Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Public Assessment Report for Linagliptin

Proprietary Product Name: Trajenta

Sponsor: Boehringer Ingleheim (Australia) Pty Ltd

December 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

I. Introduction to Product Submission

Submission Details

Type of Submission	New Chemical Entity
Decision:	Approved
Date of Decision:	21 October 2011
Active ingredient(s):	Linagliptin
Product Name(s):	Trajenta
Sponsor's Name and Address:	Boehringer Ingelheim (Australia) Pty Ltd 78 Waterloo Rd North Ryde NSW 2113
Dose form(s):	Film-coated tablet
Strength(s):	5 mg
Container(s):	Aluminium (Al)/Al blister pack
Pack size(s):	10 tablets (sample pack) 30 tablets
Approved Therapeutic use:	Trajenta is indicated in adult patients with Type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, as add on to metformin, sulphonylureas or metformin plus sulphonylueras.
Route(s) of administration:	Oral (PO)
Dosage:	Adult: the recommended dose is 5 mg once daily.
ARTG Number (s)	175499

Product Background

This AusPAR describes the application by Boehringer Ingelheim Pty Ltd to register a new chemical entity, linagliptin (Trajenta), as an oral agent for the treatment of Type 2 diabetes mellitus in conjunction with diet and exercise, as monotherapy or as an add on to metformin, sulphonylureas, thiazolidinediones or metformin plus sulphonylureas

Linagliptin is stated to be a synthetic, non peptide, reversible inhibitor of dipeptidyl-peptidase-4 (DPP4). Linagliptin is stated to be rapidly acting. Through inhibition of DPP4, linagliptin inhibits the proteolytic degradation of the incretins GLP-1 and GIP. The increased actions of GLP-1 and GIP result in increased glucose dependent insulin secretion, decreased glucagon secretion, delayed gastric emptying and increased satiety. Whilst linagliptin is a new chemical entity it does not have a novel mechanism of action.

The Advisory Committee on Prescription Medicines (ACPM) has considered several drugs in this class including sitagliptin, vildagliptin and saxagliptin.

Currently, *sitagliptin* is registered for the treatment of diabetes mellitus Type 2 in persons 18 years of age and older who have failed dietary measures and exercise: as dual

combination therapy with metformin or with a sulfonylurea or with a thiazolidinedione where the use of a thiazolidinedione is considered appropriate.

Vildagliptin: Treatment of diabetes mellitus Type 2 in persons 18 years of age and older, as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes with one of metformin, a sulfonylurea or pioglitazone when diet, exercise and the single agent do not result in adequate glycaemic control.

Saxagliptin: Treatment of diabetes mellitus Type 2 in persons 18 years of age and older, as an adjunct to diet and exercise to improve glycaemic control in patients with Type 2 diabetes with one of metformin, a sulfonylurea or pioglitazone when diet, exercise and the single agent do not result in adequate glycaemic control.

Saxagliptin is also indicated for initial combination therapy with metformin in a subset of patients.

Regulatory Status

The international regulatory status update for the similar applications submitted by Boehringer Ingelheim seeking registration of Trajenta linagliptin tablet is presented in Table 1 below.

Table 1. Summary of International regulatory status

Country	*Submission Date*	*Application status*
US	2-JUL-2010	APPROVED 2-MAY-2011
EU	30-JUN-2010	APPROVED 24-AUG-2011
Canada	16-AUG-2010	APPROVED 28-JUL-2011
Switzerland	6-AUG-2010	Ongoing
New Zealand	Not submitted	–

Product Information

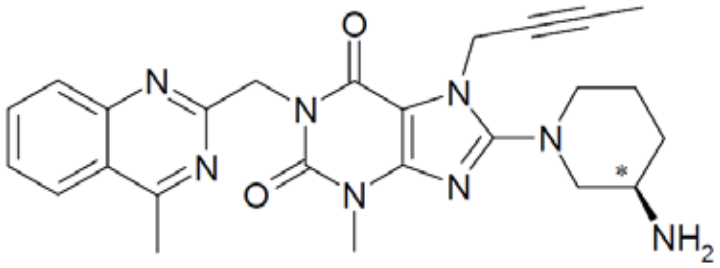
The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

II. Quality Findings

Drug Substance (active ingredient)

Linagliptin is made by chemical synthesis. It has one chiral centre and is presented as a single (*R*) enantiomer (See Figure 1).

Figure 1. Chemical structure of Linagliptin.



linagliptin [BI 1356]

Linagliptin solubility is high. The drug substance is milled. There is limited particle size control. Particle size does not significantly affect tablet dissolution. Impurity controls are acceptable.

Drug Product

The proposed Trajenta tablets are film-coated, immediate release tablets. They are not scored. The formulation is conventional.
Some early clinical trials used significantly higher doses than are now proposed. The tablets proposed for registration have the same formulation as that used in all Phase III clinical batches, except that the latter included yellow iron oxide in the film coat. Some early clinical trials used an oral powder as well as uncoated tablets (25, 50 and 200 mg). Other Phase II trials used 0.5, 1, 2.5, 5 and 10 mg tablets.
Linagliptin solubility is highly soluble (BCS[1]) from pH 1 to pH 8.0. Boehringer Ingelheim has argued that dissolution is very unlikely to limit drug absorption.

