Assessment report

Jentadueto

linagliptin / metformin hydrochloride

Procedure No.: EMEA/H/C/002279

Note

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

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List of abbreviations

ALD	Approximate Lethal Dose
ALT	Alanine aminotransferase (plasma)
AP	Applicant's Part (or Open Part) of a DMF
API	Active Pharmaceutical Ingredient
AR	Assessment Report
ASM	Active Substance Manufacturer
ASMF	Active Substance Master File = Drug Master File
AST	Aspartate aminotransferase (plasma)
AUC0-24h,ss	Area under the plasma-concentration-time curve from zero to 24 hours steady state
BA	Bioavailability
BCS	Biopharmaceutical Classification System
BE	Bioequivalence
BI 1356	Linagliptin
bid	Twice daily (bis in die)
BP	British Pharmacopoeia
CEP	Certificate of Suitability of the European Pharmacopoeia
CFU	Colony Forming Units
Cmax,ss	Maximum plasma level, steady state
CMS	Concerned Member State
CoA	Certificate of Analysis
Crl:CD(SD)	Charles River Labs strain of rats (Sprague Dawley rats)
Crl:WI(Han)	Charles River Labs Wistar strain of rats (Wistar Han rats)
CRS	Chemical Reference Substance (official standard)
CYP	Cytochrome P450
DPP-4	Dipeptidyl Peptidase 4
DMF	Drug Master File = Active Substance Master File
DoE	Design of Experiments
DP	Drug Product
DS	Drug Substance
DSC	Differential Scanning Calorimetry
EDQM	European Directorate for the Quality of Medicines
f	Female(s)
GD	Gestation Day
GLP	Good Laboratory Practice
GLP-1	Glucagon-Like Peptide-1
h	Hour(s)
HCl	Hydrochloric acid
HDPE	High Density Polyethylene
HsdHan: Wist	Harlan Ltd Wistar strain of rats (Han Wistar rats)
IPC	In-process control
IR	Infrared
IU	International Units
JP	Japanese Pharmacopoeia
KF	Karl Fischer
LDPE	Low Density Polyethylene

LOA	Letter of Access
LOD	Limit of Detection
LOQ	(1) Limit of Quantification, (2) List of Questions
m	Male(s)
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MATE	Multidrug And Toxin Extrusion Antiporter
MEB	Medicines Evaluation Board
MRHD	Maximum Recommended Human Dose
MS	Mass Spectrometry
MTD	Maximum Tolerated Dose
ND	Not detected
NLT	Not less than
nM	Nanomolar (nmol/L)
NMR	Nuclear Magnetic Resonance
NMT	Not more than
NOAEL	No Observed Adverse Effect Level
No. (Animal)	number
OCT	Organic Cation Transporter
oGTT	Oral Glucose Tolerance Test
OOS	Polychlorotrifluoro ethylene
PDE	Permitted Daily Exposure
PE	Polyethylene
Ph.Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
PK	Pharmacokinetic
PMAT	Plasma Membrane Monoamine Transporter
PP	Polypropylene
PVC	Polyvinyl chloride
PMAT	Plasma Membrane Monoamine Transporter
QOS	Quality Overall Summary
RH	Relative Humidity
RMS	Reference Member State
RP	Restricted Part (or Closed Part) of a DMF
RRT	Relative retention time
RSD	Relative standard deviation
RVG #	Marketing Authorisation number in NL
SPC	Summary of Product Characteristics
UV	Ultraviolet
USP/NF	United States Pharmacopoeia/National Formulary
XRPD	X-Ray Powder Diffraction

* This is a general list of abbreviations. Not all abbreviations will be used.

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Boehringer Ingelheim International GmbH submitted on 29 June 2011 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Jentadueto, 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 21 January 2010.

The applicant applied for the following indication: For patients with type 2 diabetes mellitus:

Jentadueto is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of linagliptin and metformin.

Jentadueto is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC - complete and independent application.

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 test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/3/2010 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market exclusivity

Not applicable.

Scientific Advice/Protocol Assistance

The applicant received Scientific Advice from the CHMP on 22-25 September 2008. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

Licensing status

A new application was filed in the following countries: USA, Switzerland, Indonesia, Korea, Argentina, Brazil, Columbia, Mexico and Peru.

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

1.2. Manufacturers

Manufacturer responsible for batch release

Boehringer Ingelheim Pharma GmbH & Co. KG

Binger Strasse 173

D-55216 Ingelheim am Rhein

Germany

Steps taken for the assessment of the product

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

Rapporteur: **Pieter de Graeff** Co-Rapporteur: **Karsten Bruins Slot**

1. The application was received by the EMA on 29 June 2011.
2. The procedure started on 20 July 2011.
3. The Rapporteur's first Assessment Report was circulated to all CHMP members on 07 October 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 07 October 2011.
4. During the meeting on 14-17 November 2011, 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 18 November 2011.
5. The applicant submitted the responses to the CHMP consolidated List of Questions on 12 January 2012.
6. The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 24 February 2012.
7. During the CHMP meeting on 12-15 March 2012, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
8. The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 April 2012.
9. The Rapporteurs circulated the Joint Assessment Report on the applicant's written responses to the List of Outstanding Issues to all CHMP members on 7 May 2012 and 21 May 2012.
10. During the meeting on 21-24 May 2012, 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 Jentadueto on 24 May 2012.

2. Scientific discussion

2.1. Introduction

Problem statement

Type 2 diabetes mellitus (T2DM) is a disease affecting more than 180 million people worldwide and particularly in the industrialised countries the incidence of this disorder is increasing. The prevalence is expected to rise to 300 million people by the year 2025. T2DM is characterised by multiple metabolic

abnormalities involving insulin resistance, impaired insulin secretion, and increased glucose production. Morbidity and mortality associated with T2DM 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.

About the product

Jentadueto is a fixed dose combination of linagliptin and metformin hydrochloride.

Linagliptin (BI 1356) is a selective, orally administered, xanthine-based inhibitor of dipeptidylpeptidase-4 (DPP-4) with a 50% Inhibitor Concentration (IC50) of 1 nM. DPP-4 inhibitors are antidiabetic agents that lower blood glucose by extending the short half life of glucagon-like peptide 1 (GLP-1), which is secreted by intestinal L-cells in response to a meal, and glucose-dependent insulinotropic peptide (GIP), both of which exert glucose-dependent insulinotropic effects and thereby contribute to the maintenance of post-meal glycaemic control. GLP-1 lowers blood glucose by increasing the glucose-stimulated insulin release and by limiting glucagon secretion to slow gastric emptying and to induce satiety. DPP-4 inhibitors maintain long-term β-cell function, which has been demonstrated in animal models. Inhibition of DPP-4 bears little risk of hypoglycaemia in patients with diabetes mellitus because GLP-1 activity ceases when plasma glucose concentration falls below 55 mg/dl. Linagliptin is predominantly excreted unchanged via the faeces. Renal excretion is a minor pathway of elimination of linagliptin at therapeutic doses. A Marketing Authorisation for linagliptin (Trajenta 5mg) was granted in the EU by the EC on the 24th of August 2011.

Metformin has been used in Europe for over 50 years and, together with lifestyle modification, is recommended by the European Association for the Study of Diabetes (EASD) as the first-line treatment for T2DM. The immediate release dosage forms are widely approved with tablet strengths of 500 mg, 850 mg and 1000 mg approved in several countries. Although its mechanism of action is not yet fully understood, metformin lowers blood glucose levels primarily by suppressing hepatic gluconeogenesis. It is believed that this is achieved through metformin-induced activation of adenosine monophosphate-activated protein kinase, an energy-regulating enzyme in the liver. Furthermore, metformin improves the insulin sensitivity of peripheral tissues, decreases gastrointestinal tract glucose absorption, and acts as an insulin sensitiser without exerting any direct effect on pancreatic β-cell insulin secretion. Through these mechanisms, metformin therapy typically leads to substantial reductions in glycosylated HbA_{1c} but it does not promote weight gain or increase the risk of hypoglycaemia.

The combination of linagliptin with metformin may provide clinically meaningful treatment benefits by lowering glucose and reducing glycosylated haemoglobin (HbA_{1c}) further than monotherapy with either component at corresponding doses. Combining linagliptin with metformin hydrochloride simplifies the antidiabetic therapy by decreasing the number of tablets to be taken and is expected to improve patients' compliance with medication; fixed-dose combination therapy has resulted in improved compliance in patients previously treated with oral antidiabetics.

The Applicant applied for the following strengths: 2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5 mg/ 1000 mg. The recommended starting dose of Jentadueto for patients not adequately controlled on metformin alone is 2.5 mg of linagliptin twice daily (5 mg daily dose) plus the dose of metformin already being taken. For patients switching from co-administration of linagliptin and metformin, Jentadueto should be initiated at the dose of linagliptin and metformin already being taken. The applicant therefore proposed to recommend a starting dose of Jentadueto for patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a sulphonylurea is 2.5 mg of linagliptin twice daily (5 mg total daily dose) and a dose of metformin similar to the dose already being taken. When linagliptin plus metformin is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required due to the risk of hypoglycaemia. For the different doses of metformin, Jentadueto is available in strengths of 2.5 mg linagliptin plus 850 mg metformin hydrochloride and 2.5 mg linagliptin plus 1,000 mg metformin hydrochloride.

Type of Application and aspects on development

The clinical development program of linaglipin/metformin was designed to demonstrate the safety and efficacy of linagliptin as monotherapy, metformin as monotherapy and linagliptin and metformin as FDC in patients with T2DM. The program included 24 phase I studies, 4 phase II and 9 phase III studies for linagliptin as monotherapy, 6 phase I, 2 phase II and 4 phase III studies for the FDC. No dedicated studies with metformin as monotherapy were conducted. The pharmacokinetics, safety, and efficacy profiles of metformin as monotherapy are well known and well established in the literature.

The development programme of linagliptin/metformin complies with the CHMP Guideline "Note for guidance on the Clinical Investigation of Medicinal Products for the treatment of diabetes mellitus (CPMP/EWP/1080/00)". This guideline is currently under revision.

Scientific advice was provided by the CHMP in September 2008 (EMEA/CHMP/SAWP/ 472394/2008) on the non-clinical and clinical aspects of the development program. The CHMP requested a clinical study to show equivalence of twice daily dosing of linagliptin 2.5 mg with once daily dosing of linagliptin 5 mg. This study was subsequently conducted by the Applicant and its results are presented in this Marketing Authorisation application.

A product-specific waiver (P/3/2010) has been agreed for linagliptin/metformin by the PDCO.

2.2. Quality aspects

2.2.1. Introduction

Jentadueto is presented as film-coated tablets containing two active substances linagliptin and metformin hydrochloride. Two strengths of the product with the same amount of linagliptin (2.5 mg) but with different amounts of metformin hydrochloride (850 mg or 1000 mg) were developed.

The tablets are oval and biconvex. The 2.5 mg/850 mg tablets are light orange, debossed with "D2/850" on one side and the company logo on the other. The 2.5 mg/1000 mg tablets are light pink, debossed with "D2/1000" on one side and the company logo on the other.

Excipients used in the formulation of Jentadueto are well known excipients commonly used in tablet formulations, such as arginine, copovidone, magnesium stearate, maize starch and colloidal anhydrous silica. These excipients are used to manufacture the tablet cores which are then coated with film coating consisting of hypromellose, titanium dioxide (E171), talc, propylene glycol and iron oxides, yellow and red (E172) (coating for the 2.5 mg/850 mg strength) or iron oxide, red (E172) (coating for the 2.5 mg/1000 mg strength).

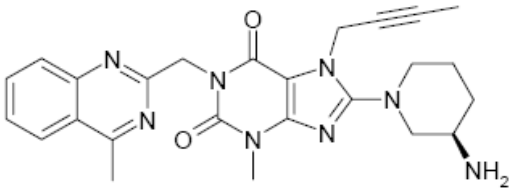
The tablets are packed either in perforated unit dose blisters consisting of an aluminium lidding foil and a PVC/polychlorotrifluoro ethylene/PVC based forming foil (alu/PVC/PCTFE/PVC blisters), or in high-density polyethylene (HDPE) bottles with plastic screw caps.

Initially the applicant applied for 3 strengths of the product 2.5 mg/500 mg, 2.5 mg/850 mg, and 2.5 mg/1000 mg, all to be taken twice daily (bid). However during the evaluation the lowest strength (2.5 mg/500 mg) was withdrawn.

2.2.2. Active Substance

Linagliptin

Linagliptin is chemically designated as 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 and has the following structure:



It is a white to yellowish crystalline solid substance, slightly hygroscopic. 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. Linagliptin is classified as class III compound according to the Biopharmaceutics Classification System (BCS) due to its incomplete oral systemic bioavailability and the moderate permeability observed in Caco-2 cells.

Linagliptin has one chiral centre at the 3-aminopiperidine moiety. The substance used for the manufacture of Jentadueto tablets is the (R) enantiomer.

Linagliptin simultaneously exists in two polymorphic forms The two polymorphic forms do not differ with regard to relevant physicochemical properties and therefore the solid-state differences are unlikely to have any impact on bioavailability.

The chemical structure of linagliptin has been confirmed by means of UV, IR, ^{1}H- and ^{13}C-NMR spectroscopy and mass spectrometry (MS). The content of carbon, hydrogen and nitrogen have been determined by elemental analysis. The absolute configuration of the active substance at the chiral carbon has been determined by means of X-ray crystallography. The solid state properties of linagliptin were characterised using light microscopy, thermal analysis (TG and DSC) and X-ray powder diffraction.

Manufacture

The synthetic process for linagliptin consists of three steps during which simple commercially available molecules are used as starting materials. The synthesis is followed by milling process.

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. Appropriate specifications for starting materials and reagents have been established.

Potential impurities were well discussed with regards to their origin and characterised. The levels of the impurities with an acceptance criterion higher than max.0.15% were supported by the results of toxicological studies and appropriate specification limits have been set.

The synthetic process does not involve Class 1 solvents or metal catalysts. The Class 2 solvents 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 active substance specifications include tests with suitable limits for appearance (visually), identification (IR, HPLC and melting point), impurities (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 sufficiently described and validated in accordance with the Note for Guidance on Validation of Analytical Methods.

Batch analysis results have been provided for 14 commercial scale batches manufactured according to the proposed synthetic process. All results were consistent from batch to batch and demonstrated compliance with the proposed active substance specifications.

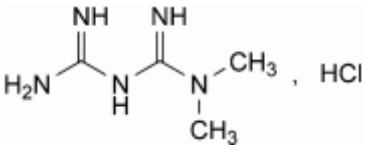
Stability

Stability studies have been performed in accordance with ICH requirements on three commercial scale batches manufactured by the proposed route of synthesis. The samples were stored for up to 36 months under the conditions for long term storage (25°C/60% RH) and up to 6 months under accelerated conditions (40°C/75% RH). The stability results presented were satisfactory and supported the proposed retest period.

In addition, one batch was subjected to forced degradation 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 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.

Metformin hydrochloride

Metformin hydrochloride is chemically designated as 1,1-dimethylbiguanide monohydrochloride according to the IUPAC nomenclature and has the following structure:



This active substance is described in the Ph. Eur.

It is a white or almost white crystalline powder. The substance is freely soluble in water, slightly soluble in ethanol and practically insoluble in acetone and methylene chloride. Metformin hydrochloride is classified as BCS class III compound.

The chemistry, manufacturing and control information on metformin hydrochloride has been evaluated by the EDQM and a European Certificate of Suitability of the Monograph of the European Pharmacopoeia (CEP) has been issued. A copy of the CEP has been provided. The CEP includes an additional test for a residual solvent used during the last step of synthesis. The retest period and type of the container for storing the substance are also included in the certificate. In addition holder of the certificate has declared the absence of use of material of human or animal origin in the manufacturing process of the metformin hydrochloride.

Batch analysis data of the five commercial scale batches of metformin hydrochloride were provided. The results were within the specification limits, consistent from batch to batch and demonstrated compliance with the Ph. Eur. monograph for this substance.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The objective of the product development was to obtain an immediate release solid oral dosage form. A twice-a-day dosing regimen was chosen due to the pharmacokinetics of metformin hydrochloride. The therapeutic dose of linagliptin of 5 mg once a day was divided into two doses of 2.5 mg each in order to match this dosing regimen.

Initial compatibility studies with the active substances showed degradation of linagliptin when combined with metformin hydrochloride. Several concepts to overcome this instability were considered for the final formulation, including physical separation in the pharmaceutical form (bilayer tablets) or addition of a stabilizer. Screening trials with excipients with a potentially stabilising effect on linagliptin were performed in order to find a suitable stabilizer for the formulation. The selection of excipients including their corresponding levels in the finished product is based on formulation experiments where

the resulting tablets were assessed with regard to mechanical tablet properties, dissolution, assay, content uniformity, chemical and physical stability as well as *in vivo* bioavailability studies.

The manufacturing process is based on a granulation process. Glidant and lubricant are added in a blending step followed by tablet compression. The tablet cores are than film-coated. During development of the product the blending time and the tablet compression process were optimised.

The proposed commercial formulation was used practically unchanged from the very beginning of the development. Only a minor adjustment was made in the pigments in the film coat to meet the requested colours prior to the manufacture of the primary stability batches, which also served as supplies for the three pivotal clinical bioequivalence trials. Pivotal clinical studies were performed with combinations of tablets containing linagliptin (2.5 mg and 5 mg) and metformin hydrochloride tablets (500 mg and 1000 mg). The applicant performed bioequivalence studies to compare the mono dose products to the proposed fixed dose combination products for all three strengths. The test products were full scale batches manufactured at the intended commercial manufacturing site. In parallel to the bioequivalence studies, *in vitro* dissolution of the test and reference products was compared at three pH. The dissolution profiles were similar with regard to linagliptin and dissimilar with regard to metformin hydrochloride. As bioequivalence was shown *in vivo*, this prevailed over the *in vitro* findings.

Adventitious agents

None of the excipients used for Jentadueto are of animal or human origin.

Magnesium stearate used is of vegetable origin, arginine is manufactured by fermentation methods.

Manufacture of the product

Jentadueto film-coated tablets are manufactured using conventional process consisting of granulation, tablet compression and coating. Operating parameters and in-process controls were studied to evaluate their effects on the final drug product properties. Based on this analysis, critical steps were identified and IPC acceptance criteria were defined.

Due to the low content of linagliptin per unit dose and in accordance with the NfG on Process Validation, manufacture of this product was regarded as a non standard process for which validation data on full-scale batches are needed. No formal process validation data have been provided by the applicant and only a process evaluation report for all strengths of the finished product. The data presented in the process evaluation report were obtained from process evaluation trials at full production scale based on the intended commercial manufacturing process for the tablets. The results indicated that the manufacturing process was reproducible and provides product that complies with the in-process and finished product specifications.

In addition the applicant confirmed that formal process validation will be performed on three consecutive commercial scale batches per tablet strength prior to marketing of the product and provided the validation protocol. This was accepted by the Committee.

Product specification

The product specification includes tests for appearance (visual), identification of both active substances and arginine (HPLC), loss on drying (weighing), dissolution (HPLC/UV), uniformity of dosage units: content uniformity of linagliptin (HPLC) and mass variation of metformin hydrochloride (weighing), assay (HPLC) and degradation products (HPLC).

The analytical methods used for testing have been adequately described and validated in accordance with ICH guidelines.

Batch analysis data have been provided on nine commercial scale batches from the proposed commercial manufacturing site, demonstrating compliance with the proposed release specification. In addition, batch analysis data from two smaller batches produced at the development site were provided.

Stability of the product

Stability data of three batches of each strength 2.5 mg/500 mg and 2.5 mg/1000 mg film-coated tablets and one batch of 2.5 mg/850 mg film-coated tablets were submitted in support of the application. The batches were packaged in both proposed commercial container/closure system. The stability studies have been carried out according to ICH requirements. A bracketing approach was applied to different dosage strengths and bottle sizes.

No significant changes were observed during the primary stability studies. Statistical evaluation of the assays of linagliptin, metformin hydrochloride, and arginine supported the proposed shelf-life in both container closure systems.

In addition to the primary stability studies, the tablets were subjected to stress stability testing investigating the effects of elevated temperature, humidity, and light. The finished product was stable with respect to elevated temperature and light and susceptible to humidity. The proposed storage conditions for the blisters and bottles with regard to protection from moisture are therefore justified.

In-use stability studies were also performed for the product packed in bottles. The largest bottle contains 180 tablets. Based on a twice daily dosage regimen, this bottle will be kept for 90 days. The in-use stability studies were performed with two primary stability batches of each strength stored at long term conditions for nine and twenty four months prior to the study. No significant changes were observed. Loss on drying increased during storage but remained well within the shelf-life limit. On the basis of the provided in-use stability data, no temperature storage condition is necessary for the bottles after opening.

On the basis of the provided stability data, the assigned shelf life and storage conditions as defined in the SmPC is well supported.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of Jentadueto has been adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted in support of the marketing authorisation application.

The active substances are well characterised and documented. Although linagliptin simultaneously exists in two polymorphic forms, this does not have an impact on relevant physicochemical properties. The quality of metformin hydrochloride is assured by a European Certificate of Suitability of the Monograph of the European Pharmacopoeia (CEP).

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.

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 manner. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

2.3. Non-clinical aspects

2.3.1. Introduction

A comprehensive non-clinical development was conducted to support the chronic use of linagliptin in humans. Metformin is considered a well known active substance indicated for treatment of T2DM, with an established non-clinical and clinical safety profile. There is a limited amount of non-clinical data on metformin, and no new original data was submitted. The applicant performed an extensive review of the literature. In the light of the longstanding clinical use of metformin, this was considered to be acceptable by the CHMP. Non-clinical studies conducted with the combination of linagliptin and metformin were limited to repeat-dose toxicity studies and reproduction toxicity studies in line with the Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005). This was considered acceptable by the CHMP.

Pivotal studies regarding linagliptin and the combination of linagliptin and metformin were performed in compliance with GLP. Metformin is a well-established substance. It is not known whether published studies with metformin were performed in compliance with GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Linagliptin

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 PD 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, linagliptin reduced less significantly blood glucose levels than in normal animals.

In Rhesus monkeys and Beagle dogs, linagliptin inhibited DPP-4 activity by >70% within 30 min which was maintained for at least 7 hours. However, no blood glucose levels were measured to strengthen these 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. This demonstrates the suitability of cynomolgus monkeys as animal model.

Long duration of action in terms of both inhibition of DPP-4 and glycaemic control was, 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 HbA1c after 14 and 28 days. This improved hyperglycaemia could not be explained by improved insulin sensitivity by linagliptin.

Metformin

Metformin belongs structurally to the biguanides and is an insulin sensitizing drug, which improves fasted and postprandial plasma glucose in patients with T2DM. The mechanism of action of metformin is still not fully elucidated. However its anti-diabetic action is based on decreased hepatic glucose production via suppressed gluconeogenesis, decreased absorption of glucose from the intestine and improved insulin sensitivity. In addition, metformin was shown to increase GLP-1 release in obese patients with or without type 2 diabetes.

The pharmacological action of metformin has minor or no effect on insulin secretion, but reduces the demand of insulin due to its insulin sensitizing effect by increasing peripheral uptake of glucose. The pharmacological actions of metformin are, therefore, targeted towards the liver, the muscle and the adipose tissue. Further, metformin is not associated with an increased risk of hypoglycaemic episodes.

Linagliptin/metformin

The pharmacodynamic effects of the combination of linagliptin and metformin were studied *in vitro*. This study, which was not performed with the fixed-dose combination product, was conducted in order to evaluate additive or synergistic effects of the free combination of linagliptin and metformin. Male db/db mice were orally dosed once daily for one week with either vehicle, linagliptin (1 mg/kg), metformin (200 mg/kg), or a combination of linagliptin (1 mg/kg) and metformin (200 mg/kg). An oral glucose tolerance test (oGTT) was performed 16 h after the last compound administration. The baseline values for fasting glucose before the glucose challenge were lower in all treatment groups than in the control group (-25% with linagliptin; -40% with metformin; - 44% with the combination). To assess the effect of the different treatments on glucose excursion, the baseline value was subtracted from all glucose measurements and an AUC was calculated. The AUC for glucose excursion was reduced by 13% with linagliptin and by 19% with metformin. The combined treatment of linagliptin and metformin resulted in a significant reduction of the AUC for glucose excursion by 37%.

No additional primary pharmacodynamic studies were submitted for the fixed dose combination linagliptin/metformin which was considered acceptable.

Secondary pharmacodynamic studies

Linagliptin

Secondary pharmacodynamic studies (non-GLP) were performed to investigate neurological, cardiovascular, pulmonary, gastrointestinal and renal effects. Single doses were given. A modified Irwin test was performed in mice at oral dosages of up to 30 mg/kg for testing potential effects of linagliptin on the Central Nervous System (CNS). No compound-induced effect was seen suggesting the absence of any influence of linagliptin on overt behaviour at the tested dosages.

For assessing effects on renal function and clinical chemistry parameters, rats were treated orally with a dose of 3, 10 or 30 mg/kg linagliptin. Based on the endpoints of the study linagliptin did not influence kidney function or integrity.

Metformin

No secondary pharmacodynamic assays were performed with metformin. These studies were not considered necessary in view of the extensive clinical experience accumulated over the many years on the market.

Linagliptin/metformin

No secondary pharmacodynamic studies were performed on the fixed dose combination linagliptin/metformin based on the data available for each compound which was considered acceptable.

Safety pharmacology programme

Linagliptin

The core battery studies (ICHS7A and ICHS7B) were all conducted according to GLP except for the *in vitro* assays. Single doses were given if not stated otherwise.

Potential effects on the CNS were investigated in rats after oral administration of 6, 60 or 600 mg/kg linagliptin. In a modified Irwin study, no marked or consistent behavioural or physiological changes were seen. In addition, no significant effects on body temperature or spontaneous locomotor activity were observed.

A comprehensive cardiovascular profiling was performed both *in vitro* and *in vivo*. Linagliptin had no effect on the hERG-mediated potassium current at concentrations up to 10 µM. In the Guinea pig papillary muscle assay, concentrations up to 10 µM did not affect resting membrane potential, action potential amplitude and overshoot, and maximal upstroke velocity. There was a concentration dependent shortening of the action potential beginning at 0.3 µM that increased up to a 7% shortening (of APD90) at 10 µM. These *in vitro* studies indicated that linagliptin has a low proarrhytmic potential based on a delayed ventricular repolarization. Potential *in vivo* effects of linagliptin on the cardiovascular system were studied in the telemetered Cynomolgus monkey at dosages of 12, 60 and 150 mg/kg. High plasma concentrations of up to 18900 nM (1703x clinical Cmax) were reached at a dose of 150 mg/kg. There were no relevant treatment-related changes in the ECG (lead II) at doses up to 150 mg/kg. Cardiovascular investigations were also conducted in repeat-dose toxicity studies. In the 4-week toxicity study in Beagle dogs, doses up to 9 mg/kg/day (210x clinical Cmax) were free from any relevant effect of linagliptin on blood pressure, heart rate and ECG. Changes seen at 45 mg/kg/day (955x clinical Cmax) were considered to be pseudo-allergy related. In Cynomolgus monkeys, which did not show any signs of pseudo-allergy after oral administration with linagliptin, no treatment-related changes were detected in the ECG and blood pressure measurements in the toxicity studies up to 12 months duration and at dosages up to and including 300 mg/kg/day (2523x clinical Cmax). In conclusion, the preclinical safety data did not indicate any linagliptin-related cardiovascular risk.

Effects on respiratory function were tested in rats given oral dosages of 0, 6, 60 or 600 mg/kg linagliptin. Oral dosages of 6 or 60 mg/kg produced no effect on respiratory rate, tidal volume and minute volume. At a dosage of 600 mg/kg, a statistically significant increase in tidal volume and a significant decrease in respiration rate and minute volume at 30 min post-dose were seen. A dose level of 600 mg/kg was associated with a plasma level of 3099x clinical Cmax. Therefore, the slight and isolated respiratory effects seen at 600 mg/kg are considered to be without relevance for human safety.

In conclusion, the safety pharmacology assessment of neurological, cardiovascular and respiratory effects supports the clinical development of linagliptin.

Metformin

No formal safety pharmacology studies have been performed on metformin. These studies were not considered necessary by the CHMP in view of the extensive clinical experience accumulated over the many years on the market.

Linagliptin/metformin

No safety pharmacology studies were performed on the fixed dose combination linagliptin/metformin based on the data available for each compound which was considered acceptable as well.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were submitted for the combination linagliptin/metformin based on the data available for each compound which is considered acceptable.

2.3.3. Pharmacokinetics

Methods of analysis

Linagliptin

The HPLC-MS/MS assay for the quantification of linagliptin has been validated adequately in rat plasma. Acceptable linearity, precision, accuracy and specificity of linagliptin were observed over the concentration range 0.100 to 100 nmol/L.

Metformin

The HPLC-MS/MS method for the measurement of metformin has been validated adequately in rat plasma. Acceptable linearity, precision, accuracy and specificity of metformin were observed over the concentration range 50 to 25000 nM.

Absorption

Linagliptin

In vitro studies showed that linagliptin is a moderately permeable drug and a substrate for P-glycoprotein. Linagliptin is a substrate for OATP8, OCT2, OAT4, OCTN1 and OCTN2, suggesting a possible OATP8-mediated hepatic uptake, OCT2-mediated renal uptake and OAT4-, OCTN1- and OCTN2-mediated renal secretion and re-absorption of linagliptin *in vivo*.

Oral bioavailability of linagliptin appeared to be moderate in mice (18-44%), rats (51-55%), monkeys (41-69%) and humans (30%). Maximum blood concentrations of linagliptin were generally reached between 5 minutes and 1 h post-dose in mice, rabbits and monkeys. In the rat, the maximum blood concentration was between 0.5 and 4 h post-dose following oral administration. 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 behavior of linagliptin was also observed in rats and rabbits, which may be due to a saturation of P-glycoprotein mediated active secretion and DPP-4 binding. Food had a moderate influence on the plasma profiles of linagliptin but not on the overall extent of absorption in rats.

Metformin

Metformin hydrochloride is highly soluble but lowly permeable. Thus, metformin can be classified as BCS class III drug. The oral bioavailability in rats was low to moderate (about 30%) in the dose range between 50 and 200 mg/kg. Passive permeation, active uptake by cation transporters (e.g. PMAT) or other saturable processes may play a role in oral absorption of metformin. This could cause non-linear pharmacokinetics. However metformin showed a linear PK profile between 50 and 900 mg/kg in rats. This may be due to the investigated dose range, where transport mechanisms are already saturated and non-linear PK could be expected at markedly lower doses only. Although the overall contribution of metabolic transformation of metformin is low, a slight entero-hepatic first pass metabolism was suggested in rats. No studies addressing the absorption of metformin have been performed to support this application. The above data are based on published literature and this was considered acceptable by the CHMP.

