain circumstances, and therefore these potential risks will be followed in the RMP. Very elderly patients (above 75 years) and patients with hepatic impairment were not investigated in sufficient numbers and the use of linagliptin in these patients cannot be recommended.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

Risk Management Plan

The applicant submitted a risk management plan.

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	*4.4 Special warnings and precautions for use* <u>Hypoglycaemia</u> When linagliptin was added to a sulphonylurea (on a background of metformin), the incidence of hypoglycaemia was increased over that of placebo. Sulphonylureas are known to cause hypoglycaemia. Therefore, caution is advised when linagliptin is used in combination with a sulphonylurea. A dose reduction of the

		sulphonylurea may be considered *4.8 Undesirable effects* In the placebo controlled studies 5.0% of patients experienced "hypoglycaemia" as an adverse reaction under linagliptin. 86.8% of these were mild and 13.2% were moderate. None of the hypoglycaemias was classified as severe Hypoglycaemia is listed as very common adverse reaction when linagliptin is combined with metformin and a sulphonylurea.
Pancreatitis	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	*4.8 Undesirable effects* Pancreatitis was reported more often in patients randomized to linagliptin (1 per 538 person-years versus zero in 433 person years for comparator) Pancreatitis is listed as adverse reaction (frequency not know) for linagliptin, irrespective of combination with metformin, or metformin and a sulphonylurea
Important potential risks		
Skin lesions	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	
Hypersensitivity reactions	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	*4.8 Undesirable effects* Hypersensitivity is listed as adverse reaction for linagliptin (frequency not known), for linagliptin combined with metformin (frequency uncommon), and when combined with

		metformin and a sulphonylurea (frequency not known)
Infections	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	
Worsening of renal function	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	
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 (ongoing CV-safety study and ongoing study 1218.63 in patients >70 year). Ongoing CV meta-analyses of phase 3 and 4 programme at appropriate time points	*Section 5.1 Pharmacodynamic properties* <u>Cardiovascular risk</u> 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.

Old patients (> 80 years)	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data (ongoing CV-safety study and study 1218.63 in patients >70 year)	*Section 4.2 'Special populations'* <u>Elderly</u> No dose adjustment is necessary based on age. *Section 5.2 'Pharmacokinetic properties'* <u>Geriatric</u> 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 based on a population pharmacokinetic analysis of Phase I and Phase II data. Elderly subjects (65 to 80 oldest patients was 78 years) had comparable plasma concentrations of linagliptin compared to younger subjects.
Severe renally impaired patients	Routine pharmacovigilance and analysis of ongoing clinical trial safety data (study 1218.43)	*Section 4.2 'Special populations'* <u>Renal impairment</u> For patients with renal impairment, no dose adjustment for Trajenta is required. *5.2 'Pharmacokinetic properties'* <u>Renal insufficiency</u> A multiple-dose, open-label study was conducted to evaluate the pharmacokinetics of linagliptin (5 mg dose) in patients with varying degrees of chronic renal insufficiency compared to normal healthy control subjects. The study included patients with renal insufficiency classified on the basis of creatinine clearance as mild (50 to <80 ml/min), moderate (30 to <50

		ml/min), and severe (<30 ml/min), as well as patients with ESRD on hemodialysis. In addition patients with T2DM and severe renal impairment (<30 ml/min) were compared to T2DM patients with normal renal function. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula. CrCl = (140 – age) x weight/72 x serum creatinine [x 0.85 for females], where age is in years, weight in kg, and serum creatinine is in mg/dl. Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects. In moderate renal impairment, a moderate increase in exposure of about 1.7 fold was observed compared with control. Exposure in T2DM patients with severe RI was increased by about 1.4 fold compared to T2DM patients with normal renal fucntion. Steady-state predictions for AUC of linagliptin in patients with ESRD indicated comparable exposure to that of patients with moderate or severe renal impairment. In addition, linagliptin is not expected to be eliminated to a therapeutically significant degree by hemodialysis or peritoneal dialysis. Therefore, no dosage adjustment of linagliptin is necessary in patients with any degree of