The proposed shelf life is 30 months, store below 30°C. No changes on storage were detected.

Chemistry and quality control aspects are considered acceptable.

Bioavailability

Linagliptin does not racemise *in vivo*. Pharmacokinetics are non-linear ("less than proportionally from 2.5 to 5 mg, more than proportionally from 25 to 100 mg and approximately proportionally for doses 100–600 mg"). Linagliptin pharmacokinetics have been summarised by A. J. Scheen.[2]

Scheen refers to a published account of Study 1218.7, which used radioactive carbon (^{14}C) labelled drug given to healthy volunteers in parallel groups either intravenously (5 mg: n=6) or as an oral solution (10 mg: n=6). After oral doses, the fraction absorbed based on total radioactivity in plasma was estimated to be 37%. Faecal recovery was dominant, giving 58.2% (IV) or 84.7% (oral) of the radioactivity, whereas urinary radioactivity excretion accounted for 30.8% (IV) or 5.4% (oral) of the radioactive dose administered. Unchanged linagliptin was the most abundant radioactive species in all matrices investigated. Metabolite levels were low.

[1] The Biopharmaceutics Classification System (BCS) is guidance for predicting the intestinal drug absorption provided by the U.S. Food and Drug Administration. According to the BCS, drug substances are classified as follows: Class I: high permeability, high solubility; Class II: high permeability, low solubility; Class III: low permeability, high solubility; Class IV: low permeability, low solubility.

[2] A. J. Scheen *Pharmacokinetics of dipeptidylpeptidase-4 inhibitors* Diabetes, Obesity and Metabolism Volume 12, Issue 8, pages 648–658, August 2010 DOI: 10.1111/j.1463-1326.2010.01212.x

The absolute bioavailability of a 1x10 mg linagliptin tablet formulation (versus 5 mg IV) was investigated in Study 1218.10. Because of the nonlinear pharmacokinetics, a population pharmacokinetic model was used in analysis. The absolute bioavailability of the 10 mg tablet was estimated to be 30% but with high individual variability [47% gCV%].

Comparison with an oral solution shows that related 1 and 10 mg tablets are 'optimally formulated' (Study 1218.8). The relative bioavailability of the clinical trial formulation TF II (trial formulation II) was compared to a Powder in Bottle formulation at 1 mg and 10 mg doses; bioavailability was comparable (Study 1218.8).

The concurrent intake of food caused a delay in time to maximal plasma concentration (T_{max}) of about 2 hours and a reduction in maximal plasma concentration (C_{max}) of about 15%. Intake of a high fat meal therefore reduces the rate of absorption; however it has no effect on the extent of absorption.

Quality Summary and Conclusions

The application was considered by the Pharmaceutical Subcommittee. The PSC recommended:

1. There should be no objection on pharmaceutic and biopharmaceutic grounds to approval of the application by Boehringer Ingelheim Pty Ltd to register Trajenta film coated tablet containing 5 mg of linagliptin provided all outstanding issues are addressed to the satisfaction of the TGA.
2. The PSC endorses all the questions raised by the TGA in relation to pharmaceutic and biopharmaceutic issues.

3. There is no requirement for this application to be reviewed again by the PSC before it is presented for consideration by the ACPM.

The chemistry and quality control questions have now been resolved.

Recommendation

Registration is recommended with respect to chemistry, quality control and bioavailability aspects.

III. Nonclinical Findings

Introduction

The overall quality of the nonclinical dossier was high, with all pivotal toxicity studies conducted under Good Laboratory Practice (GLP) conditions. Safety related studies not performed under GLP conditions were conducted in established laboratories and adequately documented.

Pharmacology

Primary pharmacology

Dipeptidyl peptidase IV (DPP-4) is a ubiquitous enzyme that catalyses the inactivation of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) through removal of the N-terminal dipeptide. These incretin hormones stimulate glucose-dependent insulin secretion by pancreatic β-cells and stimulate pancreatic β-cell proliferation. GLP-1 also stimulates insulin biosynthesis by pancreatic β-cells, inhibits glucagon secretion from pancreatic α-cells and inhibits gastric emptying. Linagliptin, as a DPP-4 inhibitor, is envisaged to improve glycaemic control in patients with Type 2 diabetes by enhancing the levels of the active forms of GLP-1 and GIP.

Linagliptin was shown to be a competitive and reversible inhibitor of DPP-4 with comparable potency against mouse, rat, dog and human plasma DPP-4 (50% inhibitory concentration (IC_{50}) values, 3–10 nM). The IC_{50} determined in human plasma (3.6 nM) compares favourably with the clinical trough plasma concentration (C_{min}) at steady-state at the proposed clinical dose (4.9 nM). *In vivo*, orally administered linagliptin caused marked and long lasting decreases in plasma DPP-4 activity (in mice, rats, dogs and monkeys), increased the level of the active form of GLP-1, increased insulin levels (in diabetic rats) and improved glucose tolerance (in normal and diabetic mice and diabetic rats), consistent with the proposed pharmacological action. The latter was observed at doses ≥1 mg/kg orally (PO) in mice and rats (estimated exposures were 0.6 and 0.3 times the clinical area under the plasma concentration time curve (AUC) in the respective species).