Linagliptin/metformin

Table 1. Pharmacokinetic parameters of linagliptin and metformin after multiple oral doses of linagliptin/metformin combination to rats

Dose of linagliptin/metformin (mg/kg)	Sex	Day	Linagliptin		Metformin		Study number
			C_{max} (nmol/l)	AUC_{0-24} (nmol*h/l)	C_{max} (nmol/l)	AUC_{0-24} (nmol*h/l)	
0.5/100	M	1	6.43	103	33600	214000	U09-2243
	F	1	16.7	108	36800	191000	
	M	14	11.2	136	44800	282000	
	F	14	19.3	141	46600	190000	
1/200	M	1	18.7	156	71800	418000	
	F	1	24.3	195	61600	336000	
	M	14	33.8	274	65100	439000	
	F	14	69.7	332	85100	477000	
2.5/500	M	1	38.9	281	134000	1210000	U09-1632
	F	1	49.3	307	129000	1060000	
	M	14	73.1	445	183000	1630000	
	F	14	50.3	473	223000	1960000	
5/1000	M	1	37.4	311	175000	2220000	
	F	1	74.9	512	223000	2330000	
	M	14	32.8	578	283000	3490000	
	F	14	45.9	545	313000	3760000	
10/2000	M	1	44.1	391	214000	2530000	
	F	1	54.6	621	273000	3740000	
	M	14	-	-	-	-	
	F	14	-	-	-	-	
0.5/100	M	1	9.18	123	44900	272000	U10-1492
	F	1	13.9	99.7	37200	147000	
	M	88	16.1	166	51400	221000	
	F	88	20.1	149	57400	226000	
2/400	M	1	39.0	251	103000	790000	
	F	1	64.3	313	112000	613000	
	M	88	37.1	308	123000	1160000	
	F	88	50.5	297	198000	1200000	
4/800	M	1	37.2	289	143000	1690000	
	F	1	63.0	407	182000	1480000	
	M	88	25.3	344	198000	2330000	
	F	88	21.8	309	361000	4900000	
2/800	M	1	18.8	201	144000	1500000	
	F	1	25.2	222	183000	1360000	
	M	88	15.6	253	227000	3220000	
	F	88	16.2	218	324000	4200000	
4/0	M	1	17.7	203	170000	1610000	
	F	1	25.4	208	178000	1300000	
	M	88	38.5	265	219000	2770000	
	F	88	99.4	457	305000	3870000	

Toxicokinetic studies with linagliptin/metformin combination administration in rats showed that the exposure to linagliptin increased less than dose-proportional, whereas the exposure to metformin increased dose proportionally between 500 and 1000 mg/kg but less than dose proportionally between 1000 and 2000 mg/kg. The dose-proportionality of linagliptin is in contrast with earlier findings after administration of linagliptin alone, where the exposure increased more than dose-proportional. The CHMP agrees with the Applicant that this could be explained by the different dose ranges used. At doses lower than 10 mg/kg, the disposition of linagliptin is mainly determined by saturable binding to plasma and tissue DPP-4. However, it should be noted that in case of high doses or overdosing of the linagliptin/metformin combination the AUC may increase more than dose-proportional.

No effect of linagliptin on metformin kinetics was observed. However, co-administration with metformin did affect linagliptin kinetics: the AUC of linagliptin was higher (1.4- to 2-fold) with metformin (800 mg/kg) compared to administration without metformin at day 1 in both male and female rats.

It was shown in rats that the feeding status only influenced the shape of the plasma level time curve and not the oral absorption of linagliptin. The exposure (AUC) to linagliptin was unaffected by the feeding conditions. As stated in the SmPC, food decreases the extent and slightly delays the absorption of metformin hydrochloride. Some accumulation (up to a factor 1.9) of both linagliptin and metformin was observed after repeated doses in the 2-week combination toxicity study in rats, while accumulation was not consistently found in the 13-week combination toxicity study in rats. Thus, some accumulation of linagliptin in rat plasma after repeated dosing can not be excluded.

Distribution

Linagliptin

The distribution of linagliptin was dominated by the binding to its target DPP-4 in plasma and tissues at low doses. A pronounced concentration-dependency was observed in the plasma protein binding of linagliptin. A very high binding percentage of about 99% at concentrations up to about 1 nM was observed. At concentrations beyond about 30 nM, the plasma protein binding was constant with a moderate bound fraction between 70 and 80%. The concentration dependency was shown to be caused by high affinity saturable binding to soluble DPP-4 in plasma. Thus, the plasma concentration of soluble DPP-4 may have an influence on the pharmacokinetics of linagliptin and changes in plasma protein binding are expected at therapeutic plasma levels in humans (Cmax,ss of 11.1 nM). Additionally, it should be noted, that plasma concentrations achieved in toxicology studies were generally in a range where DPP-4 binding of linagliptin in plasma is saturated. Thus, plasma protein binding of linagliptin in toxicology studies was lower than in humans during therapeutic treatment adding an additional safety margin in terms of unbound exposure.

Extensive tissue distribution was indicated by high volumes of distribution in all species (>4 l/kg). This was confirmed by whole body autoradiography in rats. Linagliptin is extensively distributed into tissues and long retention times are observed in DPP-4 containing tissues, in particular the kidneys and the liver. Alike plasma protein binding, also tissue distribution of linagliptin is dominated by DPP-4 binding as shown in mice and rats. Kidney and liver were shown to contain the major fraction of total body DPP-4 in mice and rats and therefore the high and persistent tissue levels of linagliptin even at low doses are due to high-affinity binding to DPP-4. Once DPP-4 is saturated, tissue concentrations increased linearly with dose due to nonspecific binding. This is in line with the still high volumes of distribution observed in DPP-4 deficient rats which indicate DPP-4 independent tissue distribution. Complete saturation of DPP-4 in tissue can be assumed in all toxicology studies and high exposure to linagliptin was demonstrated in Cynomolgus monkey liver and kidney tissue sampled from the animals of the 52 week toxicity study. Despite the long residence times in tissues and the long terminal half-life in plasma, steady state is achieved quickly after repeated dosing and only a limited accumulation in tissues occurs. Thus, during chronic use of low doses of linagliptin, steady state in tissue will be achieved quickly once DPP-4 is saturated. Traces of covalently bound radioactivity were found in plasma of animals and humans, which were regarded as of negligible importance considering the exceptionally low levels and the low therapeutic dose of linagliptin.

Linagliptin crosses the placenta barrier in rats and rabbits. Foetal exposure in rats reached about 50% of the maternal exposure, whereas 2-5% was found in foetuses of rabbits. Foetal exposure differs between rats and rabbits, but the foetal exposure in humans is unknown. Placental transfer in humans is expected based on the results in rats and rabbits.

Metformin

The plasma protein binding of metformin is very low. In rat plasma, only about 15% were reported to be protein bound *in vitro*. In addition, a bound fraction of about 10% was determined in a solution of 4% human serum albumin.

In rat blood, metformin is distributed slightly more into plasma than into or onto blood cells. The mean plasma-to-blood cell partition ratio was reported to be about 1.3 independent of concentrations between 1 and 20 µg/mL (7.7-230 µM) metformin. Metformin showed a slow association but also a slow disappearance from erythrocytes.

Metformin showed a moderate to high volume of distribution (2-3 l/kg) in rats, indicating extensive tissue distribution. This was confirmed experimentally by dosing [14C]radiolabelled metformin to mice and rats. High radioactivity concentrations were found in the gastrointestinal tract, kidneys, liver and the salivary glands at concentrations higher than in blood. Lower levels were observed in the heart, skeletal muscle, white fat and brain, the latter indicating that metformin and/or metabolites may cross the blood brain barrier. Liver concentrations of metformin in rats were about 3 - 4 times higher than plasma concentrations of metformin. The distribution into the isolated perfused rat liver was shown to be permeability limited and that in the organic cation transporter OCT1 knockout mice the liver concentrations were about 30 times lower than in wild type mice (study R10-2435). Thus, OCT1 was suggested to be responsible for hepatic uptake of metformin. The same study also demonstrated that OCT1 was also involved in the intestinal uptake of metformin. In a comparative study, it was demonstrated that the tissue uptake clearance of metformin in rats is markedly higher in the kidney than in the liver. It was concluded that metformin transport by renal OCT2 plays a dominant role for its pharmacokinetics whereas OCT1, which is expressed in both liver and kidney in rats and expressed in human liver is of subordinate importance.

Metformin crosses the blood-placenta-barrier in humans and the foetus is exposed to metformin.

Linagliptin/metformin

No distribution PK studies were performed on the fixed dose combination linagliptin/metformin which was considered acceptable based on the data provided for the individual compounds.

Metabolism

Linagliptin

The elimination of linagliptin in mice, rats and female rabbits was governed by non-metabolic mechanisms. Unchanged parent compound was the most abundant component in urine, faeces, bile and plasma of animals except for Cynomolgus monkeys. In monkey bile and faeces metabolites of linagliptin dominated. Linagliptin is metabolised by CYP3A4 in humans. There was no indication for a contribution of other CYP enzymes in the metabolism of linagliptin. After oral dosing, the pharmacologically inactive metabolite CD1790 was the only circulating metabolite with a systemic exposure in human plasma of >10% of parent compound systemic exposure at steady state. CYP3A4 is involved into formation of CD1790 in humans. Thus, co-administered inhibitors of CYP3A4 may influence the pharmacokinetics of linagliptin and decrease formation of CD1790. Linagliptin is a weak competitive and a weak to moderate mechanism-based inhibitor of CYP isozyme CYP3A4, but does not inhibit other CYP isozymes. It is not an inducer of CYP isozymes.

Linagliptin is not an inducer of hepatic cytochrome P450. However, linagliptin weakly inhibited CYP3A4 activity in human liver microsomes competitively. Additionally, weak to moderate mechanism based (irreversible) inhibition of CYP3A4 by linagliptin was observed (IC_{50}=36.3 µM (testosterone 6ß-hydroxylation); IC_{50}=41.6 µM (erythromycin N-demethylation); IC_{50}>100 µM (midazolam 1-hydroxylation and nifedipine oxidation)). Considering the very low plasma concentrations of linagliptin in humans ($C_{max,ss}$ of 11.1 nM) and its high plasma protein binding at therapeutic plasma levels in humans, it is very that linagliptin interacts on the pharmacokinetics of co-administered drugs.

Metformin

No relevant inhibition of CYPs by metformin was observed. The overall contribution of metabolic transformation of metformin to its elimination is low. However, in a recent study it was shown that metformin is metabolized via CYP2C11, 2D1 and 3A1/2 in rats. A slight first pass metabolism was observed in rats. Thus, although excretion of unchanged parent compound is the determining route of elimination, additional metabolic transformation of metformin is indicated.Co-administration with CYP3A4 inhibitors or inducers could affect the pharmacokinetics of linagliptin. There was no indication of a mechanism-based inhibition of CYP3A4 by metformin. Therefore, metabolic interactions between linagliptin and metformin, based on inhibition of CYP3A4 are not expected.

Linagliptin/metformin

Metabolism of the FDC linagliptin/metformin is described below under Pharmacokinetic drug interactions.

Excretion

Linagliptin

Across species, the dominant excretion route was via the faeces. The urinary excretion was shown to be dose-dependent in mice and rats. At an oral dose of 1 mg/kg, less than 1% of the dose was excreted in urine, whereas up to about 20% of the dose was excreted with urine at 30 mg/kg. As demonstrated in mice, the dose-dependency of renal excretion can be attributed to a saturable binding of linagliptin to its target DPP-4 in tissue and plasma. Biliary excretion is prominent and P-glycoprotein was shown to be involved into elimination with bile. Despite a prominent biliary excretion of parent drug, the entero-hepatic recirculation of linagliptin was lower than expected. This was attributed to a negative effect of bile on its absorption in anaesthetised rats. Besides the biliary excretion (about 80% within 6 hours after iv administration of 1 mg/kg linagliptin), about 12% of the dose was directly secreted into the intestinal lumen, independently of biliary excretion. It is likely that P-gp mediated efflux is involved into active secretion of linagliptin from the blood into the gut lumen in rats. In comparison to biliary excretion, direct secretion into gut represents a minor route of elimination. Nevertheless, it may become more important in case of hepatic (and renal) elimination impairment.

Metformin

The by far dominating excretion pathway is renal elimination of unchanged parent compound. Active secretion involving hMATE2-K and hOCT2 in the proximal tubules of the kidney is suggested in addition to glomerular filtration. Biliar excretion was low. As mentioned previously, the compound is mainly excreted unchanged.

Linagliptin/metformin

No excretion PK studies were performed on the fixed dose combination linagliptin/metformin which was considered acceptable.

Pharmacokinetic drug interactions

Linagliptin

No *in vivo* drug-drug interaction studies were performed in animals. For drug transporters or drug metabolizing enzymes where linagliptin was identified as inhibitor, relevant inhibition only occurs in the micromolar range. Considering the very low plasma concentrations of linagliptin in humans ($_{Cmax,ss}$ of 20 nM) and its high plasma protein binding at the therapeutic plasma levels in humans, it is very unlikely, that linagliptin interacts on the pharmacokinetics of co-administered drugs. The same applies for the main metabolite CD 1790.

Linagliptin is a substrate for P-gp. In addition, linagliptin undergoes a minor metabolism in humans and the main metabolite CD 1790 is formed by CYP 3A4. Thus, co-administered drugs which act on P-gp and/or CYP 3A4 may have an influence on the pharmacokinetics of linagliptin.

Metformin

Metformin is mainly excreted unchanged via urine. However, it was shown that metformin is metabolized via CYP2C11, 2D1 and 3A1/2 in the rat. Several rat studies demonstrated pharmacokinetic interactions with metformin and co-administered drugs which are substrates for CYP3A1/2 e.g. telithromycin or DA-8159 leading to decreased metformin clearance in rats. In addition, altered pharmacokinetics of metformin were described in disease models, where hepatic expression levels of these CYPs are changed, e.g. streptozotocin induced diabetes in rats or challenge of E. coli LPS in rats.

Linagliptin/metformin

Metabolism by CYP enzymes

In vitro, it was demonstrated that metformin does not inhibit any of the investigated CYP isoforms *in vivo*. Thus, as the only CYP isoform involved into the metabolism of linagliptin is CYP3A4, co-administration of metformin should not alter the metabolism of linagliptin. This was confirmed in a clinical study where no clinical meaningful interaction was observed. The contribution of metabolic transformation to the overall elimination of metformin in human is very low if at all present. Linagliptin was shown to be a moderate to poor mechanism based (irreversible) inhibitor of CYP3A4 *in vitro.* However, in a clinical study no clinically relevant interaction was observed between linagliptin and simvastatin, a known model substrate for CYP3A4. No consistent or relevant interactions have been observed in the toxicokinetic studies, where also supratherapeutic doses of both compound were dosed repeatedly in rats. Thus, drug-drug-interactions between linagliptin and metformin on a CYP level are extremely unlikely to occur.

Binding to plasma proteins

Metformin does not bind notably to plasma proteins in rats and humans and therefore, linagliptin cannot influence metformin pharmacokinetics by interaction on the plasma protein binding level. In addition, the plasma protein binding of linagliptin at therapeutic doses is characterised by a very high affinity and high specifity as it binds to soluble plasma DPP-4. On the other hand, it was shown that metformin does not inhibit DPP-4 *in vitro* and *in vivo*. Taken together, drug-drug interactions between metformin and linagliptin with respect to plasma protein binding are unlikely.

Transport by drug-transporters

Linagliptin and metformin are both substrates for OCTs. In addition, linagliptin was identified as an inhibitor of OCT1 with and IC_{50} value of 47.2 µM. Thus, upon oral administration of 5 mg linagliptin local intestinal concentrations in the range of the IC_{50} might be produced. However, such high concentrations of linagliptin in the gut would only be present for a transient period and thus, OCT1 inhibition in the gut would be limited if at all present. In all other tissues where OCT1 is expressed and also in plasma, the unbound concentrations of linagliptin are far below the IC_{50} value for OCT1 inhibition, considering the low therapeutic plasma levels. Finally, the role of OCT1 mediated transport of metformin is recognized as of minor importance. In addition, in particular OCT2, which is expressed on the basolateral membrane of the renal proximal tubule cells, was shown to play a central role in renal elimination of metformin. Due to low therapeutic plasma concentration of linagliptin and linagliptin being not an inhibitor of OCT2, a competitive inhibition of OCT2 mediated metformin transport by linagliptin in the kidney can be excluded although linagliptin was shown to distribute extensively into kidneys.

Metformin is reported to be a substrate of MATE and PMAT which are expressed on the brush boarder membrane of renal proximal tubule cells. Kidney distribution of linagliptin is due to high affinity binding to kidney DPP-4. Thus, even in tissues with high concentrations of total linagliptin, only a very low unbound concentration can be expected as most of the compound is bound tightly to DPP-4. Hence, a competitive inhibition of MATE and PMAT mediated metformin transport by linagliptin in the kidney can be excluded. On the other hand, the high doses of metformin may theoretically lead to a competitive inhibition of uptake or efflux transporters for linagliptin. However, no indications were found, that an active uptake is involved in the gastrointestinal absorption of linagliptin.

Furthermore, it was demonstrated in rats, that oral absorption and biliary excretion of linagliptin is influenced by P-gp. However, metformin most likely is neither a substrate nor an inhibitor of P-gp and therefore P-gp mediated interactions are not expected.

In addition, linagliptin was shown to be a substrate for OCT2 (but not OCT1). Thus, metformin could theoretically influence the pharmacokinetics of linagliptin by competing for OCT2 in the kidney decreasing the renal clearance of linagliptin. However, renal excretion of linagliptin is of almost negligible importance for its elimination. Thus, clinically relevant pharmacokinetic interactions at an OCT2 mediated mechanism are not expected, which was confirmed in the clinical study. Taken together, based on the available non-clinical data, clinically relevant pharmacokinetic interaction between metformin and linagliptin at the respective therapeutic dose levels is not expected in humans.

2.3.4. Toxicology

The toxicity of linagliptin has been evaluated in an extensive non-clinical program. The toxicology program included single-dose and repeat-dose toxicity studies in mice, rats, dogs and monkeys, *in vivo* and *in vitro* genotoxicity studies, reproduction and developmental toxicity studies and carcinogenicity studies. Although metformin has been marketed for many years, there are only limited non-clinical data available in published literature. Therefore, the general and reproductive toxicity of metformin was investigated in additional rat studies. Repeat-dose toxicity studies and reproduction toxicity studies were conducted with the FDC linagliptin/metformin. This is in line with the Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005).

Single dose toxicity

Linagliptin

Table 2. Single dose toxicity studies with linagliptin

Study ID	Species/ Sex/Number/ Group	Dose/Route	Observed max non-lethal dose, mg/kg	Major findings
U05-1899	Mouse M+F/3	1000 and 2000 mg/kg Oral	1000	1000: piloerection 2000: 1M+1F dead. Stasis of liver, spleen and kidney
U05-1902	Mouse M+F/3	1000 and 2000 mg/kg Oral	< 1000	1000: 1M dead. Reduced motor activity, piloerection
U05-1938	Mouse M+F/3	10, 30 and 60 mg/kg Intravenous	60	No treatment-related findings
U05-1901	Rat M+F/3	1000 and 2000 mg/kg Oral	1000	2000: 1F dead. Piloerection, blood in lung, fluid in uterus
U05-1903	Rat M+F/3	1000 and 2000 mg/kg Oral	2000	1000: piloerection
U05-1936	Rat M+F/3	10, 30, 60 and 120 mg/kg Intravenous	60	120: 2F dead. Stasis of liver and kidneys

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.

Metformin

Acute toxicity of metformin was not studied in single-dose studies, but information about this endpoint was obtained from short-duration toxicity studies in rats. These data indicated that the ALD of metformin is above 1000 mg/kg.

Linagliptin/metformin

No single dose toxicity studies were performed on the fixed dose combination linagliptin/metformin which was considered acceptable based on the data available for each compound.

Repeat dose toxicity

Linagliptin

Table 3. Repeat-dose toxicity studies with linagliptin

Study ID	Species / Sex/ Number / Group	Dose/Route mg/kg/day	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
U06-2122	Mouse M+F/5	0, 100, 300, 1000 Oral (diet)	2 weeks	Not defined	1000: Body weight gain decrease
U06-1784	Mouse M+F/6	0, 60, 120, 300, 600 Oral (gavage)	4 weeks	Not defined	120: Hyperkeratosis, epithelial hyperplasia in stomach 600: Hunched posture, piloerection. F: Liver, thymus weight decrease
U07-1536	Mouse M+F/12	0, 100, 300, 600 Oral (gavage)	3 months	100	300: ALP, ALT, AST increase Hyperkeratosis and epithelial hyperplasia in stomach 600: 3F+1M dead. Ovary weight decrease, renal weight increase, Tubular hypertrophy and basophilia in kidneys
U08-1887	Rat M+F/5	0, 100, 300, 1000 Oral (diet)	2 weeks	Not defined	1000: decreased body weight gain, food consumption decrease Piloerection, size of stomach, cecum and colon increase
U04-1714	Rat M+F/10	0, 30, 100, 300, 1000 Oral (gavage)	2 weeks	Not defined	300: Spleen weight decrease, Thymus apoptosis, excretory duct atrophy of submandibular salivary glands 1000: Not tolerated; necropsy on day 6 or 8. Histological changes in many organs

Study ID	Species / Sex/ Number / Group	Dose/Route mg/kg/day	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
U05-1937	Rat M+F/10	0, 6, 60, 600 Oral (gavage)	4 weeks	60	600: 1F dead. Piloerection, emaciation, hairless patches, decrease body weight, food consumption decrease, AST, ALT, GLDH, aldolase, bilirubin increase, Triglyceride decrease, Liver and kidney weight increase, Thymus, prostate, ovaries, pituitary weight decrease Necrosis and hyperplasia in liver, tubulus degeneration in kidneys, phospholipidosis in lung, lymph nodes, thymus, spleen and bone marrow. Atrophic salivary gland, apoptosis in prostate and lymphatic organs
U06-1874	Rat M+F/10	0, 10, 30, 100, 300 Oral (gavage)	3 months	30	100: Kidney, adrenals, thyroid weight increase, Aggregation of alveolar macrophages in lung. Glycogen accumulation in liver 300: Body weight gain decrease ALP, ALT, AST, bilirubin, creatinine, urea increase, Liver weight increase, Follicular cell hypertrophy in thyroid
U07-1910	Rat M+F/20	0, 7, 30, 100, 300 Oral (gavage)	6 months	30	100: Locomotor activity decrease ALT, GLDH increase 300: AST increase Liver, kidneys weight increase Tubular damage in kidneys, glycogen storage in liver incerase Hyperplasia of bile ducts. Phospholipidosis in lung. Mucosal irritation in stomach. Microfollicular hypertrophy in thyroid. Changes in ovaries, vagina and prostate
U06-1236	Rat M+F/5	0, 30, 60, 100 IV	1 week	30	60: Iliac lymph nodes weight increase, Thymus weight decrease 100: 1M dead. Prone, pale, breathing rate increase, Irritation at injection site
U06-1301	Rat M+F/10	0, 2.5, 10, 50 IV	2 weeks	10	50: Adrenal weight decrease

Study ID	Species / Sex/ Number / Group	Dose/Route mg/kg/day	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
U04-2187	Dog M+F/2	0, 15, 45, 150 Oral (gavage)	2 weeks	Not defined	15: Pseudo-allergic reactions, vomiting 45: Collapsis, histamine increase Apoptosis and inflamitory infiltration in bile duct, degeneration of seminiferous epithelium in testis. Lung weight increase 150: 1M dead, necrosis myocardium
U05-1944	Dog M+F/3	0, 1, 3, 9, 45 Oral (gavage)	4 weeks	9	45: Pseudo-allergic reactions, vomiting, hypotension, tachycardia, QTc-prolongation, histamine increase, inflammatory infiltration in bile duct, tubuloepithelial apoptosis/necrosis in kidney, atrophy in seminiferous tubules
U05-1978	Monkey M+F/3	0, 10, 30, 100 Oral (gavage)	2 weeks	100	No findings
U05-1950	Monkey M+F/1	300 Oral (gavage)	2 weeks	Not defined	300: Post-dose emesis
U05-2481	Monkey M+F/3	0, 10, 60, 300 Oral (gavage)	4 weeks	10	60: Salivation. Kidney weight increase Ovary, uterus weight decrease, Follicular development decrease, Thymus weight decrease Atrophy in vagina, sternal marrow and thymus 300: 1M dead. Emesis. ALT, AST, bilirubin, creatinine increase, Protein in urine increase Liver weight increase Hepatocyte glycogen increase Epithelial hypertrophy and peribiliary inflammation in bile ducts and gall bladder. Germinal centre development in lymph nodes decrease Thymus atrophy

Study ID	Species / Sex/ Number / Group	Dose/Route mg/kg/day	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
U07-1072	Monkey M+F/3	0, 4, 25, 150 Oral (gavage)	3 months	4	25: Epithelial hypertrophy/ hyperplasia, glandular degeneration, inflammatory cell infiltrate in stomach. 150: Body weight decrease Emesis, salivation. Creatinine, globulin increase, Albumin decrease, Chol, TG increase, Urinary protein increase Urinary Na and Cl decrease, Kidney weight increase, Thymus weight decrease Uterus, cervix weight decrease Cellularity in thymus and spleen decrease, Germinal centre development in madibular and mesenteric lymph nodes decrease
U08-1185	Monkey M+F/4	0, 1, 10, 100 Oral (gavage)	12 months	10	100: 1F dead. Vomiting, salivation. Body weight decrease, Ovary weight decrease, Islet cell proliferation, hypoproteinemia, Urinary protein increase
U08-2215	Monkey M+F/1	Staircase phase: 1, 2.5, 10, 25, 50 Constant phase: 40 IV	3 days per dose level 2 weeks	Not defined	50 (staircase): Shallow breathing, lethargy 40 (2 weeks constant phase): Underactive behavior
U10-1202	Monkey M+F/3	0, 1, 5, 40 IV	2 weeks	5	40: Swollen lips, muzzle and groin, shallow breathing, reddening facial skin, ECG: PG, QRS increase, Systolic blood pressure decrease

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.

Metformin

Table 4. Repeat-dose toxicity studies with metformin

Study ID	Species/Sex/ Number/Group	Dose/Route (mg/kg/day)	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
U09-2246 GLP	Rat M + F/10	0, 100, 200, 1000 Oral	2 weeks	200	1000: Body weight gain ↓ Heart: Organ weight ↑, hypertrophy of myocardium Liver: Organ weight ↑ Adrenals: Organ weight ↑, vacuolation medulla Pituritary: Organ weight ↑, hyperplasia Thymus: Organ weight ↓, size reduction cortical areas Salivary glands (infiltration, inflammation) Pancreas (depletion of zymogen granules)

The exposure increased almost proportionally with dose. Mean metformin plasma $AUC_{0\text{-}24h}$ values at dose levels of 100, 200 or 1000 mg/kg/day were 178, 374 and 2790 µM·h. The respective C_{max} values were 38.2, 70.1 or 204 µM. There was no gender related effect.

No adverse findings were seen at 100 and 200 mg/kg/day (2.4x MRHD) metformin. At 1000 mg/kg/day (17.5x MRHD), body weight gain was slightly decreased (terminal body weight 0.9x relative to control). The organ weights of the heart (1.3x relative to control), liver (1.3x) and adrenals (1.2x) were increased. In addition, a statistically significant increase in pituitary weights (1.2x) was noted in females. Thymus weights were reduced (0.8x). In correlation with the increased heart weights, a concentric hypertrophy of the ventricle myocardium was observed. The adrenal medulla (zona fasciculata) was affected by a minimal to slight cytoplasmic vacuolation. Hyperplasia of the pituitary gland (pars distalis) was found in females, atrophy of the seminal vesicles was seen in males. There were also alterations of the parotid salivary gland and size reduction of the cortical areas of the thymus. In addition, depletion of pancreatic zymogen granules was found, a finding which often correlates with under nutrition.

At high dose (17.5 x MRHD) the target organs of metformin in the rat are heart, liver, adrenals, pituitary and thymus. The NOAEL is found at 200 mg/kg (2.4 x MRHD).

Linagliptin/metformin

Table 5. Repeat-dose toxicity studies with the linagliptin/metformin combination

Study ID	Species/Sex/ Number/Group	Dose/Route (mg/kg/day)	Duration	NOEL/ NOAEL (mg/kg/day)	Major findings
U09-1632 Non-GLP*	Rat M + F/5	0/0 2.5/500 5.0/1000 10.0/2000 Oral	2 weeks	Not defined	**2.5/500 mg/kg:** Heart, adrenals: Organ weight ↑ **5/1000 mg/kg:** Body weight gain ↓ Heart: Organ weight ↑, hypertrophy of myocardium Liver: Organ weight ↑, cytoplasmic vacuolation Adrenals: Organ weight ↑, vacuolation medulla Thymus: Organ weight ↓ Salivary glands: Vacuolation Pancreas: Depletion of zymogen granules
U09-2243 GLP	Rat M + F/10	0/0 0.5/100 1/200 Oral	2 weeks	1/200	No findings
U10-1492 GLP	Rat M + F/10	0/0 0.5/100 2.0/400 4.0/800 2.0/800 4.0/0 0/800 Oral	13 weeks	0.5/100	**2.0/400 mg/kg:** Body weight gain ↓ Heart, liver, kidneys, adrenals: Organ weight ↑ Thymus: Organ weight ↓ Salivary glands: Hypertrophy of epithelium Ovaries: Number of corpora lutea ↑ **4.0/800 mg/kg, 2.0/800 mg/kg, and 0/800 mg/kg:** As lower dose in addition: Mortality (4) Heart: Myocardium: Hypertrophy, fibrosis Liver: Hepatocellular hypertrophy Kidneys: Basophilic tubules, tubulus dilatations Uterus and/or Cervix: Atrophy Stomach: Erosions of the gastric mucosa

* This non-GLP study has been designed to comply with international guidelines on repeated dose toxicity studies, e.g. "Note for Guidance on Repeated Dose Toxicity", CPMP/SWP/1042/99 and Directive 2001/83/EC.

Oral 2-week dose range finding study in rats

At the 2.5/500 mg/kg/day dose level (2.9x MRHD for linagliptin, 11x MRHD for metformin), increases in heart weight (1.3x relative to control) and adrenals weight (1.2x) were observed. Histopathological changes were seen in heart (inflammation), the thymus (apoptosis), adrenal gland (cytoplasmic vaculoation) and parotid salivary gland (vacuolation).

Dosages of 5/1000 mg/kg/day linagliptin/metformin, led to slight decrease in body weight gain (terminal body weight 0.9x relative to control). The weights of the heart (1.4x relative to control), liver (1.3x) and adrenals (1.5x) were increased. Thymus weights were reduced (0.6x). Histopathological changes were noted in heart (hypertrophy of the myocardium), liver (cytoplasmic vacuolation in females), salivary glands (vacuolation), thymus (apoptosis), adrenal medulla (cytoplasmic vacuolation), seminal vesicles (atrophy), and pancreas (depletion of zymogen granules).

Linagliptin/metformin given at dosages of 10/2000 mg/kg/day exceeded the MTD. Mortality occurred already after a single administration and the remaining animals were prematurely sacrificed.

Oral 2-week toxicity study in rats

There were no drug related findings in all dose groups. In conclusion, the NOAEL of the 2-week combination study in rats was set at 1/200 mg/kg/day linagliptin/metformin (1.9x MRHD for linagliptin/2.8x MRHD for metformin).

Oral 3-month toxicity study in rats

Linagliptin and metformin showed a different dose-exposure relationship in the tested dose range. The exposure to linagliptin increased less than proportionally with dose between 0.5 and 4.0 mg/kg/day. In contrast, the exposure to metformin at steady state increased more than proportionally with dose between 100 and 800 mg/kg/day.

At 800 mg/kg/day metformin alone or in combination with linagliptin (linagliptin/metformin at a dosage of 0/800, 2.0/800 or 4.0/800 mg/kg/day, associated with 20.9x, 23.3 or22.8 x MRHD for metformin,) the organ weights of the heart (up to 1.6x relative to control), liver (1.6x), kidneys (1.4x), and adrenals (1.6x) were increased. Thymus weights were reduced (0.6x). The ovarian (1.4x) and pituitary (0.9x) weights were affected in females. Plasma glucose was reduced (0.7x) and ALT slightly increased (up to 1.8x). Histopathological changes were noted in the heart (hypertrophy of the myocardium), liver (hepatocellular hypertrophy), kidneys (basophilic tubules), salivary glands (hypertrophy), thymus (apoptosis), adrenals (hypertrophy), ovaries (increased number of corpora lutea), stomach (erosion) and intestine. As the findings were seen in a comparable grading in all groups receiving 800 mg/kg/day metformin alone or in combination with linagliptin, all adverse effects were attributable to metformin. This also indicates that there was no enhancement of metformin-related toxicity, which is caused by the co-administration of linagliptin.

The only observed interaction between linagliptin and metformin was related to body weight gain. The decrease of body weight gain induced by metformin was magnified by linagliptin. At 800 mg/kg/day metformin the terminal body weight was 0.9x relative to control. Co-administration of 4.0 mg/kg/day linagliptin enhanced this effect to 0.8x relative to control. This effect is considered not adverse but rather an additive pharmacodynamic effect of the two anti-diabetic compounds.