		renal insufficiency.
Paediatric use	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data from the paediatric development program (P/114/200).	*Section 4.2 'Special populations'* Paediatric population The safety and efficacy of Trajenta in children and adolescents has not yet been established. No data are available. *Section 5.2 'Pharmacokinetic properties'* Paediatric population Studies characterizing the pharmacokinetics of linagliptin in paediatric patients have not been yet performed.
Pregnant and lactating patients	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	*Section 4.6 'Fertility, pregnancy and lactation'* Pregnancy 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 toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Trajenta during pregnancy. Breast-feeding 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 Trajenta 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'* <u>Hepatic impairment</u> Pharmacokinetic studies suggest that no dose adjustment is required for patients with hepatic impairment but clinical experience in such patients is lacking. *Section 5.2 'Pharmacokinetic properties'* <u>Hepatic impairment</u> In non-diabetic patients with mild moderate and severe hepatic insufficiency (according to the Child-Pugh classification), mean AUC and C_{max} of linagliptin were similar to healthy matched controls following administration of multiple 5 mg doses of linagliptin. No dosage adjustment for linagliptin is proposed for diabetic patients with mild, moderate or severe hepatic impairment.
Oncological adverse reactions	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	
Idiosyncratic adverse reactions	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	
Immunological adverse reactions	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	
Concomitant P-gp and CYP3A4 inhibitors	Routine pharmacovigilance and analysis of ongoing and	

	planned clinical trial safety data	

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Summary of the additional pharmacovigilance activities

Description	Due date
1218.74 / Ongoing CV safety study	Interim analysis (DMC safety assessemnt only): event driven, ≥ 80 adjudicated primary outcome events, and minimum duration of 1.5 years: December 2012 Final analysis due date event driven, 631 adjudicated primary outcome events December 2018
1218.63 / Ongoing study in patients >70 years	December 2011
CV meta-analyses of phase 3 and 4 programme at appropriate time points	December 2011
1218.56 / Paediatric Phase 2b Study	December 2013
1218.91 / Paediatric Study	September 2017

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

2.8. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Linagliptin is a selective, orally administered, xanthine-based DPP-4 inhibitor that lowers blood glucose levels by augmenting the glucose-stimulated insulin release through increased levels of endogenous GLP-1.

Efficacy and safety of linagliptin were studied in phase II/III studies, comparing the effects of linagliptin with placebo

-as monotherapy in general (1218.16),

-as monotherapy in patients intolerant for metformin (1218.50)

-as add-on to metformin (1218.17 and 1218.20)

-as add on to sulphonylurea ((1218.35)

-as initial combination therapy with pioglitazone (1218.15)

-as triple therapy with sulphonylurea and metformin (1218.18).

Additional relevant efficacy and safety data were obtained from the following phase II studies

- (dose finding) monotherapy study 1218.5 (internal control metformin)

- (dose finding) add-on to metformin study 1218.6 (internal control glimepiride)

- monotherapy study in patients with severe renal insufficiency (1218.43)

- linagliptin dual combination therapy with metformin (1218.62)

All submitted studies are placebo-controlled except for study 1218.20, which used glimepiride as active comparator. Pivotal efficacy studies are 1218.15, 1218.16, 1218.17 and 1218.18. However, the results of study 1218.15 (combination with pioglitazone) did not support an indication. The large active-controlled study 1218.20 is also considered important

In all studies, treatment with 5 mg linagliptin once daily resulted in a statistically significant decrease of HbA1c, the primary efficacy endpoint. In comparison to placebo, linagliptin resulted in an overall decrease in HbA1c of approximately 0.6%. However, in Caucasian or European patients, the target population of this application, the treatment effects were consistently smaller than in Asian patients. Similarly, efficacy results differed across geographical regions. However, when the results on European patients were confined to the EU population in an additional pooled subgroup analysis, the placebo-adjusted treatment effects of linagliptin were more pronounced than in non-EU patients.