Repeated administration to diabetic mice (3 mg/kg/day PO linagliptin for 8 weeks) resulted in significantly lower HbA_{1C} levels, reduced kidney glucose uptake and lower levels of triglyceride in the liver. Exposure at this dose is estimated to be ~2 times the clinical exposure (based on the exposure in study U10-1500-01).

Linagliptin is proposed for use as monotherapy or in combination with thiazolidinediones, sulphonylureas or metformin. A linagliptin/metformin combination study was conducted in diabetic mice, with significantly greater glucose tolerance seen in animals treated with the combination compared to monotherapy with either component. No other combinations were examined.

The major metabolite of linagliptin, CD1790, had no inhibitory activity against DPP-4 at concentrations up to 1 mM (300 times the clinical C_{max} for CD1790).

Secondary pharmacodynamics

In a screen against other peptidases, linagliptin was found to have detectable inhibitory activity at the human fibroblast activation protein (FAP) with an IC_{50} of 94 nM (~7.3 times the clinical plasma C_{max} at steady state). While FAP is upregulated in wound healing, there was no apparent effect on wound healing in mice at oral doses of 30 mg/kg/day (estimated relative exposure ~45x based on the exposure data from the Study U10-1500-01), suggesting the *in vitro* inhibitory activity at FAP is not of biological significance. Linagliptin produced no significant inhibition of other peptidases (DPP-II, plasmin, trypsin, thrombin, aminopeptidase N, aminopeptidase P, prolyl oligopeptidase, DPP-8 or DPP-9) at concentrations up to 10 mM (775 times the clinical C_{max}). The selectivity of linagliptin for DPP-4 over DPP-8 and DPP-9 was >10000-fold and significantly greater than that of sitagliptin (>2700; Sitagliptin [Januvia®] European Public Assessment Report (EPAR)[3]), or

[3]Sitagliptin [JANUVIA®] EPAR (2007) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000722/WC500039057.pdf

vildagliptin or saxagliptin (which are 250–400-fold selective for DPP-4 over DPP-8 and 30–75-fold selective with respect to DPP-9; Vildagliptin AusPAR[4], 2010; Saxagliptin EPAR[5]).

In a screen of approximately 50 different receptors or ion channels, the only significant inhibitory activity was at the human M_1, M_2 and M_3 muscarinic receptors, with IC_{50} values of 295 to 1000 nM. As these are >22 times the clinical C_{max}, they are unlikely to be clinically relevant. The major human metabolite of linagliptin, CD1790, had no significant inhibitory activity at circa 55 different receptors, ion channels or peptidases at clinically-relevant concentrations.

Safety pharmacology

Specialised safety pharmacology studies covered the central nervous system (CNS), cardiovascular, renal and gastrointestinal systems. Not all of the studies were GLP-compliant but there were GLP-compliant studies covering the core battery of vital organ systems in single species and the design and conduct of the studies are considered adequate overall. CNS function was unaffected in mice and rats treated with linagliptin at up to 30 mg/kg PO and 600 mg/kg PO, respectively. The respective peak plasma concentrations at these doses in mice and rats are estimated to be 140 and ~950 times the clinical C_{max}.

In vitro, no significant inhibition of the hERG K^+ channel was seen at concentrations up to 10 mM linagliptin, while a slight (9%) shortening of action potential duration was seen in guinea pig papillary muscle at this concentration; there was no effect on action potential duration at the next highest concentration, 3 µM. Given the mild nature of this effect and the no effect concentration being >2000-times the peak free level expected in patients, this finding is not considered to be of clinical concern. Cardiovascular and respiratory function were unaffected in rats and dogs at oral doses up to 600 mg/kg and 10 mg/kg (estimated exposure ratio based on C_{max} [ER_{Cmax}], 950 in rats and 170 in dogs). Moderate hypotension and tachycardia were seen in dogs treated with ≥15 mg/kg/day PO linagliptin (ER_{Cmax}, 388). This coincided with pseudoallergic reactions and increased plasma histamine levels (see *Repeat-dose toxicity*). In a specialised safety pharmacology study, Cynomolgus monkeys treated with ≥60 mg/kg/day PO ($ER_{Cmax,}$ 775) had increased heart rates; there was no effect on cardiovascular parameters at 12 mg/kg (ER_{Cmax}, 310). In repeat-dose toxicity studies, no significant electrocardiogram (ECG) effects were seen in Cynomolgus monkeys at up to 300 mg/kg/day PO linagliptin (ER_{Cmax}, >2200). Based on large safety margins in nonclinical studies, no adverse cardiovascular effects are predicted at the proposed clinical dose.