Linagliptin/metformin at 2.0/400 mg/kg/day also decreased body weight gain (terminal body weight 0.9x control). In addition, similar effects on organ weights and histology described for the animals at 0/800, 2.0/800 and 4.0/800 mg/kg/day were seen but at a lower degree.

In conclusion, a NOAEL for linagliptin/metformin of 0.5/100 mg/kg/day (1.0x MRHD for linagliptin, 1.4x MRHD for metformin) was derived. All adverse findings seen in the study were attributed to metformin. The only combination effect attributable to the linagliptin/metformin combination itself was related to body weight gain. There was no enhancement of metformin-related organ toxicity due to the co-administration of linagliptin.

Genotoxicity

Linagliptin

Table 6. Overview of genotoxicity studies

Type of test/study ID/GLP	Test system	Concentrations/ Concentration range/ Metabolising system	Results Positive/negative/ equivocal
Gene mutations in bacteria U04-1756 batch 8460060 GLP	*S. typhimurium* TA98, 100, 102, 1535, 1537	100 to 5000 µg/plate +/- S9	Negative
Chromosome aberration assay U04-1827 batch 8460060 GLP	Human lymphocytes	10 to 1000 µg/mL +/- S9	Negative
Chromosomal aberrations *in vivo* (part of 4-week toxicity studies in rats) U04-1847 batch 8460060 GLP	Micronuclei in bone marrow of rats	6, 60 and 600 mg/kg/day	Negative
Main metabolite CD 1790 (tested as racemate CD 1750):			
Gene mutations in bacteria U06-1188 batch PAC01750A1 GLP	*S. typhimurium* TA98, 100, 102, 1535, 1537	30 to 3000 µg/plate +/- S9	Negative
Gene mutations in bacteria U07-2080 batch PR4PAC01750A1 GLP	*S. typhimurium* TA98, 100, 102, 1535, 1537 Preincubation repeat	30 to 3000 µg/plate +/- S9	Negative
Chromosomal aberration assay U06-1585 batch PAC01750A1 GLP	Human lymphocytes	30 to 1000 µg/mL +/- S9	Negative

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.

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 level of CD 1790 was about 3-5% compared to the parent compound linagliptin based on AUC. In the rat bone marrow micronucleus test, 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.

Metformin

The Ames test, gene mutation test (mouse lymphoma cells), chromosomal aberrations test (human lymphocytes) and *in vivo* mouse micronucleus tests were negative with metformin.

Linagliptin/metformin

No genotoxicity studies have been performed for the combination linagliptin/metformin which is considered acceptable by the CHMP.

Carcinogenicity

Linagliptin

Table 7. Two-year carcinogenicity studies with linagliptin

Study ID /GLP	Dose/Route	Exposure (AUC, nM.h)	Species/No. of animals	Major findings
U10-1500 batch 5060170 GLP	0, 8, 25, 80 mg/kg/day Oral gavage	8: 767 25: 5180 80: 38300	CD-1 mouse M+F/60	80F: Malignant lymphoma (probably insignificant)
U10-1502 batch 5060170 GLP	0, 6, 18, 60 mg/kg/day Oral gavage	6: 1520 18: 8070 60: 66100	Wistar rat M+F/55	60: Phospholipidosis in lung

In a 2-year carcinogenicity mouse study, linagliptin did not induce carcinogenic effects, except for a significant increase in malignant lymphomas in females at 80 mg/kg/day (242x MRHD for linagliptin, 27x MRHD for metabolite CD 1790). This was attributed to a high background of lymphomas in mice, and because linagliptin is not genotoxic, lymphoid hyperplasia in spleen and thymus was not increased in female mice, exposure in females was lower than in males, and occurred only at a very high dose, 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.

Metformin

Long-term carcinogenicity studies with metformin have been performed in Sprague Dawley rats at doses of 150, 300, and 450 mg/kg/day in males and 150, 450, 900, 1200 mg/kg/day in females. These doses were approximately 2, 4, and 8 times in males, and 3, 7, 12, and 16 times the therapeutic exposures based AUC values with the maximum recommended human daily dose of 2000 mg/kg/day. No evidence of carcinogenicity with metformin was found in neither male nor female rats.

Linagliptin/metformin

The fixed dose combination of linagliptin/metformin contains two compounds assessed as non carcinogenic. The carcinogenic potential is thus fully assessed. Hence other studies assessing carcinogenic potential with the combination are not needed in accordance with the requirements of the "Guideline on the Non-Clinical Development of Fixed Combinations of Medicinal Products "(EMEA/CHMP/SWP/258498/2005).

Reproduction Toxicity

Table 8. Reproductive toxicity studies with linagliptin, metformin and linagliptin/metformin

Study type/ Study ID / GLP	Species; Number / group	Route & dose, mg/kg/day	Dosing period	Major findings	NOAEL (mg/kg &AUC, nM.h)
Linagliptin					
Male and female fertility, embryo-fœtal development U06-2047	Rat M+F/24	Oral gavage 0, 10, 30, 240	M: 29 days before mating F: 15 days before mating till GD6	240: Salivation, decrease of weight gain, food consumption decrease	30 (parental toxicity) 240 (fertility, embryonic development)
Embryo-fœtal development U05-2124	Rat F/10	Oral gavage 0, 6, 60, 600	GD 7-16	600: Maternal toxicity (decrease of body weight gain, food consumption decrease Resorption, sedation, salivation, bloody vagina) Hysterectomy: 60: Ossification delay 600: Fetal body weight decrease, Malformations increase	Not derived
Embryo-fœtal development U06-1637	Rat F/24	Oral gavage 0, 10, 30, 240	GD 7-16	240: Maternal toxicity (body weight gain, food consumption decrease) Hysterectomy: 240: Resorption rate increase, Skeletal ossification decrease, Rib anomalies increase	30 AUC: 7710
Embryo-fœtal development U05-2449	Rabbit F/6	Oral gavage 0, 100, 200, 300 In addition: 1F 400, 600 2F 600	GD 6-18	200: Body weight gain decrease ≥300: Maternal death Hysterectomy: 100: Complete resorptions 300: Malformations increase	Not derived
Embryo-fœtal development U06-1200	Rabbit F/16-18	Oral gavage 0, 4, 25, 150	GD 6-18	≥25: Body weight gain decrease 150: Food consumption decrease Hysterectomy: 150: Intrauterine death and runts, variations increase	Maternal toxicity: 4 AUC: 339 Embryo-foetal toxicity: 25 AUC: 12400

Study type/ Study ID / GLP	Species; Number / group	Route & dose, mg/kg/day	Dosing period	Major findings	NOAEL (mg/kg &AUC, nM.h)
Peri & postnatal U07-1558	Rat F/24	Oral gavage 0, 10, 30, 300	GD 6 – LD 21	F0: 300: Maternal toxicity (Salivation, body weight decrease, Food consumption decrease, Post-implantation loss increase) F1: 300: Body weight decrease, Delayed descensus testes, delayed preputial separation	30
Metformin					
Embryo-fœtal development U10-2386 GLP	Rat 24	Oral gavage 0, 200, 500, 1000	GD7-16	**500 mg/kg:** Maternal findings: Body weight gain ↓, Blood glucose on GD 7↓ Hysterectomy: Ossification delays + malformations ↑ **1000 mg/kg:** Maternal findings: Body weight gain ↓, blood glucose ↓ on GD 7, blood glucose ↑ on GD 16 Hysterectomy: Ossification delays + malformations ↑ Unilateral anophthalmia, + polydactylia	Embryo-fetal: **200** (4 x MRHD) AUC(0-24h) on GD 7: 377000 (nmol•h)/L AUC(0-24h) on GD 16: 638000 (nmol•h)/L
Linagliptin/metformin					
Embryo-fœtal development U10-2448 GLP	Rat 24	Oral gavage 0/0 1.0/200 2.5/500 5.0/1000 2.5/1000 5.0/0 0/1000	GD7-16	**1.0/200 mg/kg:** Maternal findings: Body weight gain ↓ **2.5/500 mg/kg:** Maternal findings: Body weight gain ↓, blood glucose ↓ on GD 7 Hysterectomy: Ossification delays + malformations ↑ **0/1000, 2.5/1000 and 5.0/1000 mg/kg:** Maternal findings: Body weight gain ↓, blood glucose ↓ on GD 7 Hysterectomy: Ossification delays + malformations ↑ **5.0/0 mg/kg:** No findings	Embryo-fetal: **1/200** (1.5x/ 3.3x MRHD) Mean AUC(0-24h): 238/528 nM·h/µM·h

Fertility and early embryonic development

Linagliptin

In rat studies on fertility and early embryonic development, a NOAEL of 30 mg/kg/day (49x MRHD) was derived for paternal and maternal toxicity. No effects on early embryonic development, mating, fertility and bearing live young were observed up to and including the high dosage group given 240 mg/kg/day (943x MRHD).

Metformin

Fertility of male or female rats was not affected by metformin when administered at dose up to 600 mg/kg/day, which is approximately 3 times the maximum recommended human daily dose based on body surface area comparisons.

Linagliptin/metformin

No fertility and early embryonic development studies have been performed for the combination linagliptin/metformin which is considered acceptable by the CHMP.

Embryo-foetal development

Linagliptin

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).

Metformin

Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day, which represent 3 and 6 times the maximum recommended human daily dose of 2000 mg based on body surface area comparison for rats and rabbits, respectively.

Maternal findings: data from GD 7 demonstrated a trend for dose related decrease of glucose levels 4, 8 and 24 h after treatment with doses of 500 mg/kg and 1000 mg/kgThe data from GD 16 did not provide an indication for a trend to changed glucose levels in the 200 and 500 mg/kg dose groups at any time point. In the 1000 mg/kg dose group mean body weight during treatment period fluctuated on a slightly lower level than in the Control group. Mean body weight gain of the 200, 500 and 1000 mg/kg dose groups was decreased.Fetal data: In the viscera shortened truncus brachiocephalicus and small kidney at 1000 mg/kg were seen. The skeleton showed delayed ossification indicating developmental retardation. Most variations occurred at 1000 mg/kg and three (parietal bone partly not ossified, orbitosphenoidal bone not ossified and calcaneus not ossified) at 500 mg/kg. At 1000 mg/kg split sternebra lateral axis, flat and thickened rib (unilateral and bilateral), and rib z-shaped (bilateral) as well as single unilateral anophthalmia and single unilateral polydactylia were seen. Flat and thickened rib (bilateral) were also seen at 500 mg/kg. Scapula bent inwardly at 500 and 1000 mg/kg at increased incidence and in all cases in combination with flat and thickened rib. At 1000 mg/kg additionally combination with rib z-shaped was seen.

Linagliptin/metformin

The exposure to linagliptin increased less than proportionally with the dose between 1 and 5 mg/kg linagliptin. The AUC_{0-24h} of metformin increased dose proportionally on GD 7 and more than proportionally on GD 16. The mean exposure to metformin on GD 16 at 5/1000 mg/kg/day was about 30 % higher than at 0/1000 mg/kg/day.

Treatment with linagliptin alone showed no changes in blood glucose levels. In contrast, reduction of blood glucose concentrations (up to 0.6x relative to control) was noted at all exposures to formulations containing 500 and 1000 mg/kg metformin.

In all dose groups treated with 1000 mg/kg/day metformin alone or in combination with linagliptin, means of body weight gain were significantly decreased. In the metformin mono group (0/1000 mg/kg/day), this effect was less pronounced than in the 2.5/1000 and 5/1000 mg/kg/day linagliptin/metformin combination groups. This indicates an additive pharmacodynamic effect on body weight gain induced by the administration of the two antidiabetic compounds.

Findings at hysterectomy: There was no effect on the mean number of corpora lutea, implantations, viable fetuses, resorptions as well as fetal sex and group means of preimplantation loss and resorption rate. Mean fetal body weight was significantly decreased in the 5/1000 mg/kg/day linagliptin/metformin dose group, but the individual weights were still within the spontaneous historical range. In some fetuses with ossification delay in the groups given 2.5/1000 and 0/1000 mg/kg/day linagliptin/metformin, individual fetal body weights were slightly decreased. Most skeletal variations seen at 1000 or 500 mg/kg/day metformin alone or in combination with linagliptin were ossification delays pointing to developmental retardation which is regularly balanced during later development.

At a dosage of 1000 mg/kg/day metformin given alone or in combination with linagliptin (animals dosed with linagliptin/metformin at 0/1000, 2.5/1000 and 5.0/1000 mg/kg/day, associated with 23.1x, 24.1x and 30.3x MRHD for metformin), skeletal malformations (cleft thoracal vertebral body, flat and thickened rib and scapula bent inwardly, thickened rib, rib zshaped) were observed. Most skeletal malformations and findings without classification occurred at lower incidences than in the 1000 mg/kg/day metformin mono group of the associated embryo-foetal development study. All treatment related adverse effects on the embryo were attributed to the administration of 1000 mg/kg/day metformin and there was no indication of an additive teratogenic effect attributed to the co-administration of 2.5 or 5.0 mg/kg/day linagliptin. One single visceral malformation, hydronephrosis, was diagnosed in the linagliptin/metformin group given 5.0/1000 mg/kg/day. The relationship to treatment is uncertain. Incidences of treatment related changes in the linagliptin/metformin group given 2.5/500 mg/kg/day were low. The comparison of this group with the 500 mg/kg/day metformin mono group of the associated embryo-foetal study did not reveal any differences which would suggest an additive adverse effect of linagliptin. No relevant foetal alterations and no teratogenicity occurred in animals dosed with linagliptin/metformin at a dosage of 1.0/200 mg/kg/day and this combination dosage was considered to be the NOAEL (1.5x MRHD for linagliptin, 3.3x MRHD for metformin). As mentioned previously, dosages of 500 or 1000 mg/kg/day metformin (given alone or in combination with linagliptin) affected blood glucose levels. No effect on blood glucose was seen at 200 mg/kg/day metformin. Therefore, dysglycemia and foetal morphological changes induced by metformin may be connected. No relevant fetal alterations and no teratogenicity occurred in the linagliptin mono group given 5 mg/kg/day (3.0x MRHD).

There were no embryo-toxic findings, which were related to linagliptin. There was no indication of an additive or even synergistic teratogenic effect of both compounds.

Prenatal and postnatal development, including maternal function

Linagliptin

In the pre- and postnatal development study, the NOAELs for maternal and offspring toxicity were 30 mg/kg/day (49x MRHD). Linagliptin produced maternal toxicity 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. However, the offspring's fertility was not changed.

Toxicokinetic studies in pregnant rats and rabbits showed that linagliptin and the main metabolite CD 1790 crosses the placenta and is distributed into the embryo and fetus. Linagliptin was also shown to be excreted into maternal milk.

Metformin

Animal data of excretion of metformin in milk was not provided, but it has been found that metformin is excreted in human milk. The concentrations of metformin in breast milk were generally low and the mean infant exposure to the drug was only 0.28% of the weight-normalized maternal dose. No data regarding pre- and postnatal development after metformin administration are available.

Linagliptin/metformin

No prenatal and post-natal development studies have been performed for the combination linagliptin/metformin which is considered acceptable by the CHMP based on the data available on both compounds

Local Tolerance

Linagliptin

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.

Metformin

No local tolerance studies have been performed with metformin. As Jentadueto is only intended for oral use this is considered acceptable by the CHMP.

Linagliptin/metformin

No local toterance studies have been performed for the combination linagliptin/metformin which is considered acceptable by the CHMP.

Other toxicity studies

Immunotoxicity

Linagliptin

All relevant toxicity studies for linagliptin have been performed. Antigenicity/immunotoxicity measurements were included in toxicological studies and no cause for concern was identified.

Metformin

No antigenic / immunotoxicity potential is known for metformin.

Linagliptin/metformin

In accordance with the "Note for Guidance on Immunotoxicity Studies for Human Pharmaceuticals" (CHMP/167235/2004), no additional information is considered necessary for the fixed dose combination linagliptin/metformin as the individual components show no cause for concern.

Studies on impurities

Linagliptin

In the proposed drug substance specification, the acceptance criteria of the linagliptin impurities were set at levels above the qualification threshold. These impurities were qualified before in general toxicity, carcinogenicity and genotoxicity studies, and found negative.

In the proposed drug product specification, the acceptance criteria of a degradation product of linagliptin, was set at a level above the identification threshold. Although formally not needed, toxicity studies were performed to demonstrate the biological safety of this degradation product.

Overview of new genotoxicity studies of a degradation product

Type of test/study ID/GLP	**Test system**	**Concentrations/ Concentration range/ Metabolising system**	**Results Positive/negative/ equivocal**
Gene mutations in bacteria U10-1029 GLP	*S. typhimurium* TA98, 100, 102, 1535, 1537	10 to 1000 µg/plate +/- S9	Negative
Chromosome aberration assay U10-1648 GLP	Human lymphocytes	10 to 200 µg/mL +/- S9	Negative

The new gene mutation study of the degradation product caused neither base-pair substitutions nor frameshift mutations in different strains of S. typhimurium in the presence and absence of metabolic activation when tested up to insoluble concentrations. Based on these results it was concluded, that the test substance is "Ames negative".

The degradation product, using the chromosomal aberration test in human lymphocytes *in vitro*, did not induce an increase in the number of structural and numerical chromosomal aberrations when tested up to cytotoxic and insoluble concentrations in the presence and absence of metabolic activation. Based on these results it was concluded, that the test substance is negative in this chromosomal aberration test.

In a 13-week toxicity study in the rat, the degradation product was spiked in at a concentration of 2.93%. The NOAEL derived in the study was 0.5 mg/kg/day linagliptin and a safety margin to human use of 35 for the degradation product was derived.

Metformin

For metformin hydrochloride, the Applicant makes reference to a CEP from the manufacturer of metformin hydrochloride. Metformin hydrochloride used for the manufacture of linagliptin/metformin hydrochloride film coated tablets is released in accordance with the Ph. Eur. monograph as well as the CEP. There were no impurities in Meformin DS or DP which had to be qualified.

2.3.5. Ecotoxicity/environmental risk assessment

The Environmental Risk Assessment (ERA) submitted for Jentadueto was prepared in compliance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00). The two active substances linagliptin and metformin have been assessed separately. Predicted environmental concentrations exceeded the threshold value of 0.01 µL, triggering a Phase II – Tier A for both active substances.

Linagliptin

A Phase I environmental risk assessment was performed to evaluate potential environmental risks of linagliptin. The log K_{ow} was determined according to study OECD 122 with a value of 1.7. Based on the log K_{ow} value being below 3, linagliptin is not expected to be a bio-accumulative substance. 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 below).

Table 9. 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. Thus, an extended environmental fate and effects analysis for the three compartments in Tier B is not considered to be necessary.

Since the log K_{ow} of the undissociated compound was determined to be below 3, linagliptin is considered to have no potential to bio-accumulate. Therefore, bio-concentration 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 Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00). 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.

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

Table 10. Summary of main study results

Substance (INN/Invented Name): Linagliptin					
CAS-number (if available): 668270-12-0					
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			potentially P
Toxicity	NOEC or CMR	3.2 mg/L			not T
PBT-statement :	The compound is not considered PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default	0.025	µg/L			> 0.01 threshold
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	Mean of 3 soils: Koc = 19234 L/kg Kd = 286 Mean of 2 sludges: Koc = 726 L/kg 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	4.1 49	mg/L mg/L	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	

Metformin

A Phase I environmental risk assessment was performed to evaluate potential environmental risks of metformin. The log K_{ow} was determined according to study OECD 107 with a value of 1.1 at pH 7. Based on the log K_{ow} value being below 4.5, metformin is not expected to be a bio-accumulative substance. Using the default F_{pen} and the maximum daily dose to be given in humans of 2000 mg of metformin (corrected for molar mass of hydrochloride), a $PEC_{surface\ water}$ of 7.8 µg/L was calculated.

In conclusion of the OECD 308 study, metformin dissipated rapidly from the water phase via adsorption to the sediment. Additionally, metformin rapidly degraded via the formation of several minor or transient degradation products to CO_2. On the basis of the distribution of total radioactivity between the water phase (overlying plus pore water) and the sediment (extractable and nonextractable), K_d-values for sediment can be calculated for each sampling date. From day 1 to day 7, a period with little initial degradation and with levels of about 50% of the applied radioactivity in water and around 50% in sediment, Kd values of in maximum 7.2 (river) and 6.9 (pond) were obtained. These are in line with the low values determined for soil in the adsorption test.

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 metformin. Therefore, effects on sediment organisms were considered in Tier B and a toxicity study on chironomids was conducted.

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 metformin. Therefore, effects on sediment organisms were considered in Phase II 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.

Table 11. PEC/PNEC assessments

Environmental compartment	PEC µg/L	PNEC µg/L	PEC/PNEC	Trigger value	Conclusion
Surface water	7.80	≥ 1,000	≤ 7.7×10^{-3}	1	no risk
Groundwater	1.95	1,700	1.1×10^{-3}	1	no risk
STP*	7.80*	11,000	7.1×10^{-4}	0.1	no risk
Sediment	53.9 µg/kg	1250 µg/kg	4.3×10^{-2}	1	no risk

*EMEA guidance has lowered the trigger value for the STP risk quotient (from 1 to 0.1) rather than calculating a separate PEC_{STP}. In this case, PEC_{STP} equals $PEC_{surface\ water}$.

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

Table 12. Summary of main study results

Substance (INN/Invented Name): metformin					
CAS-number (if available): 657-24-9					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	shake flask	log D_{ow} = -1.1 (pH 7.4)			Potential PBT: No
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	log D_{ow} = -1.1 at pH 7.4			not B
	BCF	not determined			
Persistence	DT50 or ready biodegradability	not ready			
		DT50 water: 9.2 (river) and 7.9 (pond) days. DT50 total system: 22.0 (r) and 22.3 (p) days. At the end of the study (day 79), 7.5% of applied radioactivity (AR) was remaining as parent compound in the total pond system, and in the river system the parent metformin was not observed any longer.			OECD 308
Toxicity	NOEC or CMR	N.A.			
PBT-statement :	metformin is not PBT, nor vPvB.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default F_{pen}	7.8 (metformin base)	µg/L			> 0.01 threshold: Y
Other concerns (e.g. chemical class)	unknown				unknown
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} =4.8 and 7.5 L/kg			2 sludges, based on K_d
	OECD 106	K_{oc} =283, 2056 and 3209 L/kg			3 soils; based on K_d
Ready Biodegradability Test	OECD 301	not ready			public literature
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	DT50 water: 9.2 (river) and 7.9 (pond) days DT50 total system: 22.0 (r) and 22.3 (p) days At the end of the study (day 79), 7.5% of applied radioactivity (AR) was remaining as parent compound in the total pond system, and in the river system the parent metformin was not observed any longer.			2 sediments
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
All toxicity test results expressed as mg metformin base / L					
Algae, Growth Inhibition Test *P. subcapitata*	OECD 201	NOEC	≥ 78	mg/L	
Daphnia sp. Reproduction	OECD 211	NOEC	17	mg/L	21 d mortality,

Test *D. magna*					reproduction
D. magna	OECD 211	LC50	38	mg/L	21 d mortality
D. magna	OECD 211	LC100	55	mg/L	21 d mortality
Fish, Early Life Stage Toxicity Test *D. rerio*	OECD 210	NOEC	≥ 10	mg/L	Result valid for hatching rate, time to hatch, surivival, length and weight.
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10	110	mg/L	EC50>1000 mg/L
Phase IIb Studies					
Sediment dwelling organism	OECD 218	NOEC	125	mg/kg	TOC 2.4%

2.3.6. Discussion on non-clinical aspects

The combination of the glucose-dependent insulin secretagogue linagliptin with the insulin sensitizing drug metformin is considered a good principle for diabetes therapy in patients with type 2 diabetes. An additive effect on glucose reduction of linagliptin and metformin was shown in a mouse disease model for diabetes (diabetic *db/db* mice). There was no relevant pharmacokinetic interaction between metformin and linagliptin.

As shown in the linagliptin non-clinical development program, signs of linagliptin-related toxicity occurred at doses far in excess of those recommended for therapy. In the 2-week and 13-week toxicity studies in the rat, the liver, kidneys, thyroid, lymphoid organs and lungs were identified as target organs of toxicity. In the 2-week rat toxicity study, no adverse findings were seen up to 100 mg/kg/day (associated with an AUC0-24h,ss of 291 times human AUC0-24h,ss at the MRHD = 291x MRHD). In the 13-week rat toxicity study a NOAEL of 30 mg/kg/day (95.6x MRHD) was derived. Linagliptin was not teratogenic in rats up to and including a dosage of 240 mg/kg/day (943x MRHD).

Metformin-related toxicity in the rat was observed in the heart, liver, kidneys, salivary glands, ovaries, thymus, gastrointestinal tract (stomach, small and large intestine) and adrenal glands at dosages associated with an exposure of 7.4x MRHD or higher. In addition, body weight gain was reduced. A NOAEL of 200 mg/kg/day (2.4x MRHD) was derived in the 2-week rat toxicity study. Metformin was not teratogenic and not embryotoxic in the rat at a dosage of 200 mg/kg/day (4.0x MRHD). Teratogenicity of metformin in the rat was observed at 500 mg/kg/day (10.9x MRHD, beginning effects) and 1000 mg/kg/day (23.2x MRHD). At these dosages, blood glucose levels were affected and dysglycaemia and fetal morphological changes induced by metformin in the rat may be connected.

In all linagliptin/metformin toxicity studies, linagliptin and metformin were tested in clinical relevant dose ratios of 1:200 and 1:400. In the general toxicity studies, the only observed interaction between linagliptin and metformin was a reduction of body weight gain. This effect is considered not adverse but rather an additive pharmacodynamic effect of the two antidiabetic compounds. In the 13-week combination toxicity study in the rat, a NOAEL for linagliptin/metformin of 0.5/100 mg/kg/day (1.0x MRHD for linagliptin, 1.4x MRHD for metformin) was derived based on metformin related findings. All adverse findings in the combination studies were attributed to metformin at dosages of 400 mg/kg/day (7.4x MRHD) or higher and no linagliptin related toxicity was observed. There was no indication of a teratogenic effect attributable to the co-administration of linagliptin and metformin. The individual compounds were shown to be not genotoxic and not carcinogenic.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical developmental plan of the combination linagliptin/metformin was limited to necessary studies. This is considered acceptable. The available non-clinical data including the results obtained from the repeat dose toxicity and reproduction toxicity studies with Jentadueto and the environmental risk assessment did not identify any new safety issues. The non-clinical safety profile of linagliptin/metformin appears to be consistent with those established for linagliptin and metformin when used as monotherapy. Based on the available non-clinical safety data with the two monotherapy compounds, linagliptin and metformin, it is concluded that the FDC should be well tolerated when used in human at the proposed dosage.

2.4. Clinical aspects

The Applicant is seeking a Marketing Authorisation for linagliptin/metformin film-coated tablets as an adjunct to diet and exercise to improve glycaemic control in adult patients inadequately controlled on their maximal tolerated dose of metformin alone, or those already being treated with the combination of linagliptin and metformin, also in combination with a sulphonylurea (i.e. triple combination therapy) in patients inadequately controlled on their maximum tolerated dose of metformin and a sulphonylurea. For patients switching from co-administration of linagliptin and metformin, Jentadueto should be initiated at the dose of linagliptin and metformin already being taken. The recommended starting dose of Jentadueto for patients inadequately controlled on dual combination therapy with the maximal tolerated dose of metformin and a sulphonylurea is 2.5 mg of linagliptin twice daily (5 mg total daily dose) and a dose of metformin similar to the dose already being taken. When linagliptin plus metformin is used in combination with a sulphonylurea, a lower dose of the sulphonylurea may be required due to the risk of hypoglycaemia. For the different doses of metformin, Jentadueto is available in strengths of 2.5 mg linagliptin plus 850 mg metformin hydrochloride and 2.5 mg linagliptin plus 1,000 mg metformin hydrochloride.

The clinical development program of Jentadueto was designed to demonstrate the safety and efficacy of linagliptin, metformin and linagliptin/metformin as FDC in patients with T2DM. No dedicated studies with metformin as monotherapy were conducted. The pharmacokinetics, safety, and efficacy profiles of metformin as monotherapy are well known. The clinical development programs for linagliptin and linagliptin/metformin are presented in table 14 and 15..

Scientific advice was provided by the CHMP in September 2008 (EMEA/CHMP/SAWP/ 472394/2008) on the clinical aspects of the development program. The CHMP requested a clinical study to show equivalence of twice daily dosing of linagliptin 2.5 mg with once daily dosing of linagliptin 5 mg. This study was subsequently conducted by the Applicant and its results are presented in this Marketing Authorisation application. The advice given has been followed in all essential parts.

2.4.1. Introduction

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.