In monotherapy, linagliptin showed relevant efficacy in European patients in the pivotal study 1218.16 (-0.52%). A slightly lower effect was achieved in the monotherapy dose-finding study 1218.5 (-0.46). In the supportive study 1218.50 in patients with intolerance to metformin, the placebo-adjusted difference in the European population was -0.15%. However, the effect in the Caucasian population was similar to results in study 1218.16 (placebo-adjusted difference: -0.43). In addition, in the supportive study 1218.05 the placebo-adjusted treatment difference was -0.50 in Caucasians.

In dual combination therapy with metformin a relevant placebo-adjusted decrease in HbA1c was found (-0.51%) in European patients of study 1218.17, supported by a change of –0.73% in the dose-finding study 1218.6. In addition, the new study 1218.62 demonstrated a placebo adjusted treatment effect of linagliptin in combination with metformin in Caucasian patients (-0.69 for 2.5 mg bid; and -0.66 for 5 mg qd).

When linagliptin was added to SU in dual therapy the placebo-adjusted effect on HbA1c in European patients was small, ie. -0.29%, and not considered clinically relevant.

The efficacy of linagliptin in combination with pioglitazone was investigated as initial combination therapy with about 50% of enrolled patients being treatment naive. Linagliptin treatment resulted in European subjects in a relatively small placebo-adjusted decrease in HbA1c of -0.37%.

Linagliptin therapy in triple combination with metformin and SU resulted in an adjusted treatment effect in European patients of -0.47%.

The treatment effect of linagliptin in terms of adjusted mean differences to placebo in HbA1c was similar in patients with normal renal function (-0.61%), and patients with mild (-0.63%) or moderate

(-0.57%) renal impairment. In the separate trial in patients with severe renal insufficiency (1218.43) the adjusted mean difference to placebo in HbA1c after 52 weeks was -0.72%.

Linagliptin was largely weight neutral except in the combination with pioglitazone where it aggravated the pioglitazone- induced weight gain for unknown reasons. A beneficial effect on weight was observed compared to glimepiride in study 1218.20 with a treatment difference of -2.49 kg at week 52.

Linagliptin also was associated with a markedly lower frequency of hypoglycaemia compared to glimepiride (overall frequencies 5.4% vs. 31.8%). This included hypoglycaemic events with blood glucose levels below 54 mg/dL (9.5% vs. 33.1%) and severe hypoglycaemic events (2.4% vs. 3.6%), although the number of severe events was low (1 vs. 9).

Uncertainty in the knowledge about the beneficial effects

Linagliptin has been shown to be effective as monotherapy in patients with intolerance to metformin, in patients with renal insufficiency that are not candidates for treatment with metformin, and as add-on treatment with metformin or with metformin + SU. However, linagliptin has not been shown to be an effective treatment in European patients as add-on to SU and add-on to pioglitazone. In addition, the design of the add-on to pioglitazone trial was not appropriate, as at least 50% of patients in the study were not failures on pioglitazone monotherapy.

Regional/racial differences in treatment response have been observed with the smallest effect of linagliptin seen in European patients. In PK studies, peak and total exposure were about 30% higher in Japanese and Chinese subjects than in Caucasian subjects. However, the median and mean level of DPP-4 inhibition was similar in the different races. Therefore, the cause of the regional/racial differences remains unclear, but treatment differences between the EU and non-EU population within Europe may best be explained by differences in pre-study diabetes care.

In the active comparator study (1218.20) both active treatments resulted in a decrease of HbA1c from baseline. However, non-inferior efficacy of linagliptin compared to glimepiride has not been convincingly demonstrated in this study. The impression that efficacy of linagliptin is not similar to that of glimepiride is supported by new data from the second part of study 1218.50, where glimepiride vs. linagliptin induced a mean decrease in HbA1c of 0.82% vs. 0.44%.