No significant effects on the renal or gastrointestinal system were evident in rats at oral doses up to 30 mg/kg (estimated ER_{Cmax}, 112) apart from slight inhibition of gastrointestinal transit.

Pharmacokinetics

Linagliptin was rapidly absorbed by the oral route in all species (mouse, rat, rabbit, dog, Cynomolgus monkey and human) with T_{max} values ranging from 0.5 to 2.5 h. Oral bioavailability ranged from 40% to 69% in rats and monkeys and 30% in humans. Exposure to linagliptin increased with dose in all species but nonlinear plasma kinetics were apparent at low doses, attributed to saturable binding of linagliptin to DPP-4 in plasma and tissues. In wild-type animals, plasma half-lives of linagliptin were long (up to 49 h in mice, 61 h in rats, 59 h in rabbits and 47 h in monkeys) and inversely-related to dose (declining to as little as 4.5 h) but were significantly shorter than in human subjects (131 h).

[4] Vildagliptin AusPAR (2010) http://www.tga.gov.au/pmeds/auspar/auspar-galvus.pdf

[5] Saxagliptin EPAR (2009) http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/001039/WC500044319.pdf

In contrast, in DPP-4 deficient mice and rats, plasma half-lives were much shorter (1.8–9.2 h) and were largely independent of dose. Moderate to high clearance was seen in mice and rats whereas only moderate clearance was seen in Cynomolgus monkeys and humans. Clearance was largely not affected by dose in animals but dose dependence for clearance was seen in human subjects. No sex differences were observed in any of the species. There was no or only modest accumulation with repeated dosing.

Plasma protein binding by linagliptin was high and concentration dependent in mouse, rat, rabbit, monkey and human plasma and comparable across species. Maximum binding was 99% in mouse, rat and human plasma but saturation of linagliptin binding was evident at >1 nM decreasing to a constant 70–80% at >100 nM. The free fraction in humans at the clinical C_{max} is estimated to be ~10%. Protein binding in the plasma from DPP-4 deficient rodents was moderate (60–82%) and independent of concentration, indicating the concentration-dependent protein binding in plasma from wild type animals was attributable to DPP-4. Likewise, distribution of linagliptin into blood cells showed positive concentration dependence in wild type animals. The volume of distribution of linagliptin was high in all species and after administration of ^{14}C-linagliptin to mice and rats, rapid and widespread distribution of radioactivity was observed. The liver, kidneys, spleen, thymus, lung and gastrointestinal tract had the greatest exposure. There was limited penetration of the blood-brain barrier. Only slight tissue accumulation was seen following repeated administration. Comparison of tissue distribution profiles in wild-type and DPP-4 deficient rodents indicated peripheral DPP-4 had a major impact on the disposition of linagliptin.

Metabolism of linagliptin included oxidation, epoxidation, N-acetylation, carboxylation, substitution of the amino group on the piperidine moiety by a hydroxy group and subsequent conjugation with cysteine, glucuronate and/or glucose. More than 50 metabolites were detected across species and matrices. Unchanged linagliptin was by far the dominant circulating species in laboratory animals (mice, rats, rabbits and monkeys) and humans. CD1790 was the only metabolite to account for >10% of drug-related material in plasma samples. All significant human metabolites were also seen in one or more animal species. *In vitro* studies indicated a major role of CYP3A4 in the formation of CD1790 *via* generation of the ketone intermediate CD10604. CD1790 was formed by reduction of CD10604 with high stereoselectivity to the *S*-isomer, a reaction catalysed by aldo-keto reductases present in multiple tissues, including the liver and human blood.

Excretion of radioactivity following oral dosing with ^{14}C-linagliptin was primarily *via* the faeces in laboratory animals (65–97% of the administered dose in mice, rats, rabbits and monkeys) and humans (82%). Unchanged linagliptin was the dominant species in both faeces and urine in all species. Biliary excretion was demonstrated in the laboratory animal species. Experiments in rats indicated a minimal effect of enterohepatic recirculation on exposure. *In vitro* studies indicated active urinary excretion and, due to saturable binding to DPP-4, the proportion of excretion in urine varied with dose in wild-type mice and rats.

Overall, the pharmacokinetic profile of linagliptin was qualitatively similar across the laboratory animal species and humans, supporting the use of the chosen species in the pivotal toxicity studies.

Pharmacokinetic drug interactions

Mechanism-based (irreversible) inhibition of human cytochrome P450 (CYP) isoform CYP3A4 was observed for linagliptin and CD1790 (respective K_I values, 1.75 and 88.3 µM; k_{inact}, 0.041 and 0.25 min^{-1}). Based on these kinetic parameters and the nanomolar

circulating levels in humans at the proposed dose, the model of Obach's [6] indicates likely limited clinical relevance. Consistent with these findings, significant inhibition of CYP3A4 activity was observed in cultures of human hepatocytes exposed to 2 μM linagliptin (replenished daily for 3 days) but not 200 nM (>15-times the clinical C_{max}).