Table 13. Linagliptin clinical development program

Study number	Type of study	Test and reference products; dosage regimen	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-100mg: 44	Moxifloxacin 400mg	HS
Phase II studies					
1218.5	Eff/Safety	3 lina doses vs PBO vs met	0.5-5mg:170	PBO: 67 Met 2000mg: 65	T2DM
1218.6	Eff/Safety	lina vs PBO vs glim	1mg-10mg:	PBO: 71	T2DM

			197	Glim 1-3mg: 65	
1218.37	Eff/Safety	lina vs sita vs PBO	5mg: 40	Sita 100mg: 41 PBO: 40	T2DM
Phase III studies					
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)
	1218.16	Lina vs. PBO	503 (100.0)	167 (33.2)	336 (66.8)
	1218.17	Lina + Met vs. Met	701 (100.0)	177 (25.2)	524 (74.8)
	1218.18	Lina + Met + SU vs. Met + SU	1058 (100.0)	265 (25.0)	793 (75.0)
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)
Additional double-blind placebo-controlled efficacy studies, 18 weeks	1218.35	Lina + SU vs. SU	245 (100.0)	84 (34.3)	161 (65.7)
	1218.50	Lina vs. PBO (in metformin-intolerant patients)	227 (100.0)	76 (33.5)	151 (66.5)
Double-blind efficacy studies with more than one linagliptin dose level (EFF-10)	1218.5	Lina vs. PBO vs. Met*	302 (100.0)	67 (22.2)	55 (18.2)[f]
	1218.6	Lina vs. PBO vs. SU*	333 (100.0)	71 (21.3)	66 (19.8)[g]
	1218.23[c]	Lina vs. PBO vs. Vog	561 (100.0)	80 (14.3)	159 (28.3)[h]
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]
Overall total			5879 (100.0)	1117 (19.0)	3872 (65.9)

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, 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

Table 14. Linagliptin/metformin clinical development program

study number	Objectives Study	Number of subjects	Test and referenc products; dosage regimen	type of study
Phase 1 Studies: Healthy Subjects				
1288.1	To investigate bioequivalence of Lina/Met vs. Lina + Met	96 (95 completed)	-Lina 2.5 mg/Met 1000 mg vs -Lina 2.5 mg+ Met 1000 mg	BE
1288.2	To investigate bioequivalence of Lina/Met vs. Lina + Met	95 (94 completed)	-Lina 2.5 mg/Met 500 mg vs -Lina 2.5 mg+Met 500 mg	BE
1288.3	To investigate bioequivalence of Lina/Met vs. Lina + Met	95 (94 completed)	-Lina 2.5 mg/Met 850 mg vs -Lina 2.5 mg+Met 850 mg	BE
1288.4	To investigate the effect of food on PK of Lina/Met	32	Lina 2.5 mg/Met 1000 mg with and without food	BE
1218.4	To investigate the relative bioavailability of linagliptin and metformin when administered together compared with the bioavailability of linagliptin and metformin when administered alone	16	-Metformin tablet 850 mg (3 doses) vs-Metformin tablet 850 mg (3 doses) + Linagliptin tablet 10 mg (steady state)	PK
1218.45	To compare 2.5 mg linagliptin twice daily (bid) and 5 mg linagliptin once daily (qd)	16	2.5 mg linagliptin bid vs 5 mg linagliptin qd	PK/PD
1218.47	To investigate relative bioavailability of Lina/Met vs. Lina + Met	20	-Lina 2.5 mg/Met 1000 mg vs-Lina 2.5mg+Met 1000 mg	BA
1218.57	To investigate bioequivalence of European and US Glucophage® reference product	56	EU Glucophage US Glucophage 500mg and 1000mg	BE
Phase 2 Studies: Patients with T2DM				
1218.6	To investigate efficacy and safety of 3 linagliptin doses in comparison with placebo; to explore the efficacy of glimepiride in comparison with placebo for sensitivity analysis	Total: 333 -Lina 1mg: 65 -Lina 5 mg: 66 -Lina 10 mg: 66 -Placebo: 71 -Glim: 65	Linagliptin tablets 1mg, 5 mg, 10 mg Placebo tablet, glimepiride tablets	Efficacy and Safety
1218.62	To investigate the influence of different dosage regimens (twice daily versus once daily versus placebo) on the efficacy and safety of linagliptin administered orally as add-on therapy to metformin.	Total: 491 -Lina 2.5 mg bid: 223 -Lina 5 mg qd: 224 Placebo 44	-Linagliptin 2.5 mg bid, -Linagliptin 5 mg qd, - Placebo	Efficacy and Safety
Phase 3 Studies: Patients with T2DM				
1218.17	To evaluate efficacy and safety of 5 mg linagliptin in comparison with placebo as add-on therapy to metformin	Total: 701 Lina: 524 Placebo: 177	-Linagliptin tablet 5mg -Placebo tablet	Efficacy and Safety
1218.18	To evaluate efficacy and safety of 5 mg linagliptin in comparison with	Total: 1058 Lina: 793 Placebo:	-Linagliptin tablet 5mg -Placebo tablet	Efficacy and Safety

	placebo as add-on therapy to metformin in combination with a sulphonylurea (SU) drug	265		
1218.20	To evaluate efficacy and safety of 5 mg linagliptin in comparison with glimepiride as add-on therapy to metformin	Total: 1551 Lina: 776 Glim*: 775	-linagliptin tablet 5mg -Glimepiride tablet 1 -4 mg	Efficacy and Safety
1218.46	To investigate efficacy and safety of twice daily dosing of Lina + Met combination therapy compared to Lina or Met monotherapy	Total: 791 Lina 2.5 g + Met 500 mg: 143 Lina 2.5 mg + Met 1000 mg: 143 Pbo: 72 Lina 5 mg 142 Met 500 mg 144 Met 1000 mg 147	-Lina 2.5 mg + Met 500 mg bid -Lina 2.5 mg + Met 1000 mg bid -Pbo -Lina 5 mg qd -Met 500 mg bid -Met 1000 mg bid -Lina 2.5 + Met 1000 mg bid (open-label for poorlycontrolled patients)	Efficacy and Safety
	Ongoing Extension Studies			
1218.40	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 an SU drug; Furthermore to assess efficacy in a descriptive exploratory way	Total: 2122 Lina 5mg: 2122	-Linagliptin tablet 5mg	Long term Safety
1218.52	To evaluate the efficacy and safety of Lina + Met over 54 weeks in patients who completed Study 1218. 46 (without rescue medication)	Total: 567 Lina 2.5 mg +Met 500 mg: 225 Lina 2.5 mg + Met 1000 mg: 171 Met 1000 mg:171	-Lina 2.5 mg +Met 500 mg bid -Lina 2.5 mg + Met 1000 mg bid -Met 1000 mg bid	Long term Safety

2.4.2. Pharmacokinetics

Although this application concerns a fixed dose combination (FDC) tablet, most clinical studies supporting the application were conducted with separate tablets of linagliptin 2.5 mg and metformin (Glucophage 1000 mg, 500 mg and 850 mg tablets). Therefore the Applicant performed three bioequivalence studies (1288.1, 1288.2 and 1288.3) to justify the extrapolation of the results of the studies conducted with the mono components to the FDC tablets. Furthermore, the applicant conducted one bioequivalence study with the European and US metformin reference products. In addition, study 1218.45 was conducted to characterize the pharmacokinetics and pharmacodynamics of 2.5 mg linagliptin twice daily, in order to support BID dosing of linagliptin in combination with metformin.

Plasma and urine concentrations of linagliptin and its metabolite CD 1790 were measured using specific and highly sensitive HPLC-MS/MS methods. Plasma concentrations of metformin were measured using validated liquid chromatography tandem mass spectrometry (LC-MS/MS) bioanalytical methods. Analytical methods for linagliptin and metformin were well described and validated.

For the statistical analysis of bioequivalence studies two different methods were used. The initial analysis included all subjects who had been dispensed study medication, the treated set. The second analysis was a sensitivity analysis using a per protocol set for evaluation of Bioequivalence (PPS-BE set), the PPS-BE set complies with the current Guideline on the the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev1). In this document he ratio of the geometric means of T/R of the PPS-BE set are presented.

Absorption

Bioavailability

Linagliptin

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). *In vitro* data in Caco-2 cells indicated that linagliptin is a substrate for P-gp. After once-daily dosing, steady-state plasma concentrations of 5 mg linagliptin are reached by the third dose. Plasma AUC of linagliptin increased approximately 33% following 5 mg doses at steady-state compared to the first dose

Metformin

The absolute bioavailability of a metformin 500 -850 mg tablet given under fasting conditions is approximately 50% to 60%.

Linagliptin/metformin

In study 1218.47 the relative oral bioavailability of a pilot scale fixed dose combination (FDC) tablet of linagliptin 2.5 mg/metformin 1000 mg, was compared with single linagliptin 2.5 mg and metformin 1000 mg tablets administered together to 20 healthy male and female subjects. The pharmacokinetic properties of these pilot scale tablets were similar to the properties of the single linagliptin and single metformin tablets given in combination.

Bioequivalence

Linagliptin

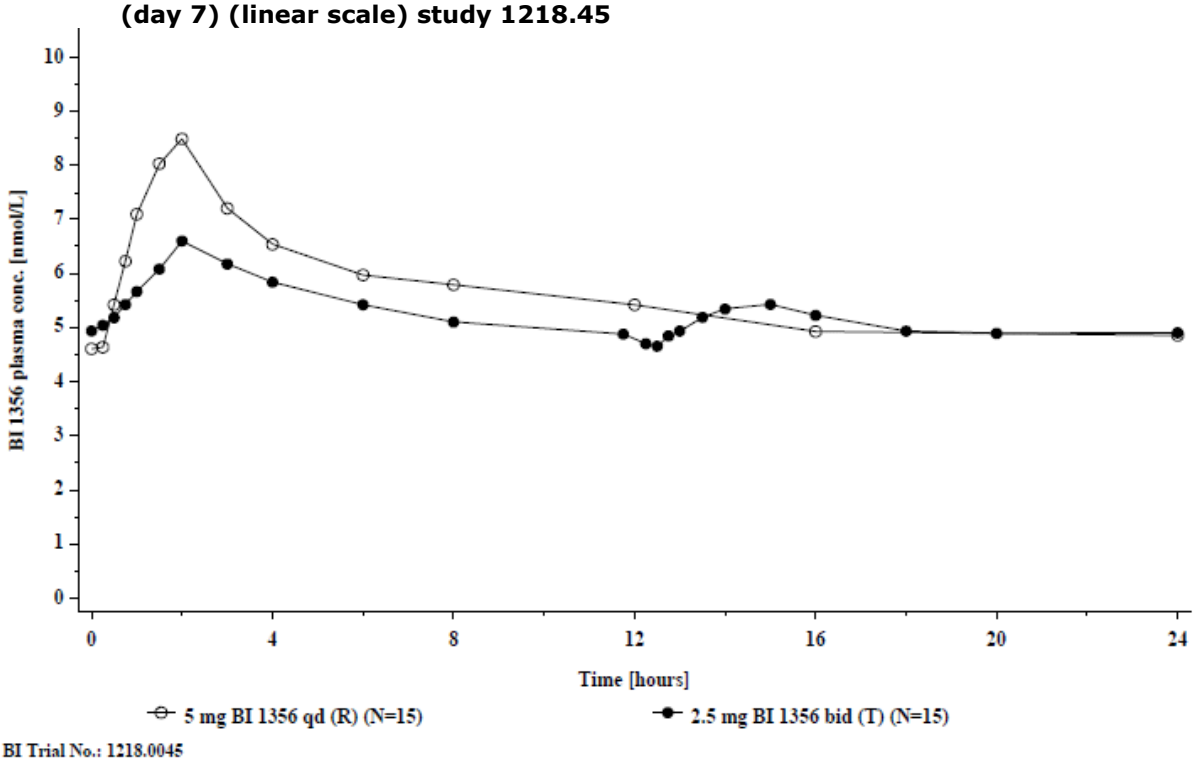
Bioequivalence of 2.5 mg linagliptin twice daily (bid) and 5 mg linagliptin once daily (qd) has been established in study 1218.45. Sixteen healthy men and women were entered in the trial, one subject discontinued due to an AE and was completely excluded from the PK analysis.

The primary endpoint in this study was $AUC_{0\text{-}24,ss}$ for linagliptin. The secondary endpoints were the PK parameters $C_{max,ss}$, C_{pre}, N, $AUC_{0\text{-}12,ss}$, $AE_{t1\text{-}t2,ss}$, $fe_{t1\text{-}t2,ss}$, $t_{max,ss}$, $CL/F,_{ss}$, and the PD parameters of DPP-4 inhibition $Eavg_{0\text{-}24,ss}$, $Eavg_{0\text{-}12,ss,}$ $E_{24,ss}$, $E_{12,ss}$, $E_{max,ss}$, and $E_{min,ss}$. Safety was monitored descriptively.

The extent of exposure over the 24-h interval at steady-state ($AUC_{0\text{-}24,ss}$) was comparable between the 5 mg once daily and 2.5 mg twice daily regimens (132 vs. 124 nmol·h/L). The $AUC_{0\text{-}24,ss}$ values generally showed a low interindividual variability with geometric coefficients of variation (gCV) of 14.2% (2.5 mg twice daily) and 18.0% (5 mg once daily). Median $t_{max,ss}$ was comparable for both dosage regimens and the morning dose and the evening dose of the twice daily regimen.

The adjusted gMean T/R ratio of $AUC_{0-24,ss}$ was 93.89% with a 90% CI of 89.49-98.51%. DPP-4 inhibition was comparable for both dosage regimens over the whole 24-h interval at steady-state. The average DPP-4 inhibition was 85.3% for the 5 mg once daily regimen and 85.8% for the 2.5 mg twice daily regimen. The plasma concentration-time profiles of this study are presented in the figure below.

Figure 1. Arithmetic mean drug plasma concentration-time profiles of BI 1356 after multiple oral administration of 5 mg BI 1356 qd (R) and 2.5 mg BI 1356 bid (T) over 7 days (day 7) (linear scale) study 1218.45



Metformin

Clinical study 1218.46 was conducted with a metformin tablet from the US market. To allow bridging of the results of this study, the Applicant conducted bioequivalence study 1218.57, with metformin tablets from the European and the US market.

In this bioequivalence study, two different metformin tablets of two different strengths administered to 56 (28 for each study part) healthy male and female subjects in an open, randomised, single dose, two-period crossover trial under fasting conditions design.

Table 15. Metformin pharmacokinetic parameters (geometric mean and geometric CV(%); tmax median, range) Study 1218.57

Treatment	AUC_{0-z} ng·h/ml	$AUC_{0-\infty}$ ng·h/ml	C_{max} ng/ml	t_{max} hr
METFORMIN 1000mg				
EUmetformin (test) (N=28)	9380± 1960	9550 ± 1960	1610 ± 440	2.5 (0.5-3.5)
US metformin (ref) (N=28)	9610 ± 1990	9810 ± 1940	1630 ± 385	2.5 (1.0-4.0)
Ratio (90% CI)	97.64 (91.8- 103.8)	97.21 (91.5- 103.3)	98.4 (90.8- 106.6)	-
CV (%)	13.6	13.3	17.7	-
METFORMIN 500mg				
EUmetformin (test) (N=27)	5810± 1310	5920 ±1310	993 ±266	2.5 (1.0-4.0)
US metformin (ref) (N=28)	5740 ± 1530	5870 ±1540	980 ±287	2.5 (1.5-4.0)
Ratio (90% CI)	102.5 (95.5-109.9)	102.37 (95.8-109.4)	102.2 (92.1- 113.6)	-
CV (%)	15.2	14.3	22.9	-
AUC_{0-z}	area under the plasma concentration-time curve from time zero to last timepoint with a plasma concentrationabove the quantification limit			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
t_{max}	time for maximum concentration			

Linagliptin/metformin

The applicant conducted three bioequivalence studies 1288.1,1288.2 and 1288.3 with the three different linagliptin/metformin FDC tablet strengths. These three bioequivalence studies have a similar design (open-label, randomised, single dose, two-way crossover, trials in healthy volunteers).

A single dose of the test product (linagliptin/metformin FDC tablet) or reference products (linagliptin tablet plus metformin tablet) were administered after an overnight fast of at least 10 h, in each treatment period separated by a washout phase of at least 35 days. The blood samples were collected in each period as per the following times: pre-dose and at 20 minutes, 40 minutes, 1 , 1.5, 2, 3, 4, 6, 8, 12, 24, 34, 48 and 72 hours post dose in each of two periods.

The primary endpoints were AUC_{0-72} and C_{max} for linagliptin and AUC_{0-tz}, $AUC_{0-\infty}$ and C_{max} for metformin. Secondary endpoints were $AUC_{0-\infty}$ and AUC_{0-tz} for linagliptin and $\%AUC_{tz-}$, AUC_{t1-t2}, t_{max}, λ_z, $t_{1/2}$, MRTpo, CL/F, Vz/F for both analytes. Safety was monitored descriptively.

The results of studies 1288.1, 1288.2 and 1288.3 are presented in the tables below.

Table 16. Linagliptin/metformin 2.5 mg/1000 mg FDC tablet vs linagliptin2.5mg tablet + metformin 1000 mg tablet: Linagliptin and Metformin pharmacokinetic parameters (Arithmic means and SD ; tmax median, range) Study 1288.1

Treatment	AUC_{0-72} nmol·h/L	$AUC_{0-\infty}$ nmol·h/L	C_{max} nmol/l	t_{max} hr
LINAGLIPTIN				
FDC (Test) (N= 96)	163 ±45.9	251 ±76.5	5.20 ±1.25	3.0 (0.7-8.0)
LINA+MET (Ref) (N=93)	192 ±39.0	235 ±64.8	5.03 ±1.20	3.0 (1.0-6.0)
Ratio (90% CI)	106.4 (102.7-110.2)	105.2 (101.2-109.3)	103.4 (100.3-106.7)	
CV (%)	14.5	16.1	12.7	-
	AUC_{0-z} Ng·h/ml	$AUC_{0-\infty}$ ng·h/ml	C_{max} ng/ml	t_{max} hr
METFORMIN				
FDC (Test) (N= 96)	11300 ±2930	11500 ±2910	1740 ±462	2.51 (0.7-4.0)
LINA+MET (Ref) (N=93)	10800±2830	11000 ±2830	1670 ±478	3.0 (1.0-4.0)
Ratio (90% CI)	103.6 (100.03-107.4)	103.4 (99.9-107.1)	104.3 (99.8 108.9)	-
CV (%)	14.6	14.3	17.9	-
AUC_{0-72}	area under the plasma concentration-time curve from time zero to 72 hours			
AUC_{0-z}	area under the plasma concentration-time curve from time zero to last timepoint with a plasma concentration above the quantification limit			
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time zero to infinity			
C_{max}	maximum plasma concentration			
t_{max}	time for maximum concentration			

Table 17. Linagliptin/metformin 2.5 mg/500 mg FDC tablet vs linagliptin2.5mg tablet + metformin 500 mg tablet: Linagliptin and Metformin pharmacokinetic parameters (Arithmic means and SD; tmax median, range) Study 1288.2

Treatment	AUC_{0-72} nmol·h/L	$AUC_{0-\infty}$ nmol·h/L	C_{max} nmol/l	t_{max} hr
LINAGLIPTIN				
FDC (Test) (N=94)	188 ± 50.6	292 ± 130	5.53 ± 1.51	3.0(0.67-8.0)
LINA+MET (Ref) (N=95)	188 ± 50.5	294 ± 91.7	5.64 ± 1.56	3.0 (1.0-8.0)
Ratio (90% CI)	100.0 (96.7- 103.4)	99.3 (95.6- 103.1)	98.2 (94.5 102.1)	-
CV (%)	13.9	15.5	16.0	-
	AUC_{0-z} ng·h/ml	$AUC_{0-\infty}$ ng·h/ml	C_{max} ng/ml	t_{max} hr
METFORMIN				
FDC (Test) (N= 94)	7530 ± 1840	7630 ± 1830	1170 ± 315	2.0 (0.7-4.0)
LINA+MET (Ref) (N=95)	7590 ± 1910	7700 ± 1880	1200 ± 329	3.0 (0.7-4.0)
Ratio treated set (90% CI)	99.4 (96.5- 102.3)	99.1 (96.4- 102.0)	97.9 (94.4- 101.5)	-
Ratio PSS-BE set (90%CI)	99.3 (96.4- 102.3)	99.1 (96.4- 101.9)	97.9 (94.4- 101.5)	-
CV (%)	12.3	11.6	14.9	-

Table 18. Linagliptin/metformin 2.5 mg/850 mg FDC tablet vs linagliptin2.5mg tablet + metformin 850 mg tablet: Linagliptin and Metformin pharmacokinetic parameters (Arithmic means and SD; tmax median, range) Study 1288.3

Treatment	AUC_{0-72} nmol·h/L	$AUC_{0-\infty}$ nmol·h/L	C_{max} nmol/l	t_{max} hr
LINAGLIPTIN				
FDC (Test) (N=95)	165 ±42.6	253 ±75.3	5.38 ±1.31	3.00 (1.0-6.0)
LINA+MET (Ref) (N=94)	160 ±42.9	224 ±72.2	5.10 ±1.19	3.00 (1.0-6.0)
Ratio (90% CI)	104.5 (100.6-108.5)	105.7 (101.1-110.5)	106.2 (102.9-109.7)	-
CV (%)	15.4	18.2	13.0	-
	AUC_{0-z} ng·h/ml	$AUC_{0-\infty}$ ng·h/ml	C_{max} ng/ml	t_{max} hr
METFORMIN				
FDC (Test) (N=95)	11400 ± 2840	11700 ± 2860	1710 ± 458	3.00 (0.7-6.0)
LINA+MET (Ref) (N=93)	11400 ± 3030	11700 ± 3020	1730 ± 501	3.00 (0.7-4.0)
Ratio (90% CI)	101.0 (98.1-103.9)	101.3 (98.4- 104.3)	100.1 (96.5-104.0)	
CV (%)	11.9	11.8	15.4	-

Influence of food

Linagliptin

Intake of food prolonged the time to reach maximum plasma concentrations by 2 hours and lowered the C_{max} by 15%. No influence on the AUC_{0-72} was observed. The other pharmacokinetic parameters of linagliptin were comparable under fasted and fed conditions. Food has no clinical relevant influence on the pharmacokinetics of the linagliptin and linagliptin itself can be administered with and without food.

Metformin

Food decreases the extent of and slightly delays the absorption of metformin, a 40% lower C_{max} and a 25% lower AUC is observed when given with food; the clinical relevance of these decreases is unknown. Metformin can be administered with and without food.

Linagliptin/metformin

The Applicant conducted study 1288.4 to investigate the effect of food on the PK of linagliptin/ metformin FDC tablet. A single dose of a FDC tablet with linagliptin 2.5 mg and metformin 1000 mg was administered to 32 healthy volunteers after an overnight fast (Reference) and after a high fat, high caloric meal (Test) with a wash out period of at least 35 days. The AUC_{0-72} and C_{max} for linagliptin and $AUC_{0-\infty}$ and C_{max} for metformin were evaluated as primary endpoints. The results of the study are summarised in table below.

Table 19. Linagliptin and Metformin pharmacokinetic parameters (Arithmic means and SD; tmax median, range) Study 1288.4

Treatment	AUC_{0-72} nmol·h/L	$AUC_{0-\infty}$ nmol·h/L	C_{max} nmol/l	t_{max} hr
LINAGLIPTIN				
Fed (Test) (N=32)	165 ±35.6	249 ±67.4	4.64 ±0.9	3.0 (1.0-12.0)
Fasting (Ref) (N=32)	167 ±36.1	257 ±76.0	5.1 ± 1.0	3.50 (1.0-8.0)
Ratio (90% CI)	98.7 (94.5-103.0)	97.6 (93.4-102.0)	91.4 (86.2-96.9)	-
CV (%)	10.1	10.4	13.9	-
	AUC_{0-z} ng·h/ml	$AUC_{0-\infty}$ ng·h/ml	C_{max} ng/ml	t_{max} hr
METFORMIN				
Fed (Test) (N=32)	11600 ±2670	11800 ± 2670	1510 ±282	4.00 (1.0-6.0)
Fasting (Ref) (N=32)	12300± 2540	12100±2500	1850 ±366	2.00 (0.7-4.0)
Ratio (90% CI)	95.2 (88.5-102.3)	96.0 (89.2- 103.2)	81.9 (76.8- 87.3)	-
CV (%)	17.3	17.3	15.2	-

Administration of 2.5 mg linagliptin and 1000 mg metformin as FDC tablet after food intake had no relevant effect on the relative bioavailability of linagliptin with regard to AUC_{0-72} and C_{max}. The exposure to metformin was similar under fed and fasted conditions with regard to $AUC_{0-\infty}$ and AUC_{0-tz}, while C_{max} was reduced. This reduction is smaller than reported in the literature for metformin... Food is not expected to have a relevant influence on the efficacy of the linagliptin and metformin FDC tablet.

Distribution

Linagliptin

Plasma protein binding of linagliptin in human plasma is concentration-dependent, decreasing from 99% at 1 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.

Metformin

Metformin protein binding in plasma is negligible, metformin partitions into erythrocytes.

Linagliptin/metformin

No additional studies have been conducted for the linagliptin/metformin FDC which is considered acceptable.

Elimination

Excretion

Linagliptin

Plasma concentrations of linagliptin decline in a triphasic manner with a long terminal half-life (terminal half-life for linagliptin more than 100 hours), that is mostly related to the saturable, tight binding of linagliptin to DPP-4 and does not contribute to the accumulation of linagliptin. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of 5 mg linagliptin, is approximately 12 hours. Plasma AUC of linagliptin increased in a less than dose-proportional manner.

Following administration of an oral [^{14}C] linagliptin dose to healthy subjects, approximately 85% of the administered radioactivity was eliminated in faeces (80%) or urine (5%) within 4 days of dosing. Renal clearance at steady state was approximately 70 mL/min.

Metformin

Metformin is excreted unchanged in the urine, with a plasma elimination half-life of approximately 6.5 hours.

Linagliptin/metformin

No additional studies have been conducted for the linagliptin/metformin FDC which is considered acceptable.

Metabolism

Linagliptin

Most of 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. *In vitro* studies indicated that linagliptin is metabolised by CYP3A4 to form its major metabolite CD1790. All metabolites contributed to less than 10 % of the excreted radioactivity. A total of the seven metabolites were identified, only two were formed at quantifiable amount, namely oxidation in the quinazoline moiety and CD1790. In plasma 16.9% of sample radioactivity in pooled samples after oral administration was identified as CD1790.

Metformin

Metformin does not undergo hepatic metabolism (no metabolites have been identified in humans).

Linagliptin/metformin

No additional studies have been conducted for the FDC linagliptin/metformin which is considered acceptable.

Special populations

Pharmacokinetics in target population

Linagliptin

The PK of linagliptin after single and multiple rising oral doses of 1 mg to 10 mg and 2.5 mg to 10 mg linagliptin were evaluated in T2DM patients using a non-compartmental approach in studies 1218.2, 1218.3 (Caucasian patients), in study 1218.12 (Japanese patients), in study 1218.26 (T2DM patients with normal and impaired renal function,), and in study 1218.55 (Black patients). The PK of patients with T2DM were also evaluated by a Pop-PK analysis using rich sampling data from trials 1218.2 and 1218.3 as well as sparse sampling data from the phase IIb studies 1218.5 and 1218.6. The pharmacokinetics of linagliptin was generally similar in healthy subjects and in patients with type 2 diabetes.

Metformin

No additional studies have been conducted for metformin which is considered acceptable.

Linagliptin/metformin

No additional studies in special populations have been conducted for the linagliptin/metformin FDC tablets. This is considered acceptable by the CHMP.

Renal impairment

Linagliptin

The influence of renal impairment 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. No dose adjustment is considered necessary in these patients.

Metformin

In patients with decreased renal function, the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance. Metformin is therefore contraindicated in patients with a creatinine clearance < 60 ml/min and the creatinine clearance should be determined before initiating treatment and regularly thereafter.

Linagliptin/meftormin

Jentadueto should not be used in patients with moderate or severe renal impairment (creatinine clearance < 60 ml/min) due to the metformin component. As metformin hydrochloride is excreted by the kidney, serum creatinine levels should be determined before initiating treatment and regularly thereafter.

Hepatic impairment

Linagliptin

In patients with mild to 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. The exposure to the main metabolite is significantly reduced, however the elimination of linagliptin by metabolism is small (less than 13%). Although the pharmacokinetic studies indicated that the exposure to linagliptin is not affected by hepatic impairment, clinical experience with linagliptin in patients with hepatic insufficiently is lacking.

Metformin

Metformin is contraindicated in patients with hepatic insufficiency. Impaired hepatic function has been associated with some cases of lactic acidosis.

Linagliptin/metformin

Jentadueto is not recommended in patients with hepatic insufficiency due to both components and this is reflected in the SmPC.

Gender and race

Linagliptin

Gender had no clinically relevant effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data. The difference in exposure was not more than 9% higher in female than in male subjects. No dosage adjustment is necessary based on gender.

Race had no obvious effect on the plasma concentrations of linagliptin based on a composite analysis of available pharmacokinetic data, including patients of Caucasian, Hispanic, African, and Asian origin. In addition the pharmacokinetic characteristics of linagliptin were found to be similar in dedicated phase I studies in Japanese, Chinese and Caucasian healthy volunteers. No dosage adjustment is necessary based on race.

Metformin

Although dedicated studies on the influence of gender or race are not available, there are no indications that the pharmacokinetics and clinical efficacy of metformin are substantially influenced by these factors.

Linagliptin/metformin

No additional studies have been conducted for the linagliptin/metformin FDC tablets. This is considered acceptable by the CHMP.

Weight

Linagliptin

The influence of weight on the pharmacokinetics of linagliptin was less than 20% and therefore not clinically relevant effect. No dosage adjustment is necessary based on BMI.

Metformin

No additional studies have been conducted with metformin. This is considered acceptable by the CHMP.

Linagliptin/metformin

No additional studies have been conducted for the linagliptin/metformin FDC tablets. This is considered acceptable by the CHMP.

Elderly population

Linagliptin

No dosage adjustment is required based on age, 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) had comparable plasma concentrations of linagliptin compared to younger subjects.

Metformin

Due to the potential for decreased renal function in elderly subjects, the metformin dosage should be adjusted based on renal function. Regular assessment of renal function is necessary.

Linagliptin/metformin

As metformin is excreted by the kidney, Jentadueto should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly. Clinical experience with patients > 80 years of age is limited and caution should be exercised when treating this population.

Paediatric population

Linagliptin

Studies characterizing the pharmacokinetics of linagliptin in paediatric patients have not yet been performed.

Metformin

Metformin is indicated in children from 10 years of age and adolescents, and may be used as monotherapy or in combination with insulin. The usual starting dose is 500 mg or 850 mg metformin hydrochloride once daily, given during meals or after meals. The diagnosis of T2DM should be confirmed before treatment with metformin hydrochloride is initiated.

No effect of metformin hydrochloride on growth and puberty has been detected during controlled clinical studies of one-year duration but no long-term data on these specific points are available. Therefore, a careful follow-up of the effect of metformin hydrochloride on these parameters in metformin hydrochloride-treated children, especially pre-pubescent children, is recommended. Only 15 subjects aged between 10 and 12 years were included in the controlled clinical studies conducted in children and adolescents. Although efficacy and safety of metformin hydrochloride in these children did not differ from efficacy and safety in older children and adolescents, particular caution is recommended when prescribing to children aged between 10 and 12 years.

After single doses of metformin hydrochloride 500 mg, paediatric patients have shown similar phamacokinetic profile to that observed in healthy adults. The data on the use of multiple doses of metformin are restricted to one study. After repeated doses of 500 mg twice daily for 7 days in paediatric patients the peak plasma concentration (C_{max}) and systemic exposure (AUC_{0-t}) were reduced by approximately 33% and 40%, respectively compared to diabetic adults who received repeated doses of 500 mg twice daily for 14 days. As the dose is individually titrated based on glycaemic control, this is of limited clinical relevance.

Linagliptin/metformin

No paediatric studies have been conducted for the linagliptin/metformin FDC tablets.

Pharmacokinetic interaction studies

Linagliptin

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 CD 1790 was found. Linagliptin is a competitive inhibitor of MAO-B and a weak inhibitor of CYP3A4/3A5 but clinical relevance of the MAO-B and CYP3A4/3A5 inhibition is considered unlikely. Furthermore, no hints on enzyme induction (CYP 1A2, 2B6 and 3A4) were found in human hepatocytes.

Based on the *in vitro* data, the effects of ritonavir (a strong CYP3A4 and P-gp inhibitor) and the effects of rifampicin (a strong CYP3A and P-gp inducer) on linagliptin pharmacokinetics as well as the effects of linagliptin on the pharmacokinetics of digoxin (a sensitive P-gp substrate) and simvastatin (sensitive CYP3A4 substrate) were investigated. Co-administration with ritonavir led to a two fold increase in exposure (AUC) and multiple co-administration of linagliptin with rifampicin resulted in an about 40% decreased linagliptin steady-state AUC presumably by increasing/decreasing the bioavailability of linagliptin by inhibition/induction of P-glycoprotein. Linagliptin did not have a clinically relevant effect on the pharmacokinetics of simvastatin or digoxine.

In addition to *in vitro* data based studies also common co-medications of T2DM patients were investigated. This included DDI studies with several antidiabetic agents. Linagliptin's pharmacokinetics were not affected to a clinical relevant degree by co-administration of glyburide, metformin and pioglitazone and linagliptin did not have a clinically relevant effect on the pharmacokinetics of glyburide , metformin and pioglitazone.

Co-administration with warfarin (CYP2C9 substrate) and a combination product of ethinylestradiol and levonorgestrel was also evaluated. Linagliptin did not have a clinically relevant effect on the pharmacokinetics of warfarin and oral contraceptives.

Metformin

Drug interactions of metformin were reported for glyburide, furosemide, nifedipine, and are likely for cationic drugs that are eliminated by renal tubular secretion (e.g. amiloride, cimetidine, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin). Certain drugs tend to produce hyperglycaemia and may cause loss of glycaemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium-channel-blocking drugs, and isoniazid. In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies. Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Linagliptin/metformin

In study 1218.4, the bioavailability of linagliptin and of metformin after concomitant multiple oral administration of 10 mg linagliptin tablets and 3 x 850 mg metformin in comparison to linagliptin and metformin given alone was investigated.