The finding of a lower number of hypoglycaemic events with linagliptin compared to glimepiride is an advantage and expected from the known mechanisms of action of these drugs. However, the observed beneficial effect of linagliptin may be overestimated considering the smaller glucose-lowering effect of linagliptin (leading to smaller HbA1c and FPG reduction).

Very elderly patients and patients with hepatic impairment have not been investigated in sufficient numbers.

Risks

Unfavourable effects

The safety database is considered large enough to sufficiently characterize the AE profile of linagliptin. The main basis for safety assessment was the SAF2 (N=3749, including all placebo-controlled trials with linagliptin 5mg). The incidence of adverse events with linagliptin was mostly comparable to placebo and active comparator groups, and the safety profile appears comparable with other DPP-4 inhibitors. Linagliptin appears to be tolerated relatively well in terms of gastrointestinal complaints. One of the adverse events consistently associated with linagliptin was an increased incidence of hypoglycaemia. This effect was small when linagliptin was used in monotherapy or in combination with

metformin and was more pronounced when linagliptin was added to a background treatment of metformin and sulfonylurea, but was not always considered causally related and medical assistance was only required in a small percentage of the patients. Increase in hypoglycaemic events in association with insulin secretagogues is also known for other antihyperglycaemic drugs that *per se* have low propensity to cause hypoglycaemia. This issue is appropriately reflected in the SmPC.

Similar to other GLP-1 based therapies, linagliptin may be associated with an increased risk of pancreatitis, although this did not appear to be an important problem in the presented trials. The relevance of the higher frequency of skin and subcutaneous tissue disorders in the linagliptin group is unknown. Other DPP-4 inhibitors have also been associated with skin reactions during preclinical studies in animals. In addition, skin exfoliation (n=5) and exfoliative dermatitis (n=1) were observed only in the linagliptin group. These issues of pancreatitis and skin reactions are adequately addressed in the SmPC and RMP and should be monitored further post licensing.

Linagliptin was consistently (AEs and ADRs and across studies) associated with a slightly enhanced incidence of muscle pain. CK increases were not observed and most of the AEs were mild. Thus, musculoskeletal AEs are not regarded as a relevant concern.

Although linagliptin generally was weight-neutral, it aggravated the pioglitazone-induced weight gain (+2.4 vs. +1.2kg for linagliptin+pioglitazone vs. pioglitazone, respectively; see study 1218.15) which may be unfavourable in respect to CV risk. The cause of the observed weight gain is unclear, but for several reasons, an indication for linagliptin in combination with pioglitazone is not acceptable.

For patients with moderate renal impairment in the placebo controlled trials, a higher overall incidence of adverse events was observed in the linagliptin group (50.0% placebo vs. 65.2% linagliptin, respectively). Therefore, linagliptin should be used with care in these patients. Patients with severe renal insufficiency were investigated in a separate trial. No major difference in AE incidence between the linagliptin and the placebo group was observed in general (94.1% linagliptin vs. 92.3% placebo, respectively). All AEs belonging to the term "renal impairment" were more frequent in the linagliptin (16.2% linagliptin vs. 6.2% placebo, respectively), but the absolute numbers were small. On average, renal function measured as eGFR was not influenced by linagliptin.

Uncertainty in the knowledge about the unfavourable effects

As discussed above under safety, the current information of linagliptin on CV risk is limited. The nature of the cardiovascular AEs with increased incidence under linagliptin was consistently related to hypertension and heart rate. On average, no increase in blood pressure or heart rate was observed in SAF-2. The results of a dedicated meta-analysis of cardiovascular events based on independent adjudication are difficult to interpret as confidence intervals are wide and data on high-risk patients limited. The available data, including comparison with active comparators (voglibose, glimepiride), did not indicate an increased risk, and there is no suspicion of a detrimental effect. These results, however, were largely dominated by the relatively high number of CV events in patients treated with glimepiride. In addition, the low incidences of cardiovascular disease in the trials reflect the fact that patients with more severe pre-existing CV disease were not included in the studies. Nevertheless, the absence of an increased cardiovascular risk is in line with other DPP-4 inhibitors, where the assessment of CV risk also had its limitations. The applicant has indicated that a follow-up study including patients with high CV risk (study 1218.63) recently started.