Linagliptin displayed no or only very weak competitive inhibitory activity against other human CYP isoforms (1A1/2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 4A11). IC_{50} values were >100 μM, more than 7750 times the clinical C_{max}. CD1790 was also shown to have no significant inhibitory activity against these isozymes; the IC_{50} at the most sensitive isozyme (15 μM at CYP2C9) was >4500 times the clinical C_{max} for the metabolite. There was no or only very weak inhibition by linagliptin of the human renal transporters OATP-B, OCT2, OAT1, OAT3, OAT4, OCTN2, OATP2, OATP8, OCTN1, OCT1 and OATP2; IC_{50} values were ≥45 μM, more than 3400-times the clinical C_{max}. Linagliptin was identified as a substrate for P-glycoprotein (K_m, 187 μM) and OATP8, OCT2, OAT4, OCTN1 and OCTN2 (K_m values not determined) but not OATP2, OATP-B, OCT1, OAT1, OAT3, MRP2 or BCRP. Linagliptin was a weak inhibitor of P-glycoprotein (IC_{50} ≥55 μM; >4250 times the clinical C_{max}). Based on the large margins between IC_{50} values and C_{max}, these activities are not considered clinically relevant. Linagliptin did not induce CYP1A2, 2B6 or 3A4 in human hepatocytes *in vitro* (≤2 μM; ~155-times the clinical C_{max}) or CYP1A, 2B, 2E1, 3A or 4A *in vivo* in rats (≤60 mg/kg/day PO for 4 days; estimated ER_{AUC}, 88). Although CYP3A4 plays a major role in the metabolism of linagliptin, given that the drug is predominantly cleared by excretion, co administration of a CYP3A4 inhibitor with linagliptin is unlikely to have a significant effect on linagliptin exposure.

Linagliptin is proposed to be used in combination with metformin, a thiazolidinedione or a sulfonylurea. No *in vivo* pharmacokinetic interaction studies were conducted with linagliptin in laboratory animals. Based on inhibition/substrate studies of CYP450 enzymes and transporters, no significant effects on other drugs are predicted at the proposed clinical dose. However, as linagliptin is a substrate for P-glycoprotein, co administration of an inhibitor or inducer of this transporter may affect linagliptin exposure.

Toxicology

Acute toxicity

Single dose toxicity studies were conducted in mice and rats following intravenous (IV) and PO administration and in monkeys using an escalating PO dosage regimen. The conduct of the set of rodent studies was in accordance with the TGA adopted European Union (EU) guideline[7]; more than one mammalian species was used, animals of both sexes were examined, the clinical (PO) and IV routes were used, the observation period (14 days) was appropriate and the animals were subjected to necropsy. The maximum non lethal oral dose was 1000 mg/kg in rats (>1800 times the clinical dose on a body surface area basis) and 150 mg/kg in monkeys (the highest dose tested; 545 times the human dose adjusted for body surface area). Oral dosing at 1000 mg/kg in mice was lethal in 1 of 12 cases (>900-times the human dose adjusted for body surface area). Overall, the data indicate low toxicity for linagliptin when taken orally. Clinical signs at the highest tested oral doses in mice and rats included hypoactivity and piloerection. Target organs for toxicity were identified as the gastrointestinal tract, liver, kidney, lungs (rats only), thymus and spleen. Novel toxicities were not observed with IV compared with PO dosing.

[6] Obach, R.S., Walsky R.L. and Venkatakrishnan K. (2007) Mechanism-based inactivation of human cytochrome p450 enzymes and the prediction of drug-drug interactions. *Drug Metab. Dispos.* **35:** 246–255.

[7] Note for guidance on single-dose toxicity (3BS1a). http://www.tga.gov.au/pdf/euguide/vol3bs1aen.pdf

Repeat-dose toxicity

Repeat-dose toxicity studies of up to 3 months duration were performed in mice, 6 months in rats, 4 weeks in dogs, 3 days in mini-pigs (without necropsy) and 12 months in Cynomolgus monkeys using the clinical (PO) route. IV studies of up to 2 weeks duration were also conducted in rats and monkeys. These IV studies did not significantly add to the characterisation of the toxicological profile. As such, the PO studies will be the focus of this assessment. The duration of the pivotal studies, the species used (rats and monkeys), group sizes and the use of both sexes were consistent with TGA adopted European Union (EU) guidelines[8]. Toxicokinetic analyses were performed in all studies; exposure ratios for linagliptin based on animal: human $AUC_{0-24\,h}$ values in selected studies are shown in Table 2. Very high multiples of the anticipated clinical exposures to linagliptin were achieved in the submitted studies. Toxicokinetic data were also obtained for CD1790 (the main human metabolite) in the pivotal repeat-dose toxicity studies and the carcinogenicity studies. Exposure ratios for CD1790 were considerably higher than for the parent in mice and monkeys and approximately half that for linagliptin in the rat.

Primary target organs for toxicity were the liver, kidneys, gastrointestinal tract and lungs.