Table 20. Linagliptin and Metformin pharmacokinetic parameters (geometric means and CV; tmax median, range) Study 1218.4

Treatment	$AUC_{□,ss}$ nmol·h/L	C_{max} nmol/l	t_{max} hr	$t_{1/2,ss}$ hr
LINAGLIPTIN				
Without metformin (ref) (N=32)	111 (29.9)	9.29 (49.8)	1.00 (0.50-2.03)	35.5 (45.4)
With metformin (test) (N=32)	133 (23.2)	9.60 (31.9)	1.50 (0.50-4.03)	42.6 (15.6)
Ratio (90% CI)	120.0 (107.3-134.1)	103.44 (86.39-123.9)	-	-
CV (%)	16.8	27.4	-	-
	$AUC_{□.ss}$ nmol·h/L	C_{max} nmol/l	t_{max} hr	$t_{1/2.ss}$ hr
METFORMIN				
Without Linagliptin (ref) (N=32)	8000 (26.9)	1930 (23.6)	1.00 (0.75-2.00)	15.6 (49.4)
With Linagliptin (test) (N=32)	8210 (32.6)	1720 (25.0)	1.50 (0.75-2.00)	13.2 (52.5)
Ratio (90% CI)	100.8 (89.2-113.9)	88.6 (78.2-100.4)	-	-
CV (%)	18.0	18.5	-	-

Co-administration of multiple TID doses of 850 mg metformin with 10 mg linagliptin once daily resulted in a 20% increase of linagliptin steady-state AUC, but did not affect linagliptin C_{max}. These results are in line with the population pharmacokinetic analysis where an equal 19.8% increase in linagliptin exposure in combination with metformin was found. The increase is considered not clinically meaningful. Linagliptin co-administration had no clinical meaningful effect on metformin exposure. Steady-state AUC and C_{max} of metformin were unchanged during linagliptin co-administration.

The interaction potential of linagliptin and metformin has been sufficiently characterised for both drugs individually. Linagliptin does not have a clinically relevant effect on the pharmacokinetics of metformin or vice versa.

2.4.3. Pharmacodynamics

Mechanism of action

Linagliptin

The mechanism of action of linagliptin 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.

Metformin

The principal metabolic effects of metformin consist of a decrease of hepatic glucose production/output and improvement of insulin-mediated glucose utilisation (i.e. increased insulin sensitivity), thereby targeting two of the primary metabolic defects contributing to both fasting and postprandial hyperglycaemia in patients with T2DM.

This implies that with metformin treatment, insulin secretion is not directly affected, although fasting insulin levels decrease as a result of improved insulin sensitivity. Through these mechanisms, metformin therapy typically leads to substantial reductions in glycosylated HbA1c, but it does not promote weight gain or increase the risk of hypoglycaemia.

Primary and Secondary pharmacology

Linagliptin

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

Linagliptin treatment resulted in a rapid, potent and long-lasting inhibition of plasma DPP-4 in clinical studies. Already after a single dose of linagliptin, DPP-4 was effectively inhibited as shown by maximum DPP-4 inhibitions of 72% and 88.5% for 2.5 and 5 mg, and >95% for doses ≥25 mg. At steady-state, plasma DPP-4 activity was inhibited over 24 h by >80% in most patients receiving 5 mg or 10 mg linagliptin once daily but not in patients receiving 2.5 mg linagliptin or lower doses. A consistent DPP-4 inhibition more than 80% at the end of the dosing interval (i.e. trough) with 5 mg linagliptin q.d. was also seen in Japanese T2DM patients, as well as in Caucasian and Japanese healthy adult subjects.

Plasma Glucose and GLP-1

The effects of linagliptin on incretin and glucose concentrations in T2DM patients were investigated during meal (MTT) and oral glucose tolerance tests (OGTT). Treatment with 5 mg linagliptin over 28 days resulted in a statistically significant increase of active glucagon like peptide 1 (GLP-1) concentrations of 18.1 pmol*h /L (p<0.0001) after a MTT compared to placebo and a statistically significant reduction of weighted mean daily glucose and postprandial plasma glucose $AUEC_{0-3h}$ of −19.9 mg/dL (p<0.0001) and −106.5 mg*h/dL (p<0.0001), respectively. Linagliptin dosing for 28 days also resulted in a relevant decrease in fasting plasma glucose concentrations of −10.8 mg/dL compared to placebo.

Short term biomarkers

As expected from the mechanism of action, multiple administration of linagliptin resulted in a significant increase in ß-cell indices based on fasting and postprandial insulin and C-peptide concentrations.

Treatment with 5 mg linagliptin caused an increase in insulin secretion, as evidenced by: a placebo-adjusted insulin secretion change (HOMA-%B) from baseline of 24.2; and a statistically significant placebo corrected change from baseline in insulin secretion rate (ISR) to glucose ratio of 28.7 pM/(mg/dL·h)(p=0.0004) after 28 days of treatment. Also peak glucagon concentrations after 4 week linagliptin treatment were reduced by −16.8 pg/mL (95% CI: −28.7, −4.9; p=0.0064) compared to placebo.

Intermediate term biomarkers

Fructosamine and 1,5-Anhydroglucitol were measured during linagliptin development as intermediate term markers of glucose control, reflecting glucose control over a period of two to three weeks. Fructosamine is formed by the reaction of the carbonyl group of glucose with an amino group of a protein, whereas 1,5-Anhydroglucitol is a naturally occurring monosaccharide contained in nearly all foods, which is found in a relatively constant amount in the blood and tissues. 1,5-Anhydroglucitol is filtered in the kidney, but nearly completely re-absorbed by a glucose transporter. Thus glucose and 1,5-Anhydroglucitol compete for reabsorption during periods of high glucose concentrations (>180 mg/dL) and consequently 1,5-Anhydroglucitol blood concentrations decrease during times of hyperglycaemia above 180 mg/dL).

The observed effect on glucose control also translated in an effect on intermediate term markers of glucose control, fructosamine and 1,5-Anhydroglucitol. As fructosamine was generally more variable in linagliptin trials, 1,5-Anhydroglucitol is assumed to be a better marker for intermediate glucose control.

Treatment with 5 mg linagliptin over 4 weeks resulted in a statistically significant increase of 1,5-Anhydroglucitol 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 substantially reduced. The concentration of 10 µg/mL 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 T2DM.

Long term biomarkers

HbA1c was measured in 3 early trials with 4 week treatment duration. Despite the short term treatment period, which does not allow HbA1c to reach a new equilibrium to display maximum treatment effects, dosing of linagliptin generally resulted in statistically significant decreases in HbA1c of up to -0.48% compared to placebo. The observed effects were similar in Caucasian and Japanese T2DM patients. HbA1c was the primary efficacy parameter used in the studies of >4 weeks duration and thus also for the pivotal studies. In these studies consistent clinically relevant reductions in HbA1c compared to placebo.

A thorough QT study was performed to demonstrate that linagliptin does not lead to QT prolongation compared to placebo (study 1218.32). The primary analysis demonstrated that, compared with placebo, the mean changes in the QTcI interval over 1 to 4 hours were −1.1 ms for the 5 mg dose and −2.5 ms for the 100 mg dose of linagliptin. The upper bound of the two-sided 90% confidence intervals was 0.5 ms for 5 mg linagliptin and −0.9 ms for 100 mg linagliptin. This was well below the predefined non-inferiority margin of 10 ms, indicating there was no clinically relevant increase in the QTcI interval following administration of 5 mg and 100 mg linagliptin compared with placebo. Similar results were obtained for the secondary endpoints. Assay sensitivity was demonstrated by the comparison of the mean QTcI interval changes from baseline over 1 to 4 hours between moxifloxacin (single administration of 400 mg) and placebo.

Metformin

Effects on Hepatic Glucose Production and Glycogenolysis

The predominant glucose-lowering mechanism of action of metformin is to reduce excessive rates of hepatic glucose production. Metformin inhibits gluconeogenesis by increasing hepatic sensitivity to insulin and decreasing the hepatic extraction of certain gluconeogenic substrates (e.g. lactate). Metformin reduces gluconeogenesis by 0.6 mg/kg per minute, in effect leading to a 75% reduction in hepatic glucose output. It is believed that this effect is achieved through metformin induced activation of adenosine monophosphate-activated protein kinase, an energy regulating enzyme expressed in the liver. Hepatic glycogenolysis is also decreased by metformin.

Effects on Peripheral Insulin Sensitivity

The extrahepatic actions of metformin include improved glucose transport and utilisation by skeletal muscle due to improvements in non-oxidative glucose disposal and glycogen synthesis. These actions result in an enhanced insulin-stimulated glucose uptake in the skeletal muscle. This involves an increase in the movement of insulin-sensitive glucose transporter molecules to the cell membrane. Additional pharmacologic actions of metformin include increased glucose oxidation and storage in glycogen and fat, and inhibition of fatty acid oxidation. Taken together, metformin acts as an insulin sensitizer without exerting any direct effect on pancreatic β-cell insulin secretion.

Effects on the Rate of Intestinal Glucose Absorption

The rate of intestinal glucose absorption is also reduced with metformin, further contributing to its blood glucose–lowering effects.

Effects on the GLP-1

In a small study in obese non-diabetic male patients it was shown that a 14-day high-dose treatment (i.e. 2.550 mg/day) with metformin was associated with a significant increase in circulating GLP-1 plasma levels after an oral glucose load [R10-5241, Module 2.7.5]. As subjects were studied during euglycaemic hyperinsulinaemic clamp conditions, the results of this study indicate that metformin determines a relevant elevation of oral glucose–stimulated GLP-1, which is not dependent on variations in circulating insulin or glucose. The mechanism for the observed increase in oral glucose stimulated GLP-1 levels determined by metformin treatment could have been principally due to either a stimulation of secretion or an inhibition of peptide inactivation, and was matter of debate over the last decade. The results of this study were confirmed by a recent study in healthy non-diabetic subjects, in whom a 2-day treatment with 1.000 mg metformin/day increased postprandial total GLP-1 plasma concentrations (4-h weighted mean) by about ~1.8-fold relative to placebo. It was also shown by the authors that metformin did not inhibit plasma DPP-4 activity either *in vitro* or *in vivo*. Based on these data it was concluded that metformin is not a DPP-4 inhibitor but rather enhances precursor GCG expression in the large intestine, thereby increasing total GLP-1 plasma concentrations, possibly by enhancing GLP-1 secretion from enteroendocrine L-cells.

Other Pharmacologic and Metabolic Effects

In addition to metformin's ability to lower blood glucose concentrations, it has been shown to exert beneficial effects on dyslipidemia, hypofibrinolysis, and obesity in patients with T2DM. Metformin has been reported to produce 10% to 20% reductions in plasma TG levels in nonhypertriglyceridemic patients and up to 50% TG reductions in hypertriglyceridemic patients due to decreased hepatic synthesis of very low density lipoprotein cholesterol. Total cholesterol (TC) levels have been reported to decrease a mean of 10%, with increases in HDL-C levels of up to 17% and decreases in LDL-C levels of up to 25%. Free fatty acid (FFA) levels have also been reported to decrease with metformin therapy.

In contrast to patients receiving sulfonylurea therapy for diabetes, those who receive metformin generally maintain or loose body weight, with loss of adipose tissue accounting for most of the weight loss. Metformin therapy is associated with a 5% net difference in weight reduction compared with sulfonylurea therapy.

Effects on Plasma Glucose and HbA1c Levels

A meta-analysis of randomized controlled trials evaluated metformin's efficacy in achieving glycaemic control, as well as its effects on body weight. In 10 placebo-controlled studies (with treatment durations ranging between 1 to 36 months), metformin monotherapy reduced fasting blood glucose (FBG) concentrations by 2.0 mM compared with placebo (95% CI, −2.4 to −1.7) and HbA1c values by 0.9 percentage points (95% CI, −1.1 to −0.7). In 9 studies comparing metformin and a sulfonylurea, both agents lowered blood glucose concentrations and HbA1c values equally.

Linagliptin/metformin

Linagliptin in combination with metformin represents a pharmacologically meaningful therapeutic combination approach, because different pathophysiological features of T2DM (e.g. impaired ß-cell function, increased hepatic glucose output/gluconeogenesis, and peripheral insulin resistance) are addressed by the complementary modes of action of both moieties.

This principle pharmacological consideration is supported by consistent clinical evidence demonstrating that novel GLP-1 based therapies display additive glucose/HbA1c lowering effects in combination with metformin. This was shown to apply to both pharmacological approaches, i.e. the strategy of activating the GLP-1 receptors by exenatide or liraglutide, and by the strategy of preventing the inactivation of endogenous GLP-1 by inhibiting DPP-4.

Regarding the primary PD variable DPP-4 inhibition it was shown by a 7-day repeat-dose study in healthy adult subjects that the linagliptin 5 mg q.d. and 2.5 mg b.i.d. treatment regimens resulted in a comparable PD response as shown by a median DPP-4 inhibition of about 80% at trough. Moreover DPP-4 inhibition was comparable for both dosage regimens over the entire 24-h (i.e. 24-h for q.d. and 2 x 12-h for b.i.d. regimen) dosing interval at steady-state. The mean average DPP-4 inhibition was 85.3% and 85.8% for the 5 mg q.d. and the 2.5 mg b.i.d. regimens, respectively (study 1218.45).

These findings were confirmed for HbA1c in study 1218.62. This study was a randomised, double-blind, placebo-controlled, 3 parallel group efficacy and safety study of linagliptin 2.5 mg b.i.d. versus 5 mg q.d. over 12 weeks as add-on therapy to a b.i.d. dose regimen of metformin in patients with T2DM and insufficient glycaemic control. According to the pre-specified criterion in the protocol, non-inferiority of linagliptin 2.5 mg b.i.d. treatment was established versus linagliptin 5 mg q.d treatment. The adjusted mean treatment difference in HbA1c from baseline to Week 12 with linagliptin 2.5 mg b.i.d. compared to linagliptin 5 mg q.d. was 0.06% (95% CI -0.07, 0.19).

2.4.4. Discussion on clinical pharmacology

The pharmacokinetics and pharmacodynamics of linagliptin were studied in 29 Phase I/II trials, involving healthy subjects, patients with T2DM, and special populations (renal or hepatic impairment, Japanese subjects). DPP-4 inhibition was considered the primary pharmacodynamic parameter, with an inhibition of 80% or more over 24 hours related to maximum effects in incretin response and glucose reduction.

Extrapolation of the pharmacokinetic and pharmacodynamic data of the linagliptin 5 mg tablet to the 2.5 mg is justified by study 1218.45, in which it was shown that a dosage regimen of linagliptin 2.5 mg twice daily can be considered bioequivalent with linagliptin 5 mg once daily, based on the exposure data over 24 hours $AUC_{0\text{-}24\ hours.}$ In this study DPP-4 inhibition >80% over 24h was achieved with multiple dosing of 2.5 mg linagliptin. In healthy individuals, linagliptin 2.5 mg twice daily was bioequivalent to linagliptin 5 mg once daily.

The applicant conducted three bioequivalence studies. Based on these studies the to be registered linagliptin 2.5 mg/metformin 1000 mg, linagliptin 2.5 mg/metformin 850 mg, linagliptin 2.5 mg/metformin 500 mg FDC tablets can be considered bioequivalent with the single dose formulation with linagliptin 2.5 mg tablet and metformin 1000 mg, 500 mg and 850 mg respectively.

Results on secondary parameters such as active GLP-1, glucose, insulin and glucagon were consistent with the primary parameter. In general, linagliptin plasma concentrations correlated well with DPP-4 activity/inhibition. Although age has been investigated as covariate, the number of elderly subjects >75 in all clinical studies was small, and pharmacodynamics has not been studied in elderly patients. 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

Bioequivalence of linagliptin 2.5 mg twice daily with linagliptin 5 mg once daily has been appropriately demonstrated. In addition it has been demonstrated that the linagliptin 2.5 mg/metformin 1000 mg, linagliptin 2.5 mg/metformin 850 mg and linagliptin 2.5 mg/metformin 500 mg FDC tablets are bioequivalent with the linagliptin 2.5 mg tablet given concomitantly with metformin 1000 mg, 850 mg and 500 mg respectively.

2.5. Clinical efficacy

2.5.1. Dose response studies

Linagliptin

The optimum daily linagliptin dose of 5 mg was determined in the linagliptin mono development programme and was primarily based on HbA_{1c} reduction and DPP-4 inhibition in the 2 dose-finding trials 1218.5 and 1218.6. Tolerability was excellent on all dose levels tested in these 2 trials (0.5 mg, 1 mg, 2.5 mg, 5 mg, and 10 mg), and no dose-dependent increase in adverse events was observed. A median DPP-4 inhibition of at least 80% was only reached with the 5 mg and 10 mg linagliptin doses, but not with lower doses. The 10 mg dose did not result in a substantially greater median DPP-4 inhibition or HbA_{1c} reduction than the 5 mg dose, and hence, the 5 mg dose was used in phase III. In the entire phase III program, linagliptin 5 mg once daily was shown to provide consistent and clinically meaningful improvements in glycaemic control, as assessed by HbA_{1c}, FPG, or postprandial glucose levels. Together with the favourable safety profile observed, the risk-benefit ratio of linagliptin is considered optimal for a daily dose of 5 mg linagliptin.

Because the pharmacokinetics of metformin require an at least twice daily dosing, for the development of the FDC the once daily dosing of 5 mg linagliptin was split into 2 daily doses of 2.5 mg. In trial 1218.45, a phase I-study comparing once daily and twice daily dosing in healthy subjects, the 2 linagliptin dosing regimens were shown to be bioequivalent in regard to AUC at steady state. The average DPP-4 inhibition was 85.3% for the 5 mg once daily regimen and 85.8% for the 2.5 mg twice daily regimen. The clinical equivalence of both posologies was demonstrated in a large, placebo-controlled, 12-week trial 1218.62 that investigated linagliptin 2.5 mg bid + metformin versus linagliptin 5 mg qd + metformin.

Metformin

Metformin in immediate release formulation is approved as tablet for oral administration in the dose strengths of 500 mg, 850 mg, and 1000 mg. In case of tolerability issues, the metformin dose should be reduced. is the Applicant therefore proposed to provide FDC tablets with linagliptin and all 3 metformin dose strengths to offer patients maximal flexibility in attaining their individual daily metformin dose.

For the key trials in this submission (1218.17, 1218.20, 1218.62, and 1218.18) the protocols specified that the daily metformin dose should be 1500 mg or above. The actual unit dose strength and the actual posology was at the investigator's discretion and depending on the patient's need and tolerability of metformin. The majority of patients in the 4 studies received a daily dose of 1500 mg to 2000 mg metformin at baseline; a considerable proportion of patients took less than 1500 mg metformin per day (range 6.3% to 8.6%). In trial 1218.46, two treatment groups with metformin mono therapy of 500 mg bid and 1000 mg bid were evaluated.

Linagliptin/metformin

The applicant proposed 3 FDC dose strengths, namely linagliptin 2.5 mg/metformin 500 mg, linagliptin 2.5 mg /metformin 850 mg, and linagliptin 2.5 mg/metformin 1000 mg. To substantiate the effectiveness of these 3 dose strengths, the placebo-controlled trials (1218.17, 1218.62, 1218.46, 1218.18) were analysed by metformin dose and posology. Emphasis was placed on the posologies of 500 mg bid, 850 mg bid and 1000 mg bid. However, except in study 1218.46, in which all patients took either metformin 500 mg bid or 1000 mg bid, the proportions of patients who received other doses or other posologies were between 42.1% (1218.62) and 58.9% (1218.17). For each of the studies (1218.17, 1218.18, 1218.20, 1218.62), the analyses that comprised all 'other' metformin doses demonstrated that the linagliptin treatment effect was similar to the efficacy observed for the planned FDC combinations.

Independent of metformin dose, the addition of linagliptin either once daily or twice daily led to a substantial and clinically meaningful reduction in HbA_{1c}. The magnitude of the combination treatment effect was largely consistent across the different metformin doses with adjusted mean changes from baseline of -0.51% to -0.70% after 24 weeks of treatment. Only for the 850 mg group in study 1218.62 no difference between metformin 850 mg and linagliptin + metformin 850 mg could be established. This was likely a consequence of the small number of patients in this analysis (metformin 850 mg n=9; linagliptin 5 mg qd + metformin 850 mg n=55, linagliptin 2.5 mg bid + metformin 850 mg, n=57). In addition, study 1218.46 showed that the combination of linagliptin 2.5 mg bid + metformin 500 mg bid was at least as effective in reducing HbA_{1c} as metformin 1000 mg bid (-1.22% vs. -1.07%), adjusted mean difference -0.14%, p=0.1903. Thus, the linagliptin 2.5 mg/metformin 500 mg FDC could be considered a useful alternative to metformin monotherapy for patients intolerant to the recommended daily metformin dose.

For all placebo-controlled trials, ANCOVA analyses demonstrated that there was no treatment-by-metformin dose effect for the reduction of HbA_{1c} (treatment-by-dose p-values 0.2172 to 0.9846). In the active-controlled study 1218.20, the adjusted mean changes (SE) from baseline in HbA_{1c} after 104 weeks of treatment were -0.10% (0.08) for linagliptin + metformin 850 mg bid and -0.12% (0.06) for linagliptin + metformin 1000 mg bid; the treatment-by-dose interaction p-value was 0.8056. Thus, it can be concluded that each of the proposed posologies of linagliptin + metformin combinations are efficacious in the reduction of HbA_{1c}. A summary of the results by metformin dose is shown below.

Table 21. Change from baseline in HbA_{1c} in placebo-controlled trials with linagliptin+metformin combinations analysed by daily metformin doses 500 mg, 850 mg and 1000 mg - FAS (LOCF)

	Change from baseline	Difference between treatments		
Study Treatment groups	Adjusted [a] mean (SE)	Adjusted [a] mean (SE)	95% CI	p-value
1218.17		**24 weeks treatment**		
850 mg Metformin				
Metformin	0.13 (0.14)			
L5 mg qd+Met vs Met	-0.56 (0.07)	-0.70 (0.15)	(-1.00, -0.39)	<0.0001
1000 mg Metformin				
Metformin	0.31 (0.16)			
L5 mg qd+Met vs Met	-0.36 (0.10)	-0.67 (0.19)	(-1.05, -0.29)	0.0005
1218.62		**12 weeks treatment**		
850 mg Metformin				
Metformin	-0.13 (0.23)			
L5 mg qd+Met vs Met	-0.50 (0.09)	-0.37 (0.24)	(-0.85, 0.11)	0.1283
L2.5 mg bid+Met vs Met	-0.51 (0.09)	-0.38 (0.24)	(-0.86, 0.10)	0.1191
L2.5 mg bid+Met vs L5 mg qd+Met		0.01 (0.13)	(-0.26, 0.24)	0.9502
1000 mg Metformin				
Metformin	0.19 (0.19)			
L5 mg qd+Met vs Met	-0.50 (0.09)	-0.69 (0.21)	(-1.10, -0.28)	0.0009
L2.5 mg bid+Met vs Met	-0.48 (0.09)	-0.67 (0.21)	(-1.08, -0.26)	0.0013
L2.5 mg bid+Met vs L5mg qd + Met		0.02 (0.12)	(-0.22, 0.26)	0.8855
1218.46		**24 weeeks treatment**		
500 mg Metformin				
Met bid	-0.64 (0.08)			
L2.5 mg bid+Met bid vs. Met bid	-1.22 (0.08)	-0.58 (0.11)	(-0.79, -0.36)	<0.0001
1000 mg Metformin				
Met bid	-1.07 (0.08)			
L2.5 mg bid+Met bid vs Met bid	-1.59 (0.08)	-0.51 (0.11)	(-0.73, -0.30)	<0.0001
1218.18		**24 weeks treatment**		
850 mg Metformin+SU				
Met+SU	-0.17 (0.12)			
L5 mg qd+Met+SU vs Met+SU	-0.79 (0.07)	-0.63 (0.14)	(-0.90, -0.36)	<0.0001
1000 mg Metformin+SU				
Met+SU	-0.05 (0.10)			
L5 mg qd+Met+SU vs Met+SU	-0.65 (0.06)	-0.60 (0.12)	(-0.83, -0.37)	<0.0001

For the 850 mg group in study 1218.62 no difference between metformin 850 mg and linagliptin + metformin 850 mg could be established. The CHMP is in agreement with the Applicant that this was likely a consequence of the small number of patients in this analysis. In addition, study 1218.46 showed that the combination of linagliptin 2.5 mg bid + metformin 500 mg bid was at least as effective in reducing HbA1c as metformin 1000 mg bid (-1.22% vs. -1.07%). However, the proposed strength 2.5 mg/500 mg was not considered acceptable by the CHMP. The minimal metformin dose assessed in the clinical studies was 1500 mg per day, which is in line with clinical practice. This is also in line with the results from the UKPDS. In this study, the efficacy of metformin in reducing T2DM complications was demonstrated, but the great majority of the patients were treated with metformin doses >1700 mg per day. Although there might be a minority of patients who cannot tolerate metformin at doses higher than 1000 mg, it is unlikely that the linagliptin 2.5 mg/metformin 500 mg FDC tablet offers a meaningful benefit compared to the administration of the separate components. In addition, the low dose FDC tablet could promote initial combination therapy which is not approved and not covered by current diabetes treatment guidelines.

2.5.2. Main studies

Linagliptin

Four pivotal efficacy studies were submitted to support the registration of linagliptin 5 mg (Trajenta) (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 by the number of previous antidiabetic treatments as described below.

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; 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 studies 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 LOFC (with observations obtained under rescue medication not being replaced) 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%).

The study period was from 15 April 2008 to 19 June 2009.

Methods

Design

This was a 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 were recruited in this study.

HbA_{1c} at screening was 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%.

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 %).

Table 22. 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).

Table 23. 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.

Table 24. 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: -0.48 [-0.69; -0.28, 95 % CI] for HbA1c (mean difference).

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

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%.

Table 25. 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, 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 T2DM 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). The study period was 15 February 2008 to 06 May 2009.

Methods

Design

This was a 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 were included in this study.

HbA_{1c} at screening was 7.0% to 10.0% in treatment naïve patients and 6.5% to 9.0% in pretreated patients. HbA1c at start of run-in was between 7.0% and 10.0%.

There were no limitations in the degree of renal impairment in this study.

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

The primary and secondary endpoints are described above in the general method section above.

In addition, PK/PD of linagliptin (plasma concentrations at trough after 12 and 24 weeks of treatment) was also an endpoint.

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.

Table 26. 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.

Table 27. 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 not considered as influencing the study results.

No interim analysis was planned or performed for this study.

Baseline data

At study start, the 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.

43.1% of patients had an eGFR of ≥ 90 mL/min, 3.6% had an eGFR 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.

Table 28. 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.

Table 29. 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: -0.69 [-0.86; -0.53, 95 % CI] for HbA1c (mean difference). The FAS-completers showed a smaller placebo adjusted treatment effect: -0.56 [-0.73; -39, 95 % CI] 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%.

Table 30. 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.

Table 31. 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 treated in Asia, Europe, North America, South America and New Zealand. The study period was 31 January 2008 to 18 May 2009.

Methods

Design

This was a 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 were included. 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 was 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 was 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

The primary and secondary endpoints are already covered in the general methods 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 highest percentage of randomized study participants were from Asia (39.5%), 26.1% were from Europe, 18.7% from North America and 15.7% from South America.

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.

Table 32. 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 not considered as influencing the study results.

No interim analysis was planned or performed for this study.

Baseline data

At study start, the 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%).

59.1% of patients had an eGFR of ≥ 90 mL/min, 37.6% had an eGFR 60 to < 90 mL/min and 3.3% had an eGFR 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

Table 33. 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.

Table 34. 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: -0.68 [-0.84; -0.53, 95 % CI] p<.0001 for HbA1c (mean diference). The FAS-completers showed a smaller placebo adjusted treatment effect: -0.57 [-0.72; -42, 95 % CI] 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%.

Table 35. 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. The study period was from 25 February 2008 to 21 May 2009.

Methods

Design

This was a 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 were included.

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.

Table 36. 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 not considered as influencing the study results.

No interim analysis was planned or performed for this study.

Baseline data

At study start, the 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.

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.

Table 37. 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%.

Table 38. 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: -0.61 [-0.73; -0.49, 95 % CI] p<.0001) for HbA1c (mean difference).

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).

Table 39. 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%).

Metformin

Antidiabetic therapy with metformin is associated with dose-related reductions in HbA_{1c} and FPG. According to literature data, treatment with metformin 500 to 2000 mg per day decreases HbA_{1c} levels by 0.4% to 2.0% and decreases FPG levels by 5.4 to 68.4 mg/dL.

No additional clinical efficacy studies have been conducted for metformin as monotherapy However, efficacy data for metformin monotherapy are available from the placebo-controlled trials for the combination therapy with linagliptin and metformin, where metformin was taken either as background therapy as in studies 1218.17 and 1218.62 or as study medication as in study 1218.46 (metformin 500 mg bid or 1000 mg bid). Placebo-controlled efficacy data for metformin monotherapy from study 1218.46 are shown in the table below. After 24 weeks of treatment, both metformin doses led to reductions in HbA_{1c} and FPG that were consistent with literature data.

Table 40. Change from baseline in HbA_{1c} [%] and FPG [mg/dL] for metformin groups in study 1218.46 - FAS (LOCF)

Study/ treatment group	Number of patients	Baseline, mean (SD)	Change from baseline		Difference to placebo		
			Mean (SD)	Adjusted mean (SE)	Adjusted mean (SE)	95% CI	p-value
1218.46 / [a]			**Endpoint assessed after 24 weeks**				
HbA_{1c}							
Placebo	65	8.67 (0.95)	0.13 (1.17)	0.13 (0.11)			
Met500	141	8.66 (0.90)	-0.63 (1.05)	-0.64 (0.08)	-0.77 (0.14)	(-1.04, -0.50)	<0.0001
Met 1000	138	8.52 (0.87)	-1.02 (1.01)	-1.07 (0.08)	-1.20 (0.14)	(-1.47, -0.93)	<0.0001
FPG							
Placebo	61	203.3 (51.5)	6.0 (55.8)	10.2 (5.26)			
Met500	136	190.6 (46.6)	-13.4 (52.5)	-15.8 (3.52)	-26.0 (6.34)	(-38.4, -13.5)	<0.0001
Met 1000	132	190.6 (52.2)	-30.2 (42.9)	-32.2 (3.58)	-42.3 (6.37)	(-54.8, -29.8)	<0.0001

[a] Models include baseline FPG, continuous baseline HbA_{1c}, prior antidiabetic drugs, and treatment

Linagliptin/metformin

Study 1218.46

Methods

Design, randomisation, blinding and treatment

This was a phase 3 multinational, randomised, double-blind, placebo-controlled, parallel group, factorial design study to compare the efficacy and safety of twice daily administration of the free combination of linagliptin 2.5 mg + metformin 500 mg or of linagliptin 2.5 mg + metformin 1000 mg, with the individual components of metformin (500 mg or 1000 mg, twice daily) and linagliptin (5 mg, once daily) over 24 weeks in drug naïve (47.5%) or previously treated (4 weeks washout and 2 weeks placebo run-in) T2DM patients with insufficient glycaemic control. The study period was from 5 December 2008 to 26 May 2010.

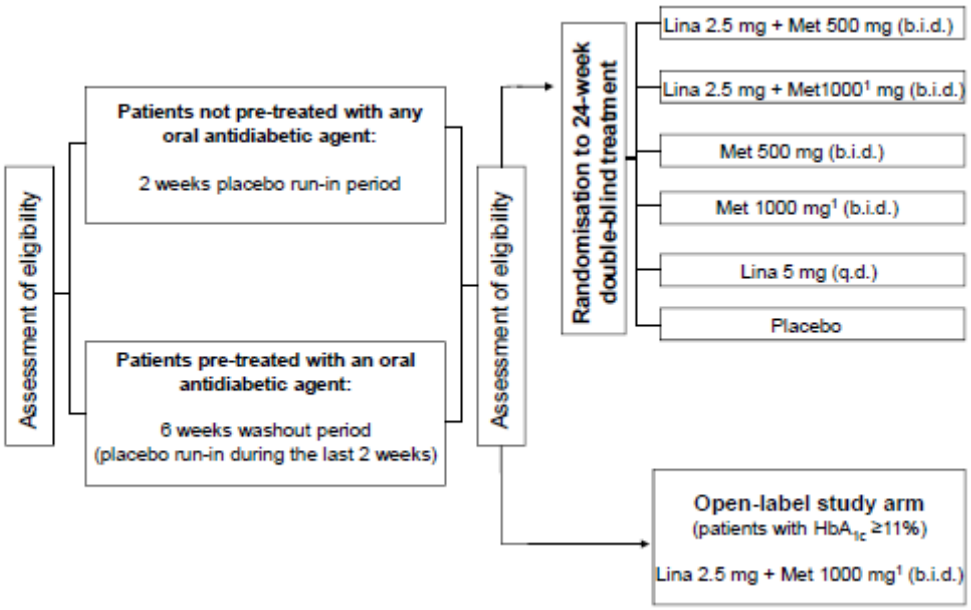
Patients who met the trial eligibility criteria at the end of the 2-week placebo run-in period were randomly assigned to one of the treatment groups in a 1 (placebo):2:2:2:2:2 ratio. Randomisation was stratified by baseline A1C and number of prior oral antidiabetic drug (OADs).