Death rate with linagliptin (incidence rate 1.9) was higher in comparison to placebo (incidence rate 0) but numbers were very small and data are inconclusive.

The number of patients with hepatic impairment being treated with linagliptin was too low to yield any relevant information in a subgroup analysis. Its use cannot be recommended. Very elderly patients

(>75 yrs) have also not been investigated in sufficient numbers. Therefore currently, the use of linagliptin cannot be recommended in these populations.

Phototoxicity did not occur during treatment with linagliptin. However, the individual study reports describe 4 patients with photosensitivity with linagliptin. The seriousness of these adverse events caused by linagliptin was mild to moderate. The 2 cases of angioedema that occurred in the linagliptin group may be due to co-medication. These issues are mentioned in the SmPC.

The increased incidence of hypoglycaemia in combination with SU and metformin is not surprising. Other gliptins have also been associated with this problem when combined with SU derivatives as also indicated in their SmPCs. Thus, this problem has also been addressed in the SmPC of linagliptin.

The higher incidence of infections has also been described with other DPP-4 inhibitors. The DPP-4 inhibitors may be relatively specific for GLP-1, but the long-term consequences of DPP-4 inhibition and its effects on other DPP-4 substrates, particularly with respect to immune function, are unknown. Although the increased incidence of infections with linagliptin was relatively small in comparison to placebo (19.1% vs. 20.6%) and linagliptin was not associated with a decrease in absolute lymphocyte count, it is important to realize that these observations were done in relatively short term trials, and potential long term effects remain a concern. This should be monitored closely post marketing, an issue that has been addressed in the risk management plan.

The safety assessment after co-administration with the potent CYP 3A4/P-gp inhibitor ritonavir demonstrated that the total exposure of linagliptin was increased. However, this is not expected to affect safety.

Benefit-risk balance

Importance of favourable and unfavourable effects

The most important favourable effect of linagliptin is lowering of the HbA1c. This effect appears relatively small in comparison to the effects of other drug classes, such as metformin, insulin and SU preparations. The treatment response (HbA1c) was generally lower in European/Caucasian patients compared to Asian patients. When the results were confined to the EU population in an additional pooled analysis, the placebo-adjusted treatment effects of linagliptin were more pronounced providing further reassurance that linagliptin is an effective treatment in the population applied for.

Linagliptin's additive effect to non-responders to SU derivatives is currently questionable. The effect on HbA1c was -0.29% in the European population. This is considered too small for justifying an indication.

In addition, add-on treatment to pioglitazone has not been appropriately investigated as the study design is not considered appropriate. CHMP guidance for add-on trials, requests that the new antidiabetic agent should be added in non-responders to the established antidiabetic agent. In this trial 50% of patients were drug-naïve, and therefore not non-responders. Considering the relatively small effect size (-0.37% decrease in HbA1c) and the increased weight gain the B/R ratio of this dual combination therapy appears unfavourable.

The effects of linagliptin and glimepiride are not considered similar. Non-inferior efficacy of linagliptin compared to glimepiride has not been demonstrated sufficiently. Therefore, no statements were included in Section 5.1 of the SmPC.

The use of linagliptin in monotherapy as alternative to metformin is considered acceptable in patients that cannot take metformin due to gastrointestinal intolerance or in patients with contraindications to metformin due to renal impairment.

Linagliptin has a primarily non-renal route of excretion. This is an advantage of linagliptin in patients with moderate to severe renal insufficiency. For patients with renal insufficiency, efficacy in subgroup analyses as well as separate trial 1218.43 seems adequate. No major difference in AE incidence between the linagliptin and the placebo group was observed in general, but currently it cannot be fully excluded that linagliptin increases the incidence of infections and causes worsening of renal function under certain circumstances. These issues will be followed as potential risks in the RMP.