Hepatocyte rarefaction, consistent with increased glycogen storage, was observed in mice (with treatment at ≥300 mg/kg/day PO for 13 weeks) and rats (mostly at ≥100 mg/kg/day PO for 13 or 26 weeks). Increased hepatocyte glycogen accumulation was also seen in monkeys (at 300 mg/kg/day PO for 4 weeks). These findings are consistent with the drug's primary pharmacology. Centrilobular basophilic granules developed in mice treated at 600 mg/kg/day PO for 13 weeks. Additional hepatic changes in rats comprised centrilobular hypertrophy and lipofuscin storage in the 6-month pivotal study (at ≥100 mg/kg/day PO) and at higher doses in 2–4 week studies, hepatocellular vacuolation and loss/necrosis of hepatocytes (≥600 mg/kg/day PO), microgranulomas and foam cell accumulation (1000 mg/kg/day PO). Microscopic changes in the bile duct were observed in rats (hyperplasia at ≥300 mg/kg/day PO for 26 weeks), dogs (epithelial apoptosis, vacuolisation and inflammatory infiltration at ≥45 mg/kg/day PO for 4 weeks) and monkeys (hypertrophy of the biliary epithelium and peribiliary inflammation at 300 mg/kg/day PO for 4 weeks). These microscopic changes were accompanied by increases in plasma alkaline phosphatase (ALP), aspartate transaminase (AST) and/or alanine transaminase (ALT) (generally modest) in all species. All hepatic findings that were observed in rats, dogs and monkeys in PO studies of ≥4 weeks duration were shown to be reversible. No-observable effect levels (NOELs) for hepatic lesions established in the pivotal studies were 30 mg/kg/day PO for rats (ER_{AUC}, 64) and 100 mg/kg/day PO for monkeys (ER_{AUC}, 837); and in the longest studies in other species, 100 mg/kg/day PO in mice (ER_{AUC}, 582 [13 weeks]) and 9 mg/kg/day PO in dogs (ER_{AUC}, 31 [4 weeks]).

[8] Guideline on repeated dose toxicity. CPMP/1042/99. Rev 1. http://www.tga.gov.au/pdf/euguide/swp104209enrev1.pdf

Table 2. Relative exposure to linagliptin in selected repeat dose toxicity studies (table continued across two pages).

Species (strain)	Study	Treatment duration	Dose (mg/kg/day); PO	AUC_{0-24h} (µM·h)	Exposure ratio
Mouse (CD-1)	U06-1784	4 weeks	60	62	405
			120	115	752
			300	316	2065
			600	533	3484
	U07-1536	13 weeks	100	89	582
			300	271	1771
			600	504	3294
	U10-1500-01 carcinogenicity	104 weeks	8	0.91	6
			25	6.0	39
			80	46	301
Rat (Wistar/ Han Wistar)	U04-1714-01	2 weeks	30	7.1	46
			100	48	314
			300	193	1261
			1000	293	1915
	U05-1937	4 weeks	6	0.51	3
			60	24	157
			600	350	2288
	U06-1874	13 weeks	10	1.4	9
			30	10	65
			100	61	399
			300	181	1183
	U07-1910	26 weeks	7	0.85	6
			30	9.8	64
			100	57	373
			300	254	1660
	U10-1502-01 carcinogenicity	104 weeks	6	1.4	9
			18	7.6	50
			60	61	399
Dog (Beagle)	U04-2187	2 weeks	15	13	85
			45	90	588
			150	363	2373
	U05-1944	4 weeks	1	0.24	1.6

Species (strain)	Study	Treatment duration	Dose (mg/kg/day); PO	AUC_{0-24h} (µM·h)	Exposure ratio
			3	1.1	7
			9	4.8	31
			45	30	196
Monkey (Cynomolgus)	U05-1978 /1950	2 weeks	10	8.1	53
			30	36	235
			100	149	974
			300	646	4222
	U05-2481	4 weeks	10	11	72
			60	76	497
			300	552	3608
	U07-1072	13 weeks	4	2.7	18
			25	20	131
			150	249	1627
	U08-1185-01	52 weeks	1	0.34	2.2
			10	6.5	42
			100	128	837
Human	U10-1139-01	steady state	5 mg	0.153	–

Nephrotoxicity was evident as tubular atrophy, epithelial vacuolation, tubular basophilia and epithelial cell necrosis in mice treated with linagliptin at 600 mg/kg/day PO for 13 weeks (NOEL, 300 mg/kg/day PO; ER_{AUC}, >1700) and as diffuse basophilia (from 100 mg/kg/day PO), focal basophilic tubules, tubular pigment storage, interstitial inflammation, tubular protein casts and pyelitis (at 300 mg/kg/day PO) in rats in the pivotal 6 month study (NOEL, 30 mg/kg/day PO; ER_{AUC}, 64). Higher doses in the shorter studies in rats resulted in tubular epithelial hypertrophy, degeneration of tubules, fatty change of the tubular epithelium (at 600 mg/kg/day PO for 4 weeks) and vacuolation of the distal tubules and hyperplasia of the proximal tubules (1000 mg/kg/day PO for 2 weeks). Minimal apoptosis/necrosis of the renal medulla was seen in dogs treated at 45 mg/kg/day PO for 4 weeks (NOEL, 9 mg/kg/day PO; ER_{AUC}, 31). No histological changes were seen in the kidneys of monkeys in the pivotal 12 month study (≤100 mg/kg/day PO; ER_{AUC}, 837) or in the shorter studies (≤300 mg/kg/day PO for 4 weeks or ≤150 mg/kg/day PO for 13 weeks; ER_{AUC}, >1600). Tissue distribution studies indicated significant retention of drug related material (primarily unchanged linagliptin) in the zona intermedia of rat kidneys; this appeared to occur to a lesser extent in the mouse and not at all in the monkey. The finding is consistent with the very high level of expression of linagliptin's target, DPP-4, in the rat