All subjects were randomly assigned to double blind study drug utilizing a double-dummy design to ensure adequate blinding.

Subjects with baseline HbA1C of ≥11% were enrolled into an open-label arm. Details of the study design are given in the figure below.

Patients who regularly completed the randomised period of this study were offered to participate in an extension trial (study 1218.52).

Figure 2. Overview of the study design



[1] Patients who received 1000 mg metformin had to undergo a 2-week forced titration

Study Participants

Main inclusion criteria

- Male and non-fertile or contraceptive-using female patients age ≥18 and ≤ 80 with T2DM, either treatment naïve or previously treated with not more than one oral antidiabetic drug. Antidiabetic therapy had to be unchanged for 10 weeks prior to the date of informed consent.
- HbA1C at screening for patients undergoing washout of previous antidiabetic medication: HbA1C ≥7.0 to ≤10.5%, for patients not undergoing washout: A1C ≥7.5 to <11.0%
- HbA1C at start of run-in: ≥7.5 to <11.0%
- Body mass index (BMI) ≤40 kg/m^2

Main exclusion criteria

- MI, stroke, or TIA within 6 months prior to the date of informed consent
- Impaired hepatic function, defined as serum levels of either alanine transaminase (ALT/SGPT), aspartate transaminase (AST/SGOT), or alkaline phosphatase (ALP) above 3x the upper limit of normal (ULN)
- Treatment with rosiglitazone, pioglitazone, GLP-1 analogues, insulin, or anti-obesity drugs (e.g. sibutramine, rimonabant, orlistat) within 3 months prior to the date of informed consent
- Current treatment with systemic steroids at time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent
- Renal failure or renal impairment at screening (estimated glomerular filtration rate[eGFR] <60 mL/min)
- Gastric bypass

- Dehydration by clinical judgement of the investigator
- Unstable or acute congestive heart failure
- Acute or chronic metabolic acidosis (present in patient history)
- Hereditary galactose intolerance.

Outcomes/endpoints

Primary endpoint :

The primary endpoint was change in HbA1C from baseline to week 24.

Secondary endpoints:

- Change from baseline in FPG at Week 24
- Responder rates: HbA1C< 7.0% and < 6.5%
- Reduction in HbA1C ≥ 0.5%
- Change from baseline in 2h PPG at Week 24
- Use of rescue medication

Objectives, statistical methods and sample size

The trial was designed to demonstrate superiority of the 2 free combination treatments consisting of different doses of linagliptin plus metformin over the individual components with regards to change in HbA1C.

Sample size was calculated to detect a true difference (deltas) in mean change from baseline A1C for the individual treatment-comparisons as follows:

- Linagliptin plus metformin 500 mg vs. linagliptin: -0.8%
- Linagliptin plus metformin 1000 mg vs. linagliptin: -1.0%
- Linagliptin plus metformin 500 mg vs. metformin 500 mg: -0.5%
- Linagliptin plus metformin 1000 mg vs. metformin 1000 mg: -0.5%
- Linagliptin vs. placebo: -0.5%
- Metformin 500 mg vs. placebo: -0.8%
- Metformin 1000 mg vs. placebo: -1.0%

for a two tailed test at α = 0.05 with a power of >90%.

A standard deviation (SD) for HbA1C change from baseline of 1.1% was used for the calculation of the sample size.

Randomised part

Primary endpoint: 4 confirmatory hypotheses in regard to the HbA1C change from baseline were tested. These hypotheses were ordered hierarchically and tested sequentially at the level of α = 0.05 (2-sided).

- superiority of linagliptin 2.5 mg bid + metformin 1000 mg bid *versus* metformin 1000 mg bid
- superiority of linagliptin 2.5 mg bid + metformin 1000 mg bid *versus* linagliptin 5 mg qd

- superiority of linagliptin 2.5 mg bid + metformin 500 mg bid *versus* metformin 500 mg bid
- superiority of linagliptin 2.5 mg bid + metformin 500 mg bid *versus* linagliptin 5 mg qd

with an analysis of covariance (ANCOVA) with treatment and prior use of antidiabetic therapy as factors and baseline HbA1C as covariate.

A last observation carried forward (LOCF) approach was used to replace missing data. In general, baseline values were not carried forward, but could be used for interpolation.

Additional sensitivity analyses were performed (e.g. MMRM and observed cases approach).

Safety endpoints: descriptive statistics, for hypoglycaemic events logistic regression and Kaplan-Meier analysis.

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

Open-label arm

Primary and secondary endpoint were descriptive statistics.

The main analysis sets used were as outlined in the table below. All efficacy analyses were based on FAS and safety analysis on TS.

Analysis set	Definition
Full analysis set (FAS)	All randomised patients who received at least one dose of study medication, had a baseline HbA_{1c} measurement, and had at least one on-treatment HbA_{1c} measurement
Per-protocol set (PPS)	All patients in the FAS who did not have any important protocol violations that had an impact on the efficacy evaluation
FAS-completers	All patients in the FAS who completed a required minimum treatment duration and did not prematurely discontinue the trial
PPS-completers	All patients in the PPS who completed a required minimum treatment duration and did not prematurely discontinue the trial
MTT-set	All patients in the FAS with a valid MTT at baseline and at least one valid on-treatment MTT
TS-set	All patients who received at least one dose of study medication.

Results

Participant flow

Table 41. Disposition of randomised patients – Screened set

	Placebo N (%)	Lina 5 N (%)	Met 500 N (%)	Met 1000 N (%)
Enrolled				
Randomised	72	142	144	147
Treated[1]	72 (100.0)	142 (100.0)	144 (100.0)	147 (100.0)
Not prematurely discontinued trial medication	54 (75.0)	121 (85.2)	127 (88.2)	126 (85.7)
Prematurely discontinued trial medication	18 (25.0)	21 (14.8)	17 (11.8)	21 (14.3)
Adverse events	3 (4.2)	6 (4.2)	4 (2.8)	6 (4.1)
Study disease worsening	1 (1.4)	0 (0.0)	0 (0.0)	1 (0.7)
Other disease worsening	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)
Other AEs	2 (2.8)	5 (3.5)	3 (2.1)	5 (3.4)
Lack of efficacy[2]	6 (8.3)	3 (2.1)	4 (2.8)	2 (1.4)
Non-compliance to the protocol	2 (2.8)	3 (2.1)	1 (0.7)	3 (2.0)
Lost to follow-up	1 (1.4)	3 (2.1)	3 (2.1)	4 (2.7)
Refusal to continue trial medication	5 (6.9)	4 (2.8)	4 (2.8)	5 (3.4)
Other reason	1 (1.4)	2 (1.4)	1 (0.7)	1 (0.7)

	Lina 2.5 + Met 500 N (%)	Lina 2.5 + Met 1000 N (%)	Total N (%)
Enrolled			1770
Randomised	143	143	791
Treated[1]	143 (100.0)	143 (100.0)	791 (100.0)
Not prematurely discontinued trial medication	127 (88.8)	132 (92.3)	687 (86.9)
Prematurely discontinued trial medication	16 (11.2)	11 (7.7)	104 (13.1)
Adverse events	5 (3.5)	2 (1.4)	26 (3.3)
Study disease worsening	0 (0.0)	0 (0.0)	2 (0.3)
Other disease worsening	0 (0.0)	0 (0.0)	2 (0.3)
Other AEs	5 (3.5)	2 (1.4)	22 (2.8)
Lack of efficacy[2]	1 (0.7)	2 (1.4)	18 (2.3)
Non-compliance to the protocol	3 (2.1)	2 (1.4)	14 (1.8)
Lost to follow-up	4 (2.8)	0 (0.0)	15 (1.9)
Refusal to continue trial medication	2 (1.4)	3 (2.1)	23 (2.9)
Other reason	1 (0.7)	2 (1.4)	8 (1.0)

Note: if combined with metformin 500 mg or 1000 mg, linagliptin was administered as 2.5 mg b.i.d.
[1] In all tables 'treated' refers to treatment with randomised study drug
[2] Includes patients who discontinued due to hyperglycaemia

Conduct of the study

In total, 54 patients (6.8%) ranging from 2 patients (1.4%) in the Met 500 mg group to 17 patients (11.6%) in the Met 1000 mg group, were reported with protocol violations (PVs) related to efficacy (no PVs related to safety) that led to exclusion from the Per-Protocol-Set (PPS). The PVs were related to entrance criteria not met, trial medication and randomisation, concomitant medication, and missing data. In the open label arm 21 patients (31.8%) reported PVs.

According to the clinical stuyd report, there were a few protocol amendments mainly related to the level of HbA1C at inclusion.

During the course of the study, concerns were expressed about the overall quality of the source data documentation and study conduct at one German site. As a result from these concerns, the site was closed prematurely in the course of the extension study 1218.52. It was decided to include the data of these patients in the study analysis of 1218.46, as the audit findings were unlikely to affect the overall validity of the study data. There were no acute safety concerns for the patients.

Study 1218.62

This study was performed on request of the CHMP. It was a randomised, double-blind, placebo-controlled, 3 parallel group efficacy and safety study of linagliptin 2.5 mg twice daily versus 5 mg once daily over 12 weeks as add-on therapy to a twice daily dosing regimen of metformin in patients with type 2 diabetes mellitus and insufficient glycaemic control HbA1c ≥7.0-≤10.0%) on metformin (at least 1500 mg/day, bid or maximum tolerated dose if lower than this). Patients had to be between 18 and 80 years of age and had to have a BMI up to 45 kg/m^2. Metformin was administered as background therapy in an unchanged total daily dosage throughout the trial (including wash-out, placebo run-in, 12-week randomised treatment, and follow-up phases).

The primary endpoint was the change from baseline in HbA1c. The primary analysis was performed on the full analyses set (FAS), with a last observation carried forward (LOCF) approach used to replace missing data. Important secondary endpoints were the change from baseline in fasting plasma glucose (FPG) and the occurrence of treat-to-target response (i.e. HbA1c on treatment <7.0%).

Subject disposition

A total of 771 patients were enrolled, 491 patients were randomised in a 1:5:5 ratio to receive treatment with either placebo (44 patients), linagliptin 2.5 mg twice daily (223 patients) or linagliptin 5 once daily (224 patients). Of the 491 patients treated with randomised study medication, 464 patients (94.5%) completed the planned 12-week treatment period and 27 patients (5.5%) prematurely discontinued the trial medication. The rate of premature discontinuations was higher in the linagliptin 2.5 bid group (7.2%) compared to the linagliptin 5 qd and placebo treatment groups (4.5% and 2.3%, respectively). In the placebo group, one of the 44 treated patients discontinued (cause: Other). In the linagliptin 2.5 bid group, the most frequent reasons for premature discontinuation were due to adverse events (3.6%), refusal to continue trial medication (1.8%), and non-compliance with the protocol (1.3%). In the linagliptin 5 qd group, the most frequent reasons were due to non-compliance with the protocol (2.2%) and adverse events (1.3%).

Baseline data

More than half of the population was male (total 57.0%). Nearly two thirds of the population was White (total 65.4%) and about one third was Asian (total 33.8%). The mean age was 58.6 years (total) with the largest proportion of patients being 65 years of age or younger (total 69.5%). All three treatment groups had comparable distribution of patients across age groups. In total, the mean weight was 81.0 kg and the mean BMI was 29.6 kg/m^2. Almost three-quarters of the patients were pre-treated with metformin monotherapy (71.3% total), with comparable percentages seen across treatment groups. A total of 28.7% of patients were pre-treated with combination therapy (metformin and 1 'other' OAD) prior to study entry and underwent a washout period for the 'other' OAD.

Outcome and estimation

HbA1c

In study 1218.62, the baseline mean HbA1c percent values were comparable between the treatment groups and the overall mean HbA1c was 7.97%. The adjusted mean treatment difference in HbA1c change from baseline to Week 12 for linagliptin 2.5 twice daily over placebo was -0.74% (95% CI -0.97, -0.52), p<0.0001, Table 5 upper panel). For linagliptin 5 mg over placebo the adjusted mean difference was -0.80% (95% CI -1.02, -0.58), p<0.0001). The adjusted mean treatment difference for linagliptin 2.5 mg twice daily vs. linagliptin 5 mg once daily was 0.06% (95% CI -0.07, 0.19), indicating non-inferiority as the upper bound of the 95% confidence interval was below the pre-specified margin of 0.35% (see figure below).

Table 42. Changes from baseline in HbA1c [%] in trials 1218.62, 1218.46 - FAS (LOCF)

	Change from baseline	Difference		
Study Treatment groups	Adjusted a mean (SE)	Adjusted a mean (SE)	95% CI	p-value
1218.62		Difference between treatments 12 weeks treatment		
Met	0.28 (0.11)			
Lina 5 mg qd + Met vs Met	-0.52 (0.05)	-0.80 (0.11)	(-1.02, -0.58)	<0.0001
Lina 2.5 mg bid + Met vs Met	-0.46 (0.05)	-0.74 (0.11)	(-0.97, -0.52)	<0.0001
Lina 2.5 mg bid + Met vs Lina 5mg qd + Met		0.06 (0.07)	(-0.07, 0.19)	0.3834
1218.46	Difference between combination and components 24 weeks treatment			
Placebo	0.13 (0.11)			
Lina 2.5 mg bid + Met 500 mg bid	-1.22 (0.08)			
Met 500 mg bid	-0.64 (0.08)	-0.58 (0.11)b	(-0.79, -0.36)	<0.0001
Lina 5 mg qd	-0.45 (0.08)	-0.77 (0.11)c	(-0.99, -0.55)	<0.0001
Lina 2.5 mg bid + Met 1000 mg bid	-1.59 (0.08)			
Met 1000 mg bid	-1.07 (0.08)	-0.51 (0.11)d	(-0.73, -0.30)	<0.0001
Lina 5 mg qd	-0.45 (0.08)	-1.14 (0.11)e	(-1.36, -0.92)	<0.0001

Glim = glimepiride; Met = metformin; Lina 5 mg, Lina = linagliptin 5 mg; Lina 2.5 mg = linagliptin 2.5 mg

a Model includes continuous baseline HbA1c, prior use of antidiabetic drugs, and treatment

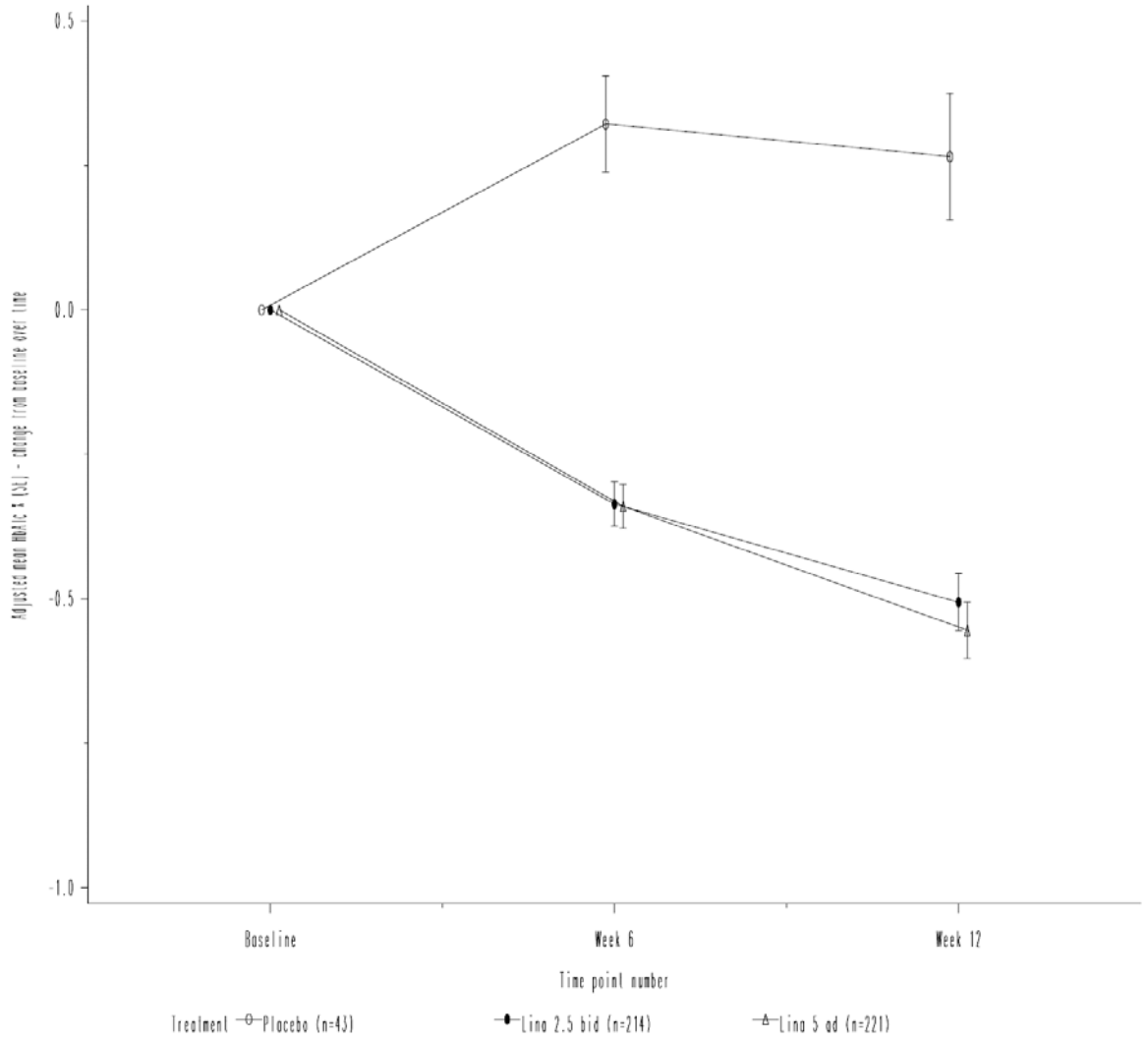
b Difference between Lina 2.5 mg + Met 500 mg bid and Met 500 mg bid;

c Difference between Lina 2.5 mg + Met 500 mg bid and Lina 5 mg qd

d Difference between Lina 2.5 mg + Met 1000 mg bid and Met 1000 mg bid

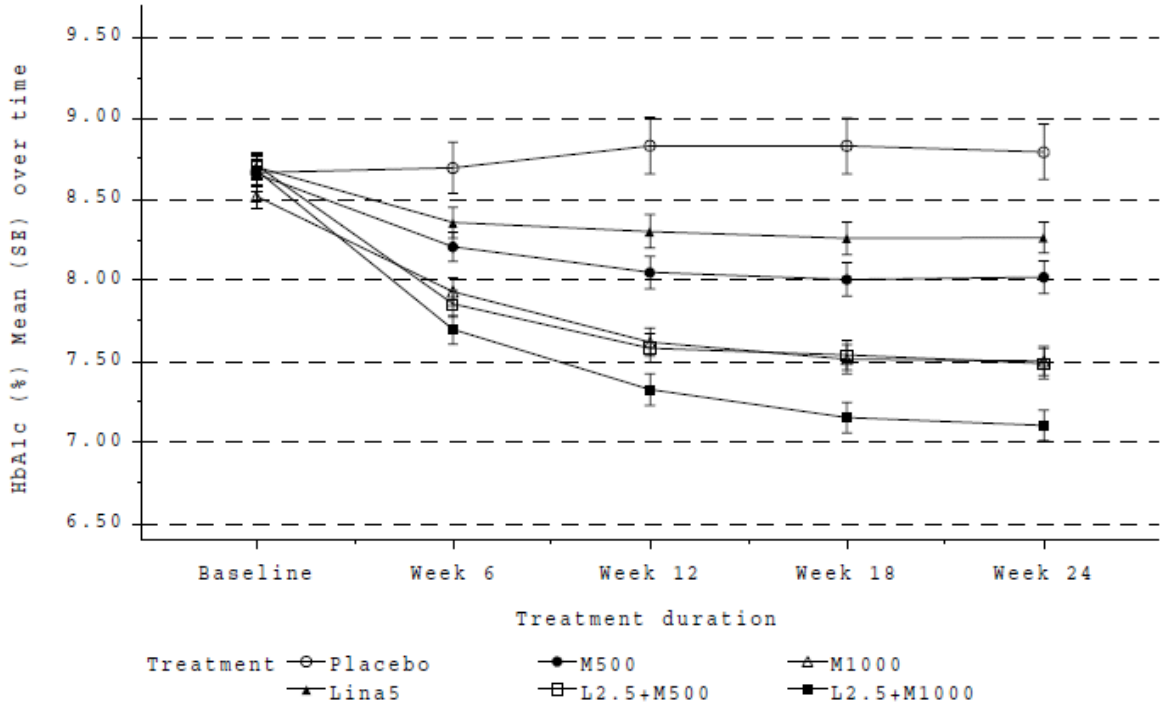
e Difference between Lina 2.5 mg + Met 1000 mg bid and Lina 5 mg qd

Figure 3. Adjusted HbA1c (%) mean change from baseline over time in study 1218.62 – FAS (OC)



Study 1218.46 yielded qualitatively similar results to other studies described above (pivotal studies for the linagliptin MAA), mean baseline HbA1c values were comparable between the treatment groups, ranging from 8.52 % in patients treated with metformin 1000 mg to 8.71% in patients treated with linagliptin 2.5 mg + metformin 500 mg. The linagliptin + metformin groups were superior to both metformin monotherapy groups and also to linagliptin monotherapy. The mean treatment difference in HbA1c from baseline to Week 24 was -0.51% for the free combination of linagliptin 2.5 mg + metformin 1000 mg compared to the individual component metformin 1000 mg, -1.14% for the free combination of linagliptin 2.5 mg + metformin 1000 mg compared to linagliptin 5mg, -0.58% for the free combination of linagliptin 2.5 mg+ metformin 500 mg compared to the individual component metformin 500 mg, and -0.77% for the free combination of linagliptin 2.5 mg+ metformin 500 mg compared to linagliptin 5 mg (see figure below). In this study, linagliptin was investigated in initial combination with metformin. At least half of the patients was not treated with oral antidiabetic drugs before inclusion in the study. This is not in line with the requested indication for linagliptin/metformin in patients that are insufficiently controlled with metformin or metformin in combination with SU. The inclusion of treatment naive patients resulted in an overestimation of the treatment effects of metformin in this study. Nevertheless, the treatment effects of linagliptin were similar in patients that were pretreated and those that were treatment naive. In this study, the treatment effect of linagliptin 2.5 mg twice daily was smaller in Asians compared to Whites (-0.42% vs. -0.65% in combination with metformin 500 mg;-0. 39% vs. -0.59% in combination with metformin 1000 mg).

Figure 4. Unadjusted mean HbA1c (%) and SE over time in study 1218.46 – FAS (LOCF)



Results of other glycaemic parameters, such as patients reaching their goal HbA1c, fasting plasma glucose, were in line with HbA1c results.

Body weight

In study 1218.17 and 1218.18, the effect of combination therapy was shown to be neutral in regard to body weight. In study 1218.20, after 104 weeks of treatment, a decrease in body weight was noted in the linagliptin + metformin group as opposed to a weight gain in the glimepiride + metformin group (treatment difference of -2.7 kg (p <0.0001)). In study 1218.46 and its extension study 1218.52 as well as in study 1218.62, the mean changes in body weight were between -1.1 kg and -0.01 kg across all treatment groups.

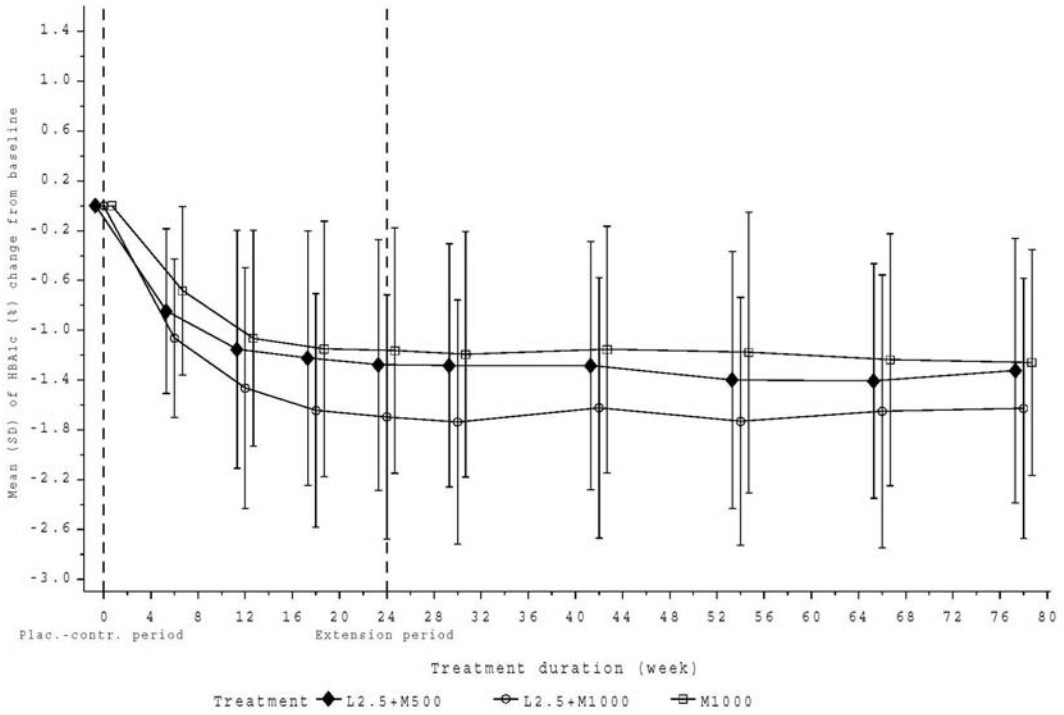
Subgroup analyses

The 24-week trials 1218.17 and 1218.46 were pooled (n=1244). For most subgroups investigated, the treatment effect was consistent and the achieved changes from baseline in HbA1c were comparable across all subcategories. Thus, the factors age, gender, ethnicity, geographical region, baseline BMI, and baseline HbA1c did not have an influence on the efficacy of the combination therapy with linagliptin + metformin. The treatment effect of linagliptin + metformin compared with metformin was almost identical in Europe (n=442) and in Asia (n=446) with HbA1c changes of -0.56% (Europe) and -0.59% (Asia), and p-values below 0.0001. Likewise, for race there was no difference between White (-0.61%) and Asian (-0.57%) patients in the efficacy of linagliptin + metformin compared with metformin (p<0.0001 for both races). Treatment effects were smaller, but acceptable in patients with prior OADs and a longer time since diagnosis of diabetes. Patients with hepatic impairment were also not investigated in sufficient amount. The number of patients aged 75 years or above was very low (in the grouping of 1218.17 and 1218.46 only 24 patients >75 years were included). It is difficult to estimate the effect of linagliptin on HbA1c in elderly patients. During the evaluation, a study in elderly patients was submitted (1218.63). This study was a phase III multi-national, randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of linagliptin (5 mg), administered orally once daily over 24 weeks in type 2 diabetic (T2DM) patients, age ≥70 years, with insufficient glycaemic control (HbA1c ≥7.0%) despite metformin and/or sulphonylurea (SU) and/or insulin therapy. 241 patients were randomised in a 2:1 ratio to receive treatment either with linagliptin 5 mg (162 patients) or placebo (79 patients). Mean age was 74.9±4.3 years. The estimated treatment difference between linagliptin (n=160) and placebo (n=78), calculated as the adjusted mean change from baseline in HbA1c at Week 24, was -0.64% (95% CI [-0.81; -0.48], p<0.0001), demonstrating superiority of linagliptin over placebo in the reduction of HbA1c.

Trials with a longer treatment duration

Long term efficacy of linagliptin in combination with metformin was investigated in the double blind extension of study 1218.46 (study 1218.52). Throughout the entire treatment duration of 78 weeks, the linagliptin 2.5 mg + metformin 1000 mg combination achieved greater reductions in mean HbA_{1c} than the metformin 1000 bid group. In addition, the proportion of patients who required rescue medication up to Week 78 was lower in the linagliptin 2.5+ metformin1000 mg bid group (12.6%) than in the metformin 1000 mg bid group (22.9%).

Figure 5. Mean change from baseline in HbA1c [%] over time in the combined studies 1218.46 and 1218.52 - FAS (OC)



Long term efficacy of linagliptin 5 mg in combination with metformin or metformin with SU was also investigated in study 1218.40, the open-label extension of study 1218.17 and 1218.18. Interim analyses were presented in the MAA for Trajenta (linagliptin). New interim analyses provided efficacy data for linagliptin up to 102 weeks. The decrease in HbA1c was maintained in the individuals that continued the use of linagliptin with metformin. However, 38.7% of the patients using linagliptin in combination with metformin required rescue medication, and 33.8% of the patients using linagliptin in combination with metformin and SU required rescue medication. The relatively large proportion of patients requiring rescue medication in the extension trials in comparison to the initial trials was a concern. However, it is conceivable that this is explained by the low threshold for the initiation of rescue therapy, the long study duration and the fact that the extension trials also allowed entry for patients who already received rescue medication in the initial trials.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting 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).