The finding of a lower number of hypoglycaemic events with linagliptin compared to glimepiride is an advantage and expected from the known mechanisms of action of these drugs. However, the beneficial effect of linagliptin may be overestimated considering the apparently smaller glucose-lowering effect of linagliptin (leading to smaller HbA1c and FPG reduction). Due to the presence of insulin resistance, hypoglycaemia, especially severe hypoglycaemia is usually not a major problem in patients with T2DM. However, (very) elderly patients are generally more prone to experiencing hypoglycaemia. Due to its mechanism of action, linagliptin is not associated with hypoglycaemia except when used in combination with a SU but the enhancement of SU-associated hypoglycaemia is also known for other antihyperglycaemic drugs and is therefore not unique to linagliptin. The low propensity of linagliptin to cause hypoglycaemia is an advantage that may be relevant in patients more prone to hypoglycaemic events.

Linagliptin is largely weight-neutral, except when given in combination with pioglitazone where it was shown to aggravate pioglitazone-induced weight gain (+ 2.4kg vs. +1.2 kg). On the other hand, linagliptin provides a weight advantage compared to SUs (-2,5 kg), which can be considered beneficial in the usually overweight/obese patients with T2DM.

Efficacy and safety are currently insufficiently investigated in certain subgroups, such as very elderly patients (>75 yrs), and patients with hepatic impairment. Linagliptin does not appear to be related to an increased cardiovascular risk, but absolute numbers of CV events were very low. The possible increased risk of infections, skin reactions, and pancreatitis is also important, but it should be acknowledged that these possible side effects have also been associated with other DPP-4 inhibitors and they will be monitored according to the RMP. Additional, potentially new safety issues, in particular photosensitivity and angioedema have been addressed in the SmPC.

Discussion on the benefit-risk balance

Although overall, linagliptin provided statistically significant glycaemic improvement, the treatment response (HbA1c) was generally lower in European/Caucasian patients compared to Asian patients. When the results in Europeans were confined to the EU population in an additional analysis, the treatment effects of linagliptin were somewhat more pronounced.

As dual therapy with metformin, and as triple therapy with metformin and SU, a clinically relevant effect was obtained. However, the effect of linagliptin appeared smaller compared to glimepiride, and non-inferiority in patients treated with metformin was not demonstrated sufficiently and a respective statement in the SmPC cannot be accepted.

The treatment effects of linagliptin in dual combination with SU and with pioglitazone appear too small to justify an indication. Its use as monotherapy as alternative to metformin is appropriate in those patients for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment.

Lack of data or availability of limited data on certain subgroups (i.e. hepatic insufficiency, very elderly) has been resolved by appropriate wording in the SmPC. More information on cardiovascular safety with linagliptin is important and will be investigated post-marketing in the ongoing CV safety study, as described in the RMP. Several possible side-effects were identified, but the risks were only mildly

elevated in comparison to placebo and comparators. Targeted follow up of adverse events of interest in the RMP may be sufficient.

In conclusion, the benefit-risk of linagliptin for the claimed indication of the treatment of patients with type 2 diabetes mellitus, to achieve glycaemic control in dual combination with SU or with pioglitazone is considered negative.

The benefit-risk of linagliptin for the claimed indication of the treatment of patients with type 2 diabetes mellitus, to achieve glycaemic control in monotherapy is acceptable as an alternative to metformin in patients for whom metformin is inappropriate due to intolerance, or contraindicated due to renal impairment.

The benefit/risk of linagliptin is also considered positive for linagliptin in dual combination with metformin or in triple combination with metformin and a SU, when this treatment, together with diet and exercise, does not provide adequate glycaemic control.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Trajenta 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."

is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 4 of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality, non-clinical and clinical properties of the active substance, the CHMP considers that linagliptin is to be qualified as a new active substance.