kidney[9] and the difference in distribution profile may largely explain the greater susceptibility of the rat to nephrotoxicity by the drug compared to the mouse and monkey.

Linagliptin produced gastric lesions, including epithelial hyperplasia and hyperkeratosis, subepithelial inflammation, mucosal erosions/necrosis and glandular degeneration, in mice at ≥120 mg/kg/day PO for 4 weeks and at ≥300 mg/kg/day PO in the 13 week study, in rats at 300 mg/kg/day PO for 26 weeks and ≥600 mg/kg/day PO in shorter studies and in monkeys at ≥25 mg/kg/day PO for 13 weeks (but not at ≤100 mg/kg/day PO in the pivotal 12-month study). At 1000 mg/kg/day PO in the 2 week rat study, as well as stomach ulceration there was epithelial vacuolation and inflammatory cell infiltration in the small intestine and mucosal haemorrhage and necrosis in the large intestine. Focal erosion/inflammation of the tongue was observed in the 4 week rat study at 600 mg/kg/day PO. Post dose salivation and/or emesis were also seen in many of the studies. These findings are consistent with a local irritant effect of the test article when administered at very high doses. Doses without gastrointestinal toxicity in rodents (100 mg/kg/day PO) and monkeys (≥4 mg/kg/day PO) are 40–1000 times higher than the clinical dose on a mg/kg basis (based on 50 kg patient body weight).

In rats, the lungs were a target organ, with increased foam cell accumulation seen at ≥300 mg/kg/day PO in the general repeat-dose studies and increased cholesterol cleft granuloma seen at 60 mg/kg/day PO in the 2 year carcinogenicity study (NOEL, 18 mg/kg/day PO; ER_{AUC}, 50). Bronchopneumonia was observed in dogs treated with linagliptin at ≥15 mg/kg/day PO for 2 weeks but this was not reproduced in the 4 week study. In addition to the lung, foam cell accumulation was also seen in the liver and/or lymphoid tissues in the rat with treatment at 1000 mg/kg/day PO for 2 weeks or 600 mg/kg/day PO for 4 weeks. The findings in rats are indicative of mild phospholipidosis and consistent with the drug's cationic amphiphilic structure. There were no similar findings in either mice or monkeys.

Clinical signs of pseudoallergic reactions (reddening and swelling of ears and upper lips accompanied by hypotension and tachycardia) were observed in dogs at doses ≥15 mg/kg/day PO (ER_{Cmax}, ~400). This was generally correlated with elevated plasma histamine levels. These pseudoallergic reactions were also observed in mini-pigs (at 150 mg/kg/day PO; ER_{Cmax}, ~700) as well as in monkeys but in the latter case only at a high IV dose (40 mg/kg/day IV; ER_{Cmax}, >6800). Pseudoallergic reactions were not observed in studies in monkeys by the oral route nor in any of the studies in mice and rats (PO or IV administration) (ER_{Cmax}, >2500). The C_{max} at the NOEL in the dog (9 mg/kg/day PO) is 178 times higher than the clinical C_{max}. The data indicate that the dog is considerably more susceptible to pseudoallergic reactions to linagliptin than rodents and primates.

Lymphoid depletion or increased apoptosis were seen in the spleen, thymus, bone marrow and mesenteric lymph node in rats treated with linagliptin at 1000 mg/kg/day PO (ER_{AUC}, 1915). Other effects observed in rats at ≥600 mg/kg/day PO included changes in the male reproductive organs (atrophy of the prostate, seminal vesicles and epididymis, vacuolation of prostate epithelial cells and seminiferous epithelial depletion), female genital tract (vacuolation of the uterine epithelium), adrenal gland, Harderian gland and skin (hair follicle degeneration). These were encountered at doses beyond the maximum tolerated dose and are considered to reflect non-specific toxicity. Mild effects on reproductive tract tissues were also noted in the pivotal 6-month rat study (diffuse hyperplasia of the prostate and altered dioestrus and mucoid change of vagina at 300 mg/kg/day PO and increased sex chord

[9] Fukasawa, K.M., K. Fukasawa, N. Sahara, M. Harada, Y. Kondo and I. Nagatsu. (1981) Immunohistochemical localisation of dipeptidyl aminopeptidase IV in rat kidney, liver and salivary glands. *J. Histochem. Cytochem.* **29:** 337-343.

stromal hyperplasia in the ovaries at ≥100 mg/kg/day PO) and are again consistent with non-specific toxicity. Thyroid follicular cell hypertrophy was increased in incidence/severity in the 13 and 26 week rat studies at ≥100 mg/kg/day PO and this is consistent with a secondary effect related to metabolic activation in the species altering thyroid hormone clearance. Relative exposure (ER_{AUC}) at the NOEL for these effects in rats (30 mg/kg/day) is 64; similar treatment related effects were not observed in the pivotal monkey study (≤100 mg/kg/day PO; ER_{AUC}, 837). Pancreatic islet cell proliferation was seen in one monkey (of 8) treated at 100 mg/kg/day PO for 12 months and is consistent with potentiation of incretin activity by linagliptin.