Table 1. 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
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
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]	10.46	-10.68
	SE	2.80	1.65
Effect estimate per comparison	FPG change from baseline after 24 weeks [mg/dL]	Comparison groups	Treatment difference (linagliptin - placebo)
		Adjusted mean	-21.13
		SE	3.14
		P-value	<0.0001

Table 2. 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
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

Table 3. Summary of Efficacy for trial 1218.46

Title: A Phase III randomised, double-blind, placebo-controlled parallel group study to compare the efficacy and safety of twice daily administration of the free combination of linagliptin 2.5 mg + metformin 500 mg or of linagliptin 2.5 mg + metformin 1000 mg, with the individual components of metformin (500 mg or 1000 mg, twice daily) and linagliptin (5 mg, once daily) over 24 weeks in drug naïve or previously treated (4 weeks washout and 2 weeks placebo run-in) type 2 diabetic patients with insufficient glycaemic control			
Study identifier	1218.46 [U10-2372]		
Design	Randomised, double-blind, placebo-controlled, factorial design with an additional open-label arm		
	Duration of main phase:		24-week treatment period with the free dose combination of linagliptin 2.5 mg + metformin 500 mg bid and linagliptin 2.5 mg + metformin 1000 mg bid, the individual components of metformin (500 mg or 1000 mg, both bid) and linagliptin 5 mg qd
	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:		optional participation in an extension trial over 54 weeks (BI trial no. 1218.52)
Hypothesis	The following 4 hypotheses were tested using a sequential testing procedure at the level of α=0.05 (2-sided): 1) Superiority of linagliptin 2.5 mg + metformin 1000 mg bid vs. metformin 1000 mg bid in terms of change in HbA_{1c} from baseline 2) Superiority of linagliptin 2.5 mg + metformin 1000 mg bid vs. linagliptin 5 mg qd in terms of change in HbA_{1c} from baseline 3) Superiority of linagliptin 2.5 mg + metformin 500 mg bid vs. metformin 500 mg bid in terms of change in HbA_{1c} from baseline 4) Superiority of linagliptin 2.5 mg + metformin 500 mg bid vs. linagliptin 5 mg qd in terms of change in HbA_{1c} from baseline		
Treatment groups	Lina 2.5 + Met 500 bid		Linagliptin 2.5 mg + metformin 500 mg bid for 24 weeks, 143 patients randomised
	Lina 2.5 + Met 1000 bid		Linagliptin 2.5 mg + metformin 1000 mg bid for 24 weeks, 143 patients randomised
	Lina 5 qd		Linagliptin 5 mg qd for 24 weeks, 142 patients randomised
	Met 500 bid		Metformin 500 mg bid for 24 weeks, 144 patients randomised
	Met 1000 bid		Metformin 1000 mg bid for 24 weeks, 147 patients randomised
	Placebo		Matching placebo for linagliptin 2.5 mg, linagliptin 5 mg, metformin 500 mg, and metformin 1000 mg for 24 weeks, 72 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
Database lock	25 June 2010		

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 classification effects and 'baseline HbA_{1c}' as linear covariate. The primary analysis was conducted at a 2-sided 5% level of significance.						
Analysis population and time point description	Full analysis set (FAS): the FAS consisted of all treated patients who had a baseline HbA_{1c} measurement and at least one on-treatment HbA_{1c} measurement.						
Descriptive statistics and estimate variability	Treatment group	Lina 2.5 + Met 500 bid	Lina 2.5 + Met 1000 bid	Lina 5 qd	Met 500 bid	Met 1000 bid	Placebo
	Number of patients	137	140	135	141	138	65
	Adjusted mean change in HbA_{1c} from baseline after 24 weeks [%]	-1.22	-1.59	-0.45	-0.64	-1.07	0.13
	SE	0.08	0.08	0.08	0.08	0.08	0.11
Effect estimate per comparison	HbA_{1c} change from baseline after 24 weeks [%]	Comparison groups			Treatment difference Lina 2.5 + Met 1000 bid vs. Met 1000 bid		
		Adjusted mean			-0.51		
		SE			0.11		
		P-value (superiority)			<0.0001		
Effect estimate per comparison	HbA_{1c} change from baseline after 24 weeks [%]	Comparison groups			Treatment difference Lina 2.5 + Met 1000 bid vs. Lina 5 qd		
		Adjusted mean			-1.14		
		SE			0.11		
		P-value (superiority)			<0.0001		
Effect estimate per comparison	HbA_{1c} change from baseline after 24 weeks [%]	Comparison groups			Treatment difference Lina 2.5 + Met 500 bid vs. Met 500 bid		
		Adjusted mean			-0.58		
		SE			0.11		
		P-value (superiority)			<0.0001		
Effect estimate per comparison	HbA_{1c} change from baseline after 24 weeks [%]	Comparison groups			Treatment difference Lina 2.5 + Met 500 bid vs. Lina 5 qd		
		Adjusted mean			-0.77		
		SE			0.11		
		P-value (superiority)			<0.0001		

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	Lina 2.5 + Met 500 bid	Lina 2.5 + Met 1000 bid	Lina 5 qd	Met 500 bid	Met 1000 bid	Placebo
	Number of patients	135	136	134	136	132	61
	Adjusted mean change in FPG from baseline after 24 weeks [mg/dL]	-33.2	-49.4	-8.6	-15.8	-32.2	10.2
	SE	3.5	3.5	3.6	3.5	3.6	5.3
Effect estimate per comparison	FPG change from baseline after 24 weeks [mg/dL]	Comparison groups			Treatment difference Lina 2.5 + Met 1000 bid vs. Met 1000 bid		
		Adjusted mean			-17.2		
		SE			5.0		
		P-value			0.0006		
Effect estimate per comparison	HbA_{1c} change from baseline after 24 weeks [%]	Comparison groups			Treatment difference Lina 2.5 + Met 1000 bid vs. Lina 5 qd		
		Adjusted mean			-40.8		
		SE			5.0		
		P-value			<0.0001		
Effect estimate per comparison	HbA_{1c} change from baseline after 24 weeks [%]	Comparison groups			Treatment difference Lina 2.5 + Met 500 bid vs. Met 500 bid		
		Adjusted mean			-17.4		
		SE			5.0		
		P-value			0.0005		
Effect estimate per comparison	HbA_{1c} change from baseline after 24 weeks [%]	Comparison groups			Treatment difference Lina 2.5 + Met 500 bid vs. Lina 5 qd		
		Adjusted mean			-24.6		
		SE			5.0		
		P-value			<0.0001		

Table 43. Summary of Efficacy for trial 1218.62

Title: A randomised, double-blind, placebo-controlled, 3 parallel group efficacy and safety study of linagliptin 2.5 mg twice daily versus 5 mg once daily over 12 weeks as add-on therapy to a twice daily dosing regimen of metformin in patients with type 2 diabetes mellitus and insufficient glycaemic control			
Study identifier	1218.62 [U11-3093]		
Design	Randomised, double-blind, placebo-controlled, parallel group comparison		
	Duration of main phase: Duration of run-in phase: Duration of extension phase:		12-week treatment period with linagliptin 2.5 mg bid, 5 mg qd, or placebo as add-on therapy to metformin 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) Not applicable
Hypothesis	3 hypotheses were tested in the following fixed sequence: (1) superiority of linagliptin 2.5 mg bid vs. placebo; (2) non-inferiority of linagliptin 2.5 mg bid vs. 5 mg qd; (3) superiority of linagliptin 5 mg qd vs. placebo.		
Treatment groups	Linagliptin 2.5 mg		Linagliptin 2.5 mg tablet bid for 12 weeks as add-on to metformin, 223 patients randomised
	Linagliptin 5 mg		Linagliptin 5 mg tablet qd for 12 weeks as add-on to metformin, 224 patients randomised
	Placebo		Placebo tablet for 12 weeks as add-on to metformin, 44 patients randomised
Endpoints and definitions	Primary endpoint	Confirmatory	HbA_{1c} change from baseline after 12 weeks of treatment
	Secondary endpoint	Exploratory	FPG change from baseline after 12 weeks of treatment
Database lock	04 November 2010		

Results and Analysis

Analysis description	**Primary Analysis:** after 12 weeks of treatment an analysis of covariance (ANCOVA) was performed to compare the change from baseline in HbA_{1c}. The model included 'treatment', 'prior use of antidiabetic agents' as fixed effects and 'baseline HbA_{1c}' as covariate. Superiority against placebo was tested at α=0.05 (2-sided). The non-inferiority of treatment with linagliptin 2.5 mg bid to 5 mg qd was tested at the level of α=0.025 (1-sided; i.e. the upper bound of a 95% confidence interval) with a non-inferiority margin of 0.35%.			
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 2.5 mg bid	Linagliptin 5 mg qd
	Number of patients	43	214	221
	Adjusted mean change in HbA_{1c} from baseline after 12 weeks [%]	0.28	-0.46	-0.52
	SE	0.11	0.05	0.05
Effect estimate per comparison	HbA_{1c} change from baseline after 12 weeks [%]	Comparison groups	Treatment difference (linagliptin 2.5 mg bid - placebo)	
		Adjusted mean	-0.74	
		SE	0.11	
		P-value	<0.0001	
	HbA_{1c} change from baseline after 12 weeks [%]	Comparison groups	Treatment difference (linagliptin 5 mg qd - placebo)	
		Adjusted mean	-0.80	
		SE	0.11	
		P-value	<0.0001	
	HbA_{1c} change from baseline after 12 weeks [%]	Comparison groups	Treatment difference (linagliptin 2.5 mg bid - linagliptin 5 mg qd)	
		Adjusted mean	0.06	
		SE	0.07	
		95% CI	-0.07, 0.19	

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. The model additionally included 'fasting plasma glucose at baseline' as covariate			
Descriptive statistics and estimate variability	Treatment group	Placebo	Linagliptin 2.5 mg bid	Linagliptin 5 mg qd
	Number of patients	40	203	213
	Adjusted mean change in FPG from baseline after 12 weeks [mg/dL]	-3.5	-17.2	-21.3

	SE	4.2	1.9	1.9
Effect estimate per comparison	FPG change from baseline after 12 weeks [mg/dL]	Comparison groups		Treatment difference (linagliptin 2.5 mg bid - placebo)
		Adjusted mean		-13.7
		SE		4.6
		P-value		0.0029
	FPG change from baseline after 12 weeks [mg/dL]	Comparison groups		Treatment difference (linagliptin 5 mg qd - placebo)
		Adjusted mean		-17.8
		SE		4.6
		P-value		0.0001
	FPG change from baseline after 12 weeks [mg/dL]	Comparison groups		Treatment difference (linagliptin 2.5 mg bid - linagliptin 5 mg qd)
		Adjusted mean		4.1
		SE		2.6
		95% CI		-1.0, 9.2

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.

Study 1218.52

This was a multinational phase III randomised, double-blind, parallel group, extension study to investigate the safety and efficacy of twice daily administration of the free combination of linagliptin 2.5 mg + metformin 500 mg or of linagliptin 2.5 mg + metformin 1000 mg *versus* monotherapy with metformin 1000 mg twice daily over 54 weeks in T2DM patients previously completing the double-blind part of study 1218.46 and not requiring rescue therapy.

There was no primary endpoint for efficacy in this study. Instead, safety and efficacy were assessed through descriptive analyses. Change in HbA1C was assessed as a secondary endpoint.

The mean HbA1C results are displayed in the below table.

Table 44. Descriptive statistics for HbA1C (%) change from baseline over time – FAS (OC*) Patients staying on same treatment in extension

	L2.5+M500			L2.5+M1000			M1000		
	n	Mean	SD	n	Mean	SD	n	Mean	SD
Baseline	113	8.61	0.87	111	8.61	0.96	109	8.47	0.85
Week 6	113	-0.85	0.66	111	-1.06	0.64	107	-0.68	0.68
Week 12	113	-1.15	0.96	108	-1.46	0.97	107	-1.06	0.87
Week 18	105	-1.22	1.02	110	-1.64	0.94	107	-1.15	1.02
Week 24	107	-1.28	1.01	108	-1.70	0.98	106	-1.16	0.99
Week 30	100	-1.32	0.91	106	-1.74	0.97	105	-1.20	0.99
Week 42	90	-1.28	1.00	96	-1.62	1.04	94	-1.15	0.99
Week 54	46	-1.38	1.16	59	-1.69	0.99	50	-1.29	0.97
Week 66	13	-1.83	0.91	18	-1.61	1.13	16	-1.53	1.16
Week 78	1	-1.00		4	-1.53	0.87	4	-0.53	0.54

*In the observed cases (OC) analysis, missing data were not replaced. Values measured after rescue medication was set to missing.

Mean HbA1C remained fairly stable in all 3 treatment groups, indicating persistence of the glucose-lowering effect of metformin monotherapy and the combination of linagliptin and metformin up to Week 54. However, one must bear in mind that only a limited number of the included subjects have reached the end of the study (78 weeks) in this partial initial combination setting that differs from the applied add-on setting.

Study 1218.20

It 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 with the linagliptin MAA. 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

Linagliptin 5 mg has been approved in combination with metformin and metformin plus sulphonylurea. In addition, linagliptin 5 mg has been approved for use 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.

The Applicant now proposes a fixed dose combination of linagliptin 2.5 mg and metformin 500 mg, 850 mg or 1000 mg bid. The lowest proposed strength, i.e. linagliptin 2.5 mg/metformin 500 mg, contains a dose of metformin with a questionable benefit in terms of effects on HbA1C and clinical outcome. In the UKPDS study, the efficacy of metformin in reducing T2DM complications was demonstrated, but the great majority of patients was treated with metformin doses >1700 mg per day. Therefore, metformin 500 mg bid is considered only a starting dose that should be increased first before linagliptin is added. The Applicant was requested by the CHMP to justify this lowest dosage strength on the basis of the clinical data of Jentadueto and of the use of metformin 500 mg bid in clinical practice taking into account effects on HbA1C, clinical outcome and intolerance of higher dosages of metformin. The Applicant decided to withdraw this lower strength during the evaluation.

The clinical development programme for the combination therapy comprised several trials. In total 3529 patients with type 2 diabetes received treatment with linagliptin and metformin (linagliptin + metformin). Overall, 2694 patients were treated for at least 24 weeks, 2081 patients for at least 52 weeks, and 1756 patients for more than 78 weeks.

The pivotal placebo-controlled trial 1218.17 investigated the efficacy of linagliptin 5 mg as add-on therapy to metformin over 24 weeks. In comparison to placebo, linagliptin was associated with a significant and relevant effect on HbA1c. This study was also included in the MAA for Trajenta (linagliptin).

One active controlled trial was performed in which linagliptin 5 mg was compared with glimepiride (1-4 mg) in patients treated with metformin (1218.20). After 104 weeks, linagliptin was associated with a decrease in HbA1c of -0.16%, and glimepiride was associated with a decrease of -0.36%. Non-inferiority was not reached. The results of this trial are appropriately described in the SmPC.

Studies investigating linagliptin 2.5 mg twice daily

Because the pharmacokinetics of metformin require at least a twice daily dosing, for the development of the FDC the once daily dosing of 5 mg linagliptin was split into 2 daily doses of 2.5 mg. This study was performed on request of the CHMP. This was a placebo-controlled study over 12 weeks that showed comparable efficacy of the linagliptin 2.5 mg twice daily regimen and the linagliptin 5 mg once daily regimen when added to metformin. The difference in efficacy was negligible and well within the non-inferiority boundaries.

An additional trial for the establishment of efficacy of linagliptin 2.5 mg twice daily was study 1218.46. This study tested 2 linagliptin-metformin combinations versus metformin in a partial first-line setting (47.5% treatment-naïve patients). The treatment effect in the linagliptin-metformin combination therapy groups versus metformin was -0.58% for linagliptin 2.5 mg bid in combination with metformin 500 mg vs. metformin 500 mg. For linagliptin 2.5 mg in combination with metformin 1000 mg vs. metformin 1000 mg, the treatment effect was -0.51%. The fact that at least half of the patients were not treated with oral antidiabetic drugs before inclusion in the study is not in line with the requested indication for linagliptin/metformin in patients that are insufficiently controlled with metformin or metformin in combination with SU. The inclusion of treatment naive patients resulted in an overestimation of the treatment effects of metformin in this study. Nevertheless, the treatment effects of linagliptin were similar in patients that were pre-treated and those that were treatment naive.

In general, the effects of linagliptin on fasting plasma glucose and treat to target proportions showed a pattern that was similar to the effects on HbA1c.

Combination with SU

Efficacy of linagliptin 5 mg once daily in combination with metformin and SU over 24 weeks was investigated in study 1218.18, where linagliptin 5 mg qd or placebo were added to ongoing therapy with metformin and an SU. This study was also included in the MAA for Trajenta. The treatment effect was clinically relevant. However, the treatment effect of linagliptin 2.5 mg twice daily in combination with metformin and SU was not investigated. It is unlikely that SU influences the efficacy and/or safety of linagliptin 2.5 mg. In healthy individuals, bioequivalence between linagliptin 5 mg once daily and linagliptin 2.5 mg twice daily has been shown. In addition, the efficacy of linagliptin 2.5 mg twice daily was similar to the efficacy of linagliptin 5 mg once daily in patients on metformin.

Long term efficacy

Data on long-term efficacy of linagliptin in combination with metformin and SU is available from patients who completed study 1218.18 and continued into trial 1218.40. The final results were provided during the evaluation. HbA1c levels remained reasonably stable. Long-term efficacy of linagliptin with metformin is also studied in new data from patients who completed study 1218.17 and continued into the open-label 78-week extension study 1218.40. The decrease in HbA1c was maintained in the individuals that continued the use of linagliptin with metformin. However, 38.7% of the patients using linagliptin in combination with metformin required rescue medication, and 33.8% of the patients using linagliptin in combination with metformin and SU required rescue medication. Nevertheless, it is conceivable that this is explained by the low threshold for the initiation of rescue therapy, the long study duration and the fact that the extension trials also allowed entry for patients who already received rescue medication in the initial trials.

Furthermore long-term data (54 weeks, interim analyses) are available from study 1218.52 (final results were provided during the evaluation), which is a double-blind metformin monotherapy-controlled extension trial in patients who completed the 24-week treatment period of study 1218.46 without requiring rescue medication. Throughout the entire treatment duration of 78 weeks, the linagliptin 2.5 mg + metformin 1000 mg combination achieved greater reductions in mean HbA1c than the metformin 1000 bid group. In addition, the proportion of patients who required rescue medication up to Week 78 was lower in the linagliptin 2.5+metformin 1000 bid group (12.6%) than in the metformin 1000 bid group (22.9%).

Subgroups

The efficacy of linagliptin and metformin over metformin could also be shown in relevant subgroups of patients. Thus factors such as age, gender, race (White vs. Asian), ethnicity, geographical region, and baseline BMI did not have an influence on the treatment effect. The presence of a washout period and the longer duration of the disease diabetes did negatively influence the treatment effect of the linagliptin/metformin combination therapy, but efficacy was acceptable. Interestingly, previous studies suggested that the treatment effect of linagliptin was lower in Whites than in Asians. However, the results of study 1218.46 suggest the opposite: the treatment effect of linagliptin 2.5 mg twice daily was smaller in Asians compared to Whites (-0.42% vs. -0.65% in combination with metformin 500 mg;-0. 39% vs. -0.59% in combination with metformin 1000 mg).

The number of patients aged 75 years or above was very low (in the grouping of 1218.17 and 1218.46 only 24 patients >75 years were included). During the evaluation, a study in elderly patients was submitted (1218.63). The estimated treatment difference between linagliptin (n=160) and placebo (n=78), calculated as the adjusted mean change from baseline in HbA1c at Week 24, was -0.64% (95% CI [-0.81; -0.48], p<0.0001), demonstrating superiority of linagliptin over placebo in the reduction of HbA1c.

2.5.4. Conclusions on the clinical efficacy

Treatment with 5 mg linagliptin once daily in combination with metformin resulted in a modest effect on the primary efficacy endpoint (HbA1c) with statistically significant reductions in HbA1c, fasting plasma glucose and postprandial glucose.

The efficacy of linagliptin 2.5 mg twice daily was similar to the efficacy of linagliptin 5 mg once daily in patients on metformin. Efficacy of the combination linagliptin 2.5 mg with metformin is acceptable.

The fixed dose combination has also not been investigated in combination with SU, but this is considered not necessary as efficacy of linagliptin 2.5 mg twice daily with metformin and SU is likely to be similar to that of linagliptin 5 mg once daily with metformin and SU.

Results of long term studies with a follow up suggest that efficacy is modest, but acceptable.

A study in elderly patients revealed that linagliptin added to ongoing treatment with glucose lowering drugs was superior to placebo after 24 weeks of treatment.

Patients with hepatic impairment were not investigated in sufficient amounts and this is reflected in the SmPC.

2.6. Clinical safety

Generally, the analysis of safety is presented separately for linagliptin monotherapy, metformin monotherapy, the combination of linagliptin + metformin, and the triple combination of linagliptin + metformin + SU. Since metformin has been in clinical use for some 50 years in the European Union, no dedicated studies to assess the safety of metformin were conducted. However, information on metformin monotherapy is included in some of the safety analysis sets (SAFs) for the linagliptin mono and combination arms.

For the evaluation of safety of the linagliptin + metformin combination, 14 clinical studies were analysed. The focus is on the safety data of the pivotal study 1218.17 (SAF-C1) (n=700) which compared linagliptin with placebo in patients who took metformin as background medication over 24 weeks. This safety analysis is supported by data from a pooled analysis of all placebo-controlled trials that used metformin either as background medication or as study treatment (n=1971) (SAF-C5). Additionally, for the establishment of the side effect profile of linagliptin 5 mg + metformin, an analysis set (SEA-2, n=1905) was generated that was based on SAF-C5 but considered solely patients who took linagliptin 5 mg resulting in an exclusion of 66 patients from study 1218.6 who took linagliptin 10 mg.

Data on long-term use of the linagliptin + metformin combination is available from the 24 week study 1218.46 with its double-blind extension trial 1218.52 to provide data over 78 weeks. This is supplemented by safety data from study 1218.20 that compared linagliptin + metformin with glimepiride + metformin over 104 weeks.

The safety of the triple combination therapy linagliptin + metformin + SU was evaluated based on the pivotal study 1218.18, a 24-week placebo-controlled trial of linagliptin added to background treatment of metformin + SU.

Adverse events of special interest were hypoglycaemia, hypersensitivity reactions, renal events (including laboratory evaluations), hepatic events (including laboratory evaluations), severe cutaneous adverse reactions, and pancreatitis. In addition, the evaluation of cardiovascular risk potentially associated with the use of linagliptin received particular attention.

Patient exposure

Overall, median exposures were similar between treatment groups. In the pooled metformin background studies the planned study durations ranged from 12 weeks (studies 1218.6 and 1218.62) to 24 weeks (studies 1218.17 and 1218.46). In the active-controlled long-term study 1218.20, 776 patients received linagliptin + metformin and 775 patients received linagliptin + glimepiride. The planned study duration was 104 weeks. A large proportion of patients in both treatment groups (linagliptin + metformin 80.5%, glimepiride + metformin 81.3%) was exposed to randomised study medication for 78 weeks or more. The mean exposure was comparable: 627 days (linagliptin + metformin) and 625 days (glimepiride + metformin). Additionally, long-term safety (n=567) included patients who completed the 24 weeks of study 1218.46, did not use rescue medication, and continued in the double-blind extension (study 1218.52). The planned treatment duration of the extension trial was 54 weeks. At the time of the interim analysis about 50% of patients had been treated in the extension trial for 24 weeks or more.

In the pivotal trial (1218.17), similar proportions of patients in both treatment groups completed the study (metformin 92.1%, linagliptin + metformin 92.5%). The most frequent reason for premature discontinuation was refusal to continue medication (metformin 2.3%, linagliptin + metformin 2.5%), followed by the occurrence of adverse events (1.7% in both treatment groups). In the pooled metformin background studies, 88.5% (metformin) and 92.2% (linagliptin + metformin) of patients completed the planned treatment period. The most frequent reason for premature discontinuation in both treatment groups were administrative issues, i.e. non-compliance with the protocol, lost to follow-up, and refusal to continue with trial medication (metformin 5.5%, linagliptin + metformin 3.7%).

In the active-controlled long-term set (study 1218.20) similar proportions of patients completed the trial period (linagliptin + metformin 75.6% vs. glimepiride + metformin 77.9%); the most frequent reasons for premature discontinuation were adverse events (linagliptin + metformin 7.9% vs. glimepiride + metformin 11.6%).

In the long-term safety set, overall 80.4% completed the planned treatment period. The proportions of premature discontinuations were lowest in the linagliptin 2.5 mg + metformin 1000 mg group (16.1%) and highest in the linagliptin 2.5mg + metformin 500 mg group (23.1%). The most frequent reasons for premature discontinuation were administrative issues (i.e. non-compliance with the protocol, lost to follow-up, and refusal to continue with trial medication) ranging from 5.6% in the metformin1000 group to 10.5% in the linagliptin 2.5 mg + metformin 500 mg group and adverse events ranging from 4.9% in the linagliptin 2.5 mg +metformin 1000 mg group to 6.8% in the metformin 1000 mg group.

In study 1218.18, the triple combination of linagliptin with metformin and SU was investigated. Median exposure of 170 days in both treatment groups was in accordance with this. Overall 92.0% (metformin + SU) and 92.7% (linagliptin + metformin + SU) completed the planned treatment period and hence the proportions of premature discontinuations were similar in both treatment groups (8.0% vs. 7.3%). The most frequent reasons for premature discontinuation were adverse events (metformin + SU 1.9%, linagliptin + metformin + SU 2.9%), non-compliance with study protocol (metformin + SU 1.5%, linagliptin + metformin + SU 2.4%), refusal to continue trial medication (metformin + SU 3.0%, linagliptin + metformin + SU 1.8%), and lack of efficacy (metformin + SU 1.5%, linagliptin + metformin + SU 0.3%).

Adverse events

In the pivotal trial 1218.17 (SAF-C1) the incidences of adverse events were comparable in the metformin (57.1%) and the linagliptin + metformin group (53.9%) (see table below). The incidence of adverse events of severe intensity was slightly higher in the linagliptin + metformin group (1.1% vs. 2.1%). Conversely the adverse events considered related to study drug by the investigators were more frequent in the metformin group (11.3% vs. 7.3%). The proportions of patients who discontinued because of adverse events (2.3% vs. 1.7%) were similar in both treatment groups as was the incidence of serious adverse events (2.8% vs. 3.4%).

Table 45. Adverse event overall summary for 1218.17 (SAF-C1) and the double-blind, placebo-controlled studies with metformin; comparing safety of linagliptin+metformin with PBO+metformin (SAF-C5) limited to patients taking linagliptin 5 mg (SEA-2) - TS

	SAF-C1 (1218.17)		SAF-C5 (Met vs. linagliptin+Met)		SEA-2 (Met vs. Lina5+Met)	
	Met N (%)	linagliptin +Met N (%)	Met N (%)	linagliptin +Met N (%)	Met N (%)	linagliptin +Met N (%)
Patients (100.0%)	177	523	583	1388	583	1322
Patients with AEs	101 (57.1)	282 (53.9)	295 (50.6)	660 (47.6)	295 (50.6)	632 (47.8)
Patients with AEs of severe intensity	2 (1.1)	11 (2.1)	10 (1.7)	29 (2.1)	10 (1.7)	27 (2.0)
Patients with investigator- defined drug-related AEs	20 (11.3)	38 (7.3)	51 (8.7)	101 (7.3)	51 (8.7)	95 (7.2)
Patients with AEs of special interest[1]	3 (1.7)	2 (0.4)	10 (1.7)	11 (0.8)	n.a.	n.a.
Patients with AEs leading to discontinuation	4 (2.3)	9 (1.7)	15 (2.6)	33 (2.4)	15 (2.6)	31 (2.3)
Patients with SAEs	5 (2.8)	18 (3.4)	15 (2.6)	41 (3.0)	15 (2.6)	37 (2.8)

n.a. = not applicable, was not performed for SEA-2
AEs = adverse events; SAEs = serious adverse events
SAF-C5 and SEA-2 are identical except for 66 patients excluded from SEA-2 because they had taken 10 mg linagliptin.
SAF-C1: Linagliptin was administered as 5 mg qd, metformin was given as background medication.
SAF-C5: Linagliptin was administered as 2.5 mg bid, 5 mg qd, or 10 mg qd; metformin was given as background medication, monotherapy (500 mg or 1000 mg, bid), or free combination therapy (500 mg or 1000 mg, together with linagliptin 2.5 mg; all bid).
[1] Including hypersensitivity reactions, renal events, and hepatic events (based on investigator-reporting, excluding severe cutaneous adverse reactions and pancreatitis).

The analyses demonstrated that the incidences of the most frequent adverse events were similar in both treatment groups in study 1218.17. The most frequent adverse events on SOC level were infections and infestations (22.0% vs. 21.6%) and gastrointestinal disorders (11.9% vs. 11.1%) both with almost identical incidences in both treatment groups. Differences of 2% or more were observed for musculoskeletal and connective tissue disorders which were more frequent in the linagliptin + metformin group (7.9% vs. 11.1%, see table below). Also injury, poisoning and procedural complications (2.3% vs. 5.0%) and respiratory, thoracic and mediastinal disorders (2.8% vs. 4.8%) were slightly more frequent in the linagliptin + metformin group than in the metformin group. Conversely, metabolism and nutrition disorders were substantially less frequent in the linagliptin + metformin group than in the metformin group (23.7% vs. 10.1%) mainly due to a lower incidence of hyperglycaemia (16.4% vs. 6.1%). Also hypoglycaemia was less frequent with linagliptin + metformin combination therapy than with metformin alone (2.8% vs. 0.6%). Furthermore, investigations (8.5% vs. 4.0%) and psychiatric disorders (2.8% vs. 0.8%) were less frequent with the combination therapy than with metformin alone. Comparing the frequencies of adverse events in the linagliptin + metformin group of the pivotal trial with those of the linagliptin group in the linagliptin mono submission demonstrates similar incidences across system organ classes.

Table 46. Adverse events occurring in more than 2% of patients in either treatment group on the preferred term level with their SOCs in SAF-C1 and/or SAF-C5 and SOCs with frequencies above 2% in either treatment group in SAF-C5, sorted by frequency in the linagliptin+metformin group of SAF-C5 - TS

	SAF-C1		SAF-C5		SEA-2	
	Met N (%)	linagliptin +Met N (%)	Met N (%)	linagliptin +Met N (%)	Met N (%)	linagliptin +Met N (%)
Patients (100.0%)	177	523	583	1388	583	1322
Patients with any adverse events	101 (57.1)	282 (53.9)	295 (50.6)	660 (47.6)	295 (50.6)	632 (47.8)
Infections and infestations	39 (22.0)	113 (21.6)	113 (19.4)	257 (18.5)	113 (19.4)	247 (18.7)
Nasopharyngitis	9 (5.1)	27 (5.2)	23 (3.9)	61 (4.4)	23 (3.9)	57 (4.3)
Urinary tract infection	9 (5.1)	16 (3.1)	18 (3.1)	39 (2.8)	18 (3.1)	37 (2.8)
Upper resp. tract infection*	4 (2.3)	15 (2.9)	13 (2.2)	32 (2.3)	13 (2.2)	32 (2.4)
Influenza	5 (2.8)	18 (3.4)	18 (3.1)	28 (2.0)	18 (3.1)	28 (2.1)
Gastrointestinal disorders	21 (11.9)	58 (11.1)	68 (11.7)	155 (11.2)	68 (11.7)	147 (11.1)
Diarrhoea	4 (2.3)	15 (2.9)	20 (3.4)	43 (3.1)	20 (3.4)	41 (3.1)
Nausea	3 (1.7)	6 (1.1)	12 (2.1)	24 (1.7)	12 (2.1)	21 (1.6)
Abdominal pain	4 (2.3)	2 (0.4)	5 (0.9)	4 (0.3)	5 (0.9)	4 (0.3)
Musculoskeletal and connective tissue disorders	14 (7.9)	58 (11.1)	45 (7.7)	127 (9.1)	45 (7.7)	124 (9.4)
Back pain	5 (2.8)	12 (2.3)	12 (2.1)	32 (2.3)	12 (2.1)	32 (2.4)
Arthralgia	3 (1.7)	11 (2.1)	11 (1.9)	24 (1.7)	11 (1.9)	24 (1.8)

	SAF-C1		SAF-C5		SEA-2	
	Met N (%)	linagliptin +Met N (%)	Met N (%)	linagliptin +Met N (%)	Met N (%)	linagliptin +Met N (%)
Patients (100.0%)	177	523	583	1388	583	1322
Patients with any adverse events	101 (57.1)	282 (53.9)	295 (50.6)	660 (47.6)	295 (50.6)	632 (47.8)
Metabolism and nutrition disorders	42 (23.7)	53 (10.1)	74 (12.7)	96 (6.9)	74 (12.7)	95 (7.2)
Hyperglycaemia	29 (16.4)	32 (6.1)	46 (7.9)	49 (3.5)	46 (7.9)	49 (3.7)
Hypoglycaemia	5 (2.8)	3 (0.6)	12 (2.1)	14 (1.0)	12 (2.1)	14 (1.1)
Hypertriglyceridaemia	5 (2.8)	2 (0.4)	9 (1.5)	4 (0.3)	9 (1.5)	4 (0.3)
Nervous system disorders	9 (5.1)	35 (6.7)	37 (6.3)	87 (6.3)	37 (6.3)	85 (6.4)
Headache	7 (4.0)	15 (2.9)	19 (3.3)	33 (2.4)	19 (3.3)	33 (2.5)
General disorders and administration site conditons	7 (4.0)	19 (3.6)	37 (6.3)	51 (3.7)	37 (6.3)	46 (3.5)
Investigations	15 (8.5)	21 (4.0)	37 (6.3)	51 (3.7)	37 (6.3)	48 (3.6)
Blood glucose increased	7 (4.0)	5 (1.0)	9 (1.5)	6 (0.4)	9 (1.5)	5 (0.4)
Injury, poisoning and procedural complications	4 (2.3)	26 (5.0)	13 (2.2)	50 (3.6)	13 (2.2)	49 (3.7)
Respiratory, thoracic and mediastinal disorders	5 (2.8)	25 (4.8)	14 (2.4)	49 (3.5)	14 (2.4)	47 (3.6)
Cough	3 (1.7)	11 (2.1)	5 (0.9)	24 (1.7)	5 (0.9)	23 (1.7)
Vascular disorders	7 (4.0)	23 (4.4)	22 (3.8)	39 (2.8)	22 (3.8)	38 (2.9)
Hypertension	6 (3.4)	17 (3.3)	17 (2.9)	29 (2.1)	17 (2.9)	28 (2.1)
Skin and subcutaneous tissue disorders	5 (2.8)	18 (3.4)	18 (3.1)	39 (2.8)	18 (3.1)	37 (2.8)

Cardiac disorders	2 (1.1)	12 (2.3)	8 (1.4)	29 (2.1)	8 (1.4)	26 (2.0)
Renal and urinary disorders	5 (2.8)	13 (2.5)	14 (2.4)	29 (2.1)	14 (2.4)	25 (1.9)
Psychiatric disorders	5 (2.8)	4 (0.8)	13 (2.2)	13 (0.9)	13 (2.2)	11 (0.8)

*Upper respiratory tract infection

SAF-C1: Linagliptin was administered as 5 mg qd; metformin was given as background medication.
SAF-C5 and SEA-2 are identical except for 66 patients excluded from SEA-2 because they had taken 10 mg linagliptin.

The profile of adverse events with the combination therapy with linagliptin + metformin + SU was consistent with that observed for linagiptin in combination with metformin. Overall, 61.2% (metformin + SU) and 67.3% (linagliptin + metformin + SU) of patients were reported with an adverse event. The frequency of patients with adverse events of severe intensity (1.5% vs. 2.5%), of adverse events leading to treatment discontinuation (1.9% vs. 3.2%), and of adverse events of special interest (0.4% vs. 1.3%) were generally low but slightly lower in the metformin + SU than in the linagliptin + metformin + SU groups. The incidence of serious adverse events was comparable between treatment groups (metformin + SU 4.2% vs. linagliptin + metformin + SU 3.2%). The percentage of patients with drug-related adverse events was higher in the linagliptin + metformin + SU group (18.3%) than in the metformin + SU group (12.2%). This was mainly due to a higher incidence of hypoglycemia (metformin + SU 7.6% vs. linagliptin + metformin+ SU 14.5%). Due to the mode of action of insulin secretagogues such as SUs, patients on combination therapy are known to be at risk of hypoglycaemic events.

Clinical laboratory evaluation and vital signs

In general, no clinically relevant findings or significant differences between linagliptin and control groups were observed for any of the measured parameters. In the trials with a duration shorter than 24 weeks, there were no changes in amylase levels. A comparison of changes in amylase values (normalized reference range: 30-110 U/L) over a 72 week period in patients dosed continuously with either metformin 1000 mg twice daily, linagliptin 2.5 mg plus metformin 500 mg twice daily, or linagliptin 2.5 mg plus metformin 1000 mg twice daily reveals that at week 12 the mean differences from baseline were 5.7, 5.1, and 9.9 U/L respectively. Fluctuations in amylase values were noted at subsequent time points, but ultimately the differences from baseline at week 78 were similar to those at weeks 12 and 24 (mean 2.1, 3.8, and 8.6 U/L respectively).

Blood pressure and pulse rates at baseline were comparable between treatment groups. Over the 24-week treatment period only minimal changes in mean values were observed both treatment groups (<1 mmHg for blood pressure and <1 bpm for pulse rate).

Hypoglycaemic events

The analysis of hypoglycaemic events was based on investigator-reporting. In the pivotal study 1218.17, the incidence of hypoglycaemia was higher in the metformin group (2.8%) than in the linagliptin + metformin group (0.6%) and this was corroborated in the set of all metformin-controlled studies SAF-C5 (metformin 2.5% vs. linagliptin + metformin 1.4%). As shown by the analysis of trial 1218.18, the addition of an SU to metformin led to a substantially higher frequency of hypoglycaemic events (16.0%) which was even higher in the triple combination group of linagliptin + metformin + SU (23.7%). In trial 1218.20, the difference between both treatment groups in hypoglycaemic events (linagliptin + metformin 7.5% vs. glimepiride + metformin 36.1%) was significant and in favour of linagliptin ($p<0.0001$). The majority of patients in all SAFs did not require assistance in case of a hypoglycaemic episode, and large proportions of patients in all SAFs had an onset of a first episode after 28 days. With combination therapy of linagliptin + metformin only 1 patient had a severe hypoglycaemic event (requiring assistance) during long-term treatment. However, in the triple combination of linagliptin + metformin + SU the incidence also of severe hypoglycaemic events appears to be increased.

Pancreatic disorders

In total, 10 cases of pancreas disorders were reported: 8 cases occurring during treatment with linagliptin + metformin, and 2 cases during treatment with glimepiride + metformin. In the post-treatment period, 2 cases of pancreas disorders were reported. None of the cases has been necrotising, haemorrhagic, or fatal. All of these cases but one (on patient in trial 1218.20 with pancreatic carcinoma) were included in the linagliptin monotherapy SCS. In clinical trials with linagliptin in combination with metformin, the incidence rate per 1000 patient-years in 3463 patients was 1.4. When the linagliptin plus metformin combination was compared to placebo plus metformin, the incidence rate per 1000 patient-years in 1322 patients treated with linagliptin plus metformin was 2.0. No events of pancreatitis were reported in the placebo plus metformin cohort of 483 patients. The incidence rate of pancreatitis for linagliptin plus metformin is similar to the data found in the linagliptin monotherapy development program. The risk of pancreatitis associated with linagliptin treatment has been added in section 4.4 of the Jentadueto SmPC.

Cardiovascular safety

Eight trials with a total of 5239 patients with T2DM were included in a cardiovascular meta-analysis in the MAA for Trajenta (linagliptin). The primary endpoint was based on adjudicated events and was a composite endpoint consisting of cardiovascular death (including fatal stroke and fatal MI), non-fatal MI, non-fatal stroke, and hospitalisation due to unstable angina. This analysis indicated that treatment with linagliptin was not associated with an increased cardiovascular risk compared with a pooled comparator group. However, linagliptin in combination with metformin was associated with angina pectoris (4 vs. 0 patients) and myocardial ischaemia (2 vs 0 patients). Linagliptin was not associated with an increase in CV risk, and the primary endpoint for linagliptin was significantly lower than for the total comparators, so this may be a chance finding.

Safety in special populations

Patients at high cardiovascular risk

A cardiovascular outcome study (study 1218.74) is currently ongoing. Patients are planned to be treated with randomised study medication for up to 400 weeks (i.e. 8 years), an interim analysis is planned to be performed based on a number of at least 80 adjudicated primary outcome events and a minimum duration of 1.5 years after randomisation of the first patient.

Elderly patients

Elderly patients might be at a higher risk of cardiovascular events. During the evaluation, a study in elderly patients was submitted (study 1218.63), where only patients of at least 70 years of age are included. Overall, 60 patients (75.9%) were reported with AEs in the placebo group and 123 patients (75.9%) were reported with AEs in the linagliptin group. The majority of the AEs were of mild or moderate intensity. Severe AEs were reported for 3 patients (3.8%) treated with placebo and 9 patients (5.6%) treated with linagliptin. Serious adverse events (SAEs) were reported for 5 patients (6.3%) in the placebo group and 14 patients (8.6%) in the linagliptin group. No patients died during the study. Two patients, both in the linagliptin group, had confirmed cardiac or cerebrovascular events adjudicated by the CEC. One patient had a non-fatal ischaemic stroke, and 1 patient was hospitalised due to coronary artery disease (unstable angina). None of the SAEs were considered drug-related. No patients aged >75 years had severe hypoglycaemia. The proportion of patients reported with investigator-defined hypoglycaemia by age group was similar for the two treatment groups in patients younger than 75 years of age (23.3% placebo; 25.3% linagliptin), but was lower in the placebo group in patients aged 75 years or older (8.3% placebo; 22.5% linagliptin). Logistic regression of the occurrence of hypoglycaemia indicated that treatment group was not associated with a significant difference in the odds of having a hypoglycaemic event (odds ratio 1.577, p = 0.2083). Age was not a significant factor (odds ratio 1.490, p = 0.2414), whereas background anti-diabetes medication (particularly SU and insulin) was significant (p = 0.0005). In this study in elderly individuals, it was also noted that more patients in the linagliptin group had increase in amylase compared to the placebo group (3.2% versus 1.3%). Increase in amylase levels is included in section 4.8 of the Jentadueto SmPC. One case with contact dermatitis was reported but it was not clear whether the event was contact dermatitis or urticaria, and causality between this event and study drug has not been established.

2.6.1. Discussion on clinical safety

The evaluation of the safety of linagliptin and linagliptin/ metformin FDC for the treatment of patients with T2DM was based on 6 phase I studies, 2 phase II studies, and 6 phase III studies. Data were analysed in several study groupings.

Analysis of the safety of linagliptin with metformin combination therapy was initially based on the pivotal studies (study 1218.17). This analysis was compared with data obtained from a pooled analysis of all metformin-controlled trials.

Most frequent adverse events

In the pivotal study, the most frequent adverse events were infections and infestations. Gastrointestinal disorders also occurred with almost identical incidences in both treatment groups. Differences of 2% or more were observed for musculoskeletal and connective tissue disorders which were more frequent in the linagliptin + metformin group. Also injury, poisoning and procedural complications and respiratory, thoracic and mediastinal disorders were more frequent in the linagliptin + metformin group. Conversely, metabolism and nutrition disorders were substantially less frequent in the linagliptin + metformin group than in the metformin group mainly due to a lower incidence of hyperglycaemia. Also hypoglycaemia was less frequent with linagliptin + metformin combination therapy than with metformin alone. Furthermore, investigations and psychiatric disorders were less frequent with the combination therapy than in the metformin group. The comparison of the adverse event incidences in the pivotal trial with the incidences in the pooled analysis of all placebo-controlled trials with metformin background indicated a similar safety profile of the linagliptin + metformin combination. The observed adverse events profile is in accordance with the safety profile of individual components such as gastrointestinal disorders (e.g. decreased appetite, nausea, vomiting, and diarrhoea) and pruritus associated with metformin; and nasopharyngitis, hypersensitivity, cough, and pancreatitis with linagliptin linagliptin. Hypoglycemia is identified as a side effect only when linagliptin and metformin are combined with sulfonylureas. This is addressed in sections 4.2 and 4.4 of the SmPC.

Subgroups

The analysis of the safety by relevant subgroups indicated that the safety profile of the linagliptin metformin combination was not influenced by age, gender, race (White and Asian), ethnicity, geographic region, renal impairment, or metformin dose.

The number of patients with hepatic impairment was too low to yield any relevant information in a subgroup analysis; these patients should not be treated with linagliptin. This issue is sufficiently addressed in the SmPC.

The assessment of safety in the study in elderly patients (1218.63) did not reveal any major concerns for treatment with linagliptin in the elderly population.

Adverse events of special interest

A comparison of changes in amylase values (normalized reference range: 30-110 U/L) over a 72 week period in patients dosed continuously with either metformin 1000 mg twice daily, linagliptin 2.5 mg plus metformin 500 mg twice daily, or linagliptin 2.5 mg plus metformin 1000 mg twice daily reveals that at week 12 the mean differences from baseline were 5.7, 5.1, and 9.9 U/L respectively. Fluctuations in amylase values were noted at subsequent time points, but ultimately the differences from baseline at week 78 were similar to those at weeks 12 and 24 (mean 2.1, 3.8, and 8.6 U/L respectively). In the study in elderly individuals, it was also noted that more patients in the linagliptin group had increase in amylase compared to the placebo group. Increase in amylase levels is included in section 4.8 of the SmPC. In total, 10 cases of pancreas disorders were reported. Although none of the cases has been necrotising, haemorrhagic, or fatal, this is an important issue. In clinical trials with linagliptin (used in combination with metformin), the incidence rate per 1000 patient-years in 3463 patients was 1.4. When the linagliptin plus metformin combination was compared to placebo plus metformin, the incidence rate per 1000 patient-years in 1322 patients treated with linagliptin plus metformin was 2.0. No events of pancreatitis were reported in the placebo plus metformin cohort of 483 patients. The incidence rate of pancreatitis for linagliptin plus metformin is similar to the data found in the linagliptin monotherapy development program. The risk of pancreatitis is appropriately covered in section 4.4 of the SmPC.

Photosensitivity reactions were reported by 4 patients: 3 cases occurring during treatment with linagliptin + metformin and 1 case during treatment with metformin. None of the events was serious, 1 event was considered drug-related. Angioedema was reported by 2 patients during treatment with linagliptin + metformin; one event was serious, both events were not assessed as drug-related. Regarding AE of special interest one case with contact dermatitis was reported in the study in elderly patients. However, it was not clear whether the event was contact dermatitis or urticaria, and causality between this event and study drug has not been established.

As for linagliptin monotherapy, linagliptin in combination with metformin was associated with angina pectoris (4 vs. 0 patients) and myocardial ischaemia (2 vs 0 patients). Although a formal meta-analysis of all randomised linagliptin studies demonstrated that linagliptin was not associated with cardiovascular risk, cardiovascular safety remains an important issue and is included as important missing information in the RMP. Higher frequencies of hypertension (0.1%) and hypertensive crisis (0.1%) were observed in the linagliptin group. A CV outcome study (study 1218.74) is currently ongoing. The results of this study will be submitted to the CHMP for review.

A higher incidence of infections has been described with other DPP-4 inhibitors. 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 incidence of infections with linagliptin was similar 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 long term effects remain a concern. This should be monitored closely post marketing.

Metformin is contraindicated for patients with GFR below 60 ml/min and this contraindication is also applicable for metformin in combination with linagliptin. This issue is considered as sufficiently addressed in the SmPC.

2.6.2. Conclusions on the clinical safety

Overall, in the phase III studies the 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. Adverse events are not different between linagliptin 2.5 mg twice daily and linagliptin 5 mg once daily.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfills the legislative requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for Pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected to occur either in the Union or in a third country.

Risk Management Plan

The applicant submitted a risk management plan (version 4.0, dated 15 May 2012), which is based on the RMP for the single component linagliptin (Trajenta) and complemented with relevant safety information for metformin. The identified and potentials risks and the areas of missing information that are proposed by the applicant are considered acceptable.

Table 47. 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 clinical trial safety data	Appropriate labelling in SmPC Section 4.2 When Jentadueto is used with SU, a dose reduction of SU may be considered to reduce risk of hypoglycaemia Section 4.4 When Jentadueto is used with SU, dose reduction of SU may be considered to reduce risk of hypoglycaemia Section 4.8 Hypoglycaemia is listed as adverse reaction for Jentadueto.
Pancreatitis	Routine pharmacovigilance and analysis of clinical trial safety data	Appropriate labelling in SmPC Section 4.8 Pancreatitis is listed as adverse reaction for Jentadueto.
Lactic acidosis	Routine pharmacovigilance and analysis of clinical trial safety data	Appropriate labelling in SmPC Section 4.2 monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in elderly Section 4.4 information on diagnosis, discontinuation of treatment and hospitalisation in case of lactic acidosis provided Section 4.5 information on increased risk for lactic acidosis in acute alcohol intoxication is provided Section 4.8 lactic acidosis is a listed side effect Section 4.9 lactic acidosis may occour in high overdose
Important potential risks		

Skin lesions	Routine pharmacovigilance and analysis of clinical trial safety data	Not applicable.
Hypersensitivity reactions	Routine pharmacovigilance and analysis of clinical trial safety data	Appropriate labelling in SmPC Section 4.3 Hypersensitivity to the active substances of Jentadueto is listed as contraindication Section 4.8 Hypersensitivity is listed as side effect for Jentadueto. Hypersensitivity is specified (e.g. urticaria, angioedema, bronchial hyperreactivity
Infections	Routine pharmacovigilance and analysis of clinical trial safety data	Not applicable.
Worsening of renal function	Routine pharmacovigilance and analysis of clinical trial safety data (planned CV-safety study 1218.74 [U10-2169])	Not applicable.
Important missing information		
Safety in subpopulations		
High risk patients with recent CV events	Routine pharmacovigilance and analysis of clinical trial safety data. Planned CV-safety study 1218.74 [U10-2169]	Not applicable.
Elderly patients (> 80 years)	Routine pharmacovigilance and analysis of clinical trial safety data (planned CV-safety study 1218.74 [U10-2169])	Appropriate labelling in SmPC Sections 4.2 Limited safety data for Jentadueto in patients >75 years of age is available and care should be exercised. Section 4.4 Serum creatinine should be be determined in elderly at least two to four times a year.
Paediatric use	Routine pharmacovigilance	Appropriate labelling in SmPC Sections 4.2 No data on safety and efficacy in children aged 0 to 18 years is available

		for Jentadueto.
Pregnant and lactating patients	Routine pharmacovigilance and analysis of clinical trial safety data	Appropriate labelling in SmPC Section 4.6 As a precautionary measure, it is preferable to avoid the use of Jentadueto during pregnancy. When becoming, or being pregnant, diabetes should be treated with insulin. Jentadueto should not be used during breastfeeding.
Oncological adverse reactions	Routine pharmacovigilance and analysis of clinical trial safety data	Not applicable.
Idiosyncratic adverse reactions	Routine pharmacovigilance and analysis of clinical trial safety data	Not applicable.
Immunological adverse reactions	Routine pharmacovigilance and analysis of clinical trial safety data	Not applicable.
Concomitant P-gp and CYP3A4 inhibitors	Routine pharmacovigilance and analysis of clinical trial safety data	Not applicable.

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

Description	Due date
1. RMP Ongoing CV safety study (study 1218.74)	Interim analysis (DMC safety assessment 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. Final report: December 2018.
2. RMP Ongoing meta-analysis of phase 3 and 4 studies	A meta-analysis of phase 3 and 4 studies is ongoing to further investigate cardiovascular safety. The final protocol should be submitted to CHMP for review within two months of the Commission Decision.

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 GLP-1. Linagliptin 5 mg has been approved in the EU as Trajenta in combination with metformin and metformin plus sulphonylurea. In addition, linagliptin 5 mg has been approved for use 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.

For other DPP-4 inhibitors sitagliptin (Januvia), vildagliptin (Galvus) and saxagliptin (Onglyza), fixed dose combinations with metformin (Janumet, Eucras and Komboglyze, respectively) have previously been approved in the European Union.

Because the pharmacokinetics of metformin require an at least twice daily dosing, for the development of the FDC the once daily dosing of 5 mg linagliptin (which is the posology of Trajenta) was split into 2 daily doses of 2.5 mg. In healthy individuals, linagliptin 2.5 mg twice daily was bioequivalent to linagliptin 5 mg once daily with respect to the exposure data over 24 hours $AUC_{0\text{-}24\ hours}$ and DPP-4 inhibition (study 1218.47). In its Scientific Advice from 2008, the CHMP requested a clinical study to show equivalence of twice daily dosing of linagliptin 2.5 mg with once daily dosing of linagliptin 5 mg (EMEA/CHMP/SAWP/472394/2008). Therefore, new clinical data were submitted. Study 1218.62 was a placebo-controlled study over 12 weeks that showed comparable efficacy of the linagliptin 2.5 mg twice daily regimen and the linagliptin 5 mg once daily regimen when added to metformin.

An additional phase III study for the establishment of efficacy of linagliptin 2.5 mg twice daily was study 1218.46. This study tested 2 linagliptin 2.5 mg-metformin combinations versus metformin. The combination of linagliptin with metformin 500 mg twice daily as well as with metformin 1000 mg twice daily demonstrated a relevant effect on HbA1c in comparison to metformin only.

The efficacy of linagliptin and metformin over metformin could also be shown in relevant subgroups of patients. Factors such as age, gender, race (White vs. Asian), ethnicity, geographical region, and baseline BMI did not have an influence on the treatment effect. Furthermore, the presence of washout of prior OADs and the time since diagnosis of diabetes did negatively influence the treatment effect of linagliptin metformin combination therapy, but efficacy was acceptable.

The clinical study in elderly patients (>70 years) showed that the glucose lowering effect of linagliptin in the elderly population is similar to that in younger patients.

Most clinical studies in the application dossier were conducted with linagliptin 2.5 mg tablets in combination with metformin tablets (1000 mg, 500 mg and 850 mg tablets). The Applicant conducted three bioequivalence studies (studies 1288.1,1288.2 and 1288.3) with the to be registered FDC tablets to justify the extrapolation of the results of the studies performed with the mono components to the FDC tablets. Based on the bioequivalence studies linagliptin 2.5 mg/metformin 1000 mg, linagliptin 2.5 mg/metformin 850 mg, linagliptin 2.5 mg/metformin 500 mg can be considered bioequivalent with the single dose formulation with linagliptin 2.5mg tablet and EU Glucophage 1000 mg, 500 mg and 850 mg respectively.

Justification for the linagliptin 2.5 mg/metformin 500 mg strength was requested by the CHMP on the basis of the clinical data of Jentadueto and of the use of metformin 500 mg bid in clinical practice taking into account effects on HbA1C, clinical outcome and intolerance of higher dosages of metformin. The Applicant decided to withdraw this lower strength during the evaluation.

Uncertainty in the knowledge about the beneficial effects

The treatment effect of linagliptin 2.5 mg twice daily in combination with metformin as dual combination therapy was investigated. The triple combination of linagliptin 2.5 mg twice daily in combination with metformin and SU was not investigated as such.

Long term efficacy of linagliptin was investigated in several trials. First, linagliptin 5 mg in combination with metformin or metformin with SU was investigated in study 1218.40, the open-label extension of studies 1218.17 and 1218.18. Interim analyses were presented with this application. New interim analyses provided efficacy data for linagliptin over up to 102 weeks. The decrease in HbA1c was maintained in the individuals that continued the use of linagliptin with metformin. However, 38.7% of the patients using linagliptin in combination with metformin required rescue medication, and 33.8% of the patients using linagliptin in combination with metformin and SU required rescue medication. The relatively large proportion of patients requiring rescue medication in the extension trials in comparison to the initial trials was a concern. However, it is conceivable that this is explained by the low threshold for the initiation of rescue therapy, the long study duration and the fact that the extension trials also allowed entry for patients who already received rescue medication in the initial trials. Second, long-term data (78 weeks) are available from study 1218.52, which is a double-blind metformin monotherapy-controlled extension trial in patients who completed the 24-week treatment period of study 1218.46 without requiring rescue medication. In the extension study, up to 54 weeks, mean HbA1c levels remained fairly stable in all 3 treatment groups. Throughout the entire treatment duration of 78 weeks, the linagliptin 2.5 mg + metformin 1000 mg combination achieved greater reductions in mean HbA_{1c} than the metformin 1000 mg bid group. In addition, the proportion of patients who required rescue medication up to Week 78 was lower in the linagliptin 2.5 + metformin1000 mg bid group (12.6%) than in the metformin 1000 mg bid group (22.9%).

The amount of patients with hepatic impairment was low.

Factors such as age, gender, race (White vs. Asian), ethnicity, geographical region, and baseline BMI did not have an influence on the treatment effect. The results with respect to race were divergent Previous studies suggested that the treatment effect of linagliptin was lower in Whites than in Asians, while the results of study 1218.46 suggest the opposite: the treatment effect of linagliptin 2.5 mg twice daily was smaller in Asians compared to Whites (-0.42% vs. -0.65%, respectively in combination with metformin 500 mg;-0. 39% vs. -0.59% respectively in combination with metformin 1000 mg).

Risks

Unfavourable effects

Overall, in the phase III studies the overall incidence of adverse events were very similar across studies, with linagliptin being mostly comparable to placebo and active comparator groups. The observed adverse events profile is in accordance with the safety profile of individual components such as gastrointestinal disorders (e.g., decreased appetite, nausea, vomiting, and diarrhoea) and pruritus associated with metformin; and nasopharyngitis, hypersensitivity, cough, and pancreatitis for linagliptin. Hypoglycaemia is identified as a side effect only when linagliptin and metformin are combined with sulfonylureas.

It is well known that metformin is contraindicated for patients with GFR below 60 ml/min. This contraindication is also applicable for metformin in combination with linagliptin.

The analysis of the safety by relevant subgroups indicated that the safety profile of the linagliptin/metformin combination was not influenced by age, gender, race (White and Asian), ethnicity, geographic region, renal impairment, or metformin dose.

A comparison of changes in amylase values over a 72 week period in patients dosed continuously with either metformin 1000 mg twice daily, linagliptin 2.5 mg plus metformin 500 mg twice daily, or linagliptin 2.5 mg plus metformin 1000 mg twice daily reveals that at week 12 the mean differences from baseline were 5.7, 5.1, and 9.9 U/L respectively. Fluctuations in amylase values were noted at subsequent time points, but ultimately the differences from baseline at week 78 were similar to those at weeks 12 and 24 (mean 2.1, 3.8, and 8.6 U/L respectively). In the study in elderly individuals, it was also noted that more patients in the linagliptin group had increase in amylase compared to the placebo group. This increase in amylase levels has been included in the SmPC. In total, 10 cases of pancreas disorders were reported. Although none of the cases has been necrotising, haemorrhagic, or fatal, this is an important issue. When the linagliptin plus metformin combination was compared to placebo plus metformin, the incidence rate per 1000 patient-years in 1322 patients treated with linagliptin plus metformin was 2.0. No events of pancreatitis were reported in the placebo plus metformin cohort of 483 patients. The incidence rate of pancreatitis for linagliptin plus metformin is similar to the data found in the linagliptin monotherapy development program. The risk of pancreatitis has been added to paragraph 4.4 "Special warnings and precautions for use".

The Safety analyses of the study in elderly patients revealed no new unexpected safety issues. The overall rate of AEs was higher than in most previous clinical trials with linagliptin, but the differences between placebo and treatment group were small.

Uncertainty in the knowledge about the unfavourable effects

Photosensitivity reactions were reported by 4 patients: 3 cases occurring during treatment with linagliptin + metformin and 1 case during treatment with metformin. None of the events was serious, 1 event was considered drug-related. Angioedema was reported by 2 patients during treatment with linagliptin + metformin; one event was serious, both events were not assessed as drug-related. Long term effects are unclear.

Angina pectoris (4 vs. 0 patients) and myocardial ischaemia (2 vs 0 patients) were associated with linagliptin treatment in combination with metformin. A formal meta-analysis of all randomised linagliptin studies was submitted. This meta-analysis demonstrated that overall linagliptin was not associated with cardiovascular risk. Somewhat higher frequencies of hypertension and hypertensive crisis were observed in the linagliptin group.

A higher incidence of infections has been described with other DPP-4 inhibitors. The long-term consequences of DPP-IV inhibition and its effects on other DPP-IV substrates, particularly with respect to immune function, are unknown. It is important to realize that these observations were done in relatively short term trials.

Benefit-risk balance

Importance of favourable and unfavourable effects

The most important favourable effect of linagliptin were added to treatment with metformin is lowering of HbA1c. This effect is relatively small in comparison to the effects of other drug classes, such as GLP-1 agonists, insulin and SU preparations. A fixed dose combination of linagliptin and metformin was a logical next step. Fixed-dose combinations may decrease the risk of medication non-compliance and this may translate into better clinical outcomes.

The triple combination of linagliptin 2.5 mg twice daily in combination with metformin and SU was not investigated. This may be a problem if SU influences the efficacy and/or safety of linagliptin 2.5 mg twice daily differently than it influences linagliptin 5 mg once daily, which is unlikely. In healthy individuals, bioequivalence of the linagliptin 2.5 mg/metformin fixed dose combination posology versus the separate components has been demonstrated. In addition, it has been demonstrated that the efficacy of linagliptin 2.5 mg twice daily was similar to the efficacy of linagliptin 5 mg once daily in patients on metformin. Therefore the CHMP considered that data submitted which include a linagliptin 5 mg qd triple combination study sufficiently support the use of Jentadueto in triple combination with a sulphonylurea.

The fact that at least half of the patients were not treated with oral antidiabetic drugs before inclusion in study 1218.46 is not in line with the requested indication for linagliptin/metformin in patients that are insufficiently controlled with metformin or metformin in combination with SU. The inclusion of treatment naive patients resulted in an overestimation of the treatment effects of metformin in this study. Nevertheless, the treatment effects of linagliptin were similar in patients that were pretreated and those that were treatment naive.

While T2DM is a progressive disease and the long term effects of linagliptin are relatively modest, long-term data from study 1218.52 demonstrated that the linagliptin 2.5 mg + metformin 1000 mg combination achieved greater reductions in mean HbA1c than the metformin 1000 mg bid group. In addition, the proportion of patients who required rescue medication up to Week 78 was lower in the linagliptin 2.5 + metformin1000 mg bid group (12.6%) than in the metformin 1000 mg bid group (22.9%).

The increase in amylase levels and the increased risk for pancreatitis in the long term are considered important concerns. The incidence rate of pancreatitis for linagliptin plus metformin is similar to the data found in the linagliptin monotherapy development program. Although none of the cases has been necrotising, haemorrhagic, or fatal, the risk of pancreatitis has included in section 4.4 of the SmPC and as an important potential risk in the RMP. In line with the SmPC guideline, increase in amylase levels has also been included in section 4.8 of the SmPC.

Photosensitivity reactions and angioedema were observed rarely. Angioedema (hypersensitivity reactions) is included in section 4.8 of the SmPC and is included in the RMP as an important potential risk.

A low number of CV events were observed with linagliptin in combination with metformin although the absolute numbers of CV events were very low. This emphasizes the need for a cardiovascular safety study. A CV outcome study is currently ongoing (study 1218.74) and is also included in the RMP.

The possible increased risk of infections and skin reactions and worsening of renal function have been included as important potential risk in the RMP. Long-term consequences of linagliptin on immune function are unknown. If present, this is likely to be a class effect of DPP-IV inhibitors. Immunological adverse reactions are included as important missing information in the RMP and will be monitored closely post marketing.

Due to its mechanism of action, linagliptin in combination with metformin has a relatively low risk for hypoglycaemia. The low propensity of linagliptin to cause hypoglycaemia when compared to SU and insulin may be relevant in patients more prone to hypoglycaemic events.

Furthermore compared to most insulins and SU the addition of linagliptin to metformin does not increase body weight. In an overweight population, this can be considered a valuable advantage.

Benefit-risk balance

The clinical short term effect of linagliptin 2.5 mg with metformin twice daily is comparable to linagliptin 5 mg once daily in combination with metformin. Linagliptin 2.5 mg twice daily was shown to be bioequivalent to linagliptin 5 mg once daily for $AUC_{0\text{-}24\ hours}$ and DPP-4 inhibition. In addition it has been demonstrated that the to be registered linagliptin 2.5 mg/metformin 1000 mg and linagliptin 2.5 mg / metformin 850 mg FDC tablets are bioequivalent with the linagliptin 2.5 mg tablet given concomitantly with EU metformin 1000 mg and 850 mg respectively.

Several possible side-effects were identified, but the risks were in general only mildly elevated in comparison to placebo and comparators. Cardiovascular risk and pancreatitis are of particular interest. A cardiovascular outcome study is currently ongoing and the results will be submitted for the CHMP for review (as stated in the RMP). Furthermore, an increased incidence of pancreatitis is of concern, as this is a potential serious life threatening disease. The risk of pancreatitis has been included in section 4.4 of the SmPC and will be further monitored.

In conclusion the CHMP considers that the benefits outweigh the risks of Jentadueto (linagliptin 2.5 mg/metformin 850 mg and linagliptin 2.5 mg/metformin 1000 mg) in the claimed indication.

Discussion on the benefit-risk balance

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

"Treatment of adult patients with type 2 diabetes mellitus:

Jentadueto is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients inadequately controlled on their maximal tolerated dose of metformin alone, or those already being treated with the combination of linagliptin and metformin.

Jentadueto is indicated in combination with a sulphonylurea (i.e. triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea."

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 Jentadue in the treatment of adult patients with type 2 diabetes mellitus:

Jentadueto is indicated as an adjunct to diet and exercise to improve glycaemic control in adult patients inadequately controlled on their maximal tolerated dose of metformin alone or those already being treated with the combination of linagliptin and metformin.

Jentadueto is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in adult patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.

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 and PSUR cycle

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 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.