The toxicological profile of linagliptin is broadly similar to that of sitagliptin, another highly selective DPP-4 inhibitor, with the liver and kidney as the primary target organs. Of note, no effects on teeth were evident in linagliptin toxicity studies, a target that was identified for sitagliptin. The profile of linagliptin was largely unlike that of the less specific DPP-4 inhibitors, vildagliptin and saxagliptin, where skin lesions in monkeys, gastrointestinal toxicity in dogs and (for vildagliptin) pulmonary effects in rodents were a feature at low exposure margins.

The toxicity of linagliptin with any of the proposed combinations (metformin, thiazolidinediones or sulphonylureas) has not been examined in submitted nonclinical studies.

Genotoxicity

The potential genotoxicity of linagliptin was investigated in the standard battery of tests, conducted in accordance with TGA adopted EU guidelines[10]. All assays were appropriately validated and conducted under GLP conditions. Appropriate bacterial strains were used in the Ames test and concentrations/doses tested were appropriate. CD1790 was tested directly for mutagenicity in the Ames test and for clastogenicity *in vitro* in human lymphocytes and indirectly (*via* metabolic formation following PO administration of linagliptin) for clastogenicity *in vivo* in the rodent micronucleus test. Neither linagliptin nor CD1790 were mutagenic in bacterial mutation assays or clastogenic *in vitro* (in human lymphocytes) or *in vivo* (in the rat micronucleus test).

Carcinogenicity

The carcinogenic potential of linagliptin by the oral route was investigated in 2 year studies in mice and rats. Group sizes were appropriate and although there were no appreciable effects on survival and body weight, suitable dose levels were selected with exposures >25 times the anticipated clinical exposure at the highest dose levels in each study, in accordance with the TGA adopted EU guideline[11]. In the mouse study, an increased incidence of lymphoma was seen in females treated with 80 mg/kg/day PO linagliptin compared to the concurrent control group. This tumour is quite common in females of this strain of mouse (mean incidence, 9.9%; maximum, 50%[12]) and the incidence (37%) was within the historical control range. In addition, there was no increase in lymphoma in treated males and no accompanying treatment related increase in the pre-neoplastic lesion, lymphoid hyperplasia, in either the spleen or thymus of animals of either sex. This tumour finding is therefore considered to be spontaneous in origin and not related to linagliptin

[10] Note for Guidance on Genotoxicity: a Standard Battery for Genotoxicity Testing of Pharmaceuticals. CPMP/ICH/174/85. http://www.tga.gov.au/pdf/euguide/ich017495en.pdf

[11] Note for Guidance on Dose Selection for Carcinogenicity Studies of Pharmaceuticals. CHMP/ICH/383/1995. http://www.tga.gov.au/pdf/euguide/ich038395final.pdf

[12] Charles River (March 2005) Spontaneous lesions in the Crl:CD-1(ICR) mouse in control groups from 18 month to 2 year studies.

treatment. No dose related or statistically-significant increase in tumour incidence was seen in the rat study. Therefore, NOELs for treatment-related tumours are considered to be 80 and 60 mg/kg/day PO in mice and rats, respectively, associated with exposure ratios of approximately 300 and 400.

Reproductive toxicity

A standard set of reproductive toxicity studies was submitted and examined fertility (in rats), embryofetal toxicity (in rats and rabbits) and pre-/postnatal development (in rats). Adequate animal numbers were used and dose levels and treatment periods were appropriate. Toxicokinetic analyses were performed in the pivotal embryofetal studies; exposure data for the other studies are extrapolated from appropriate repeat dose toxicity studies. Exposure levels achieved were significantly greater than the anticipated clinical exposure (Table 3).

Table 3. Relative exposure to linagliptin in reproductive toxicity studies

Study	Species & strain	Dose (mg/kg/day); PO	AUC_{0-24h} (µM·h)	Exposure ratio (animal:human AUC_{0-24h})
Fertility & Pre-/postnatal [extrapolated from U04-1714-01]	**Rat** (Han Wistar)	10	2.4	16
		30	7.1	46
		240[a]	155	1013
		300[b]	193	1261
Embryofetal [U06-1637]	**Rat** (Han Wistar)	10	1.7	11
		30	7.7	50
		240	154	1007
Embryofetal [U06-1200]	**Rabbit** (Himalayan)	4	0.34	2
		25	12	78
		150	307	2007
U10-1139-01	**Human**	[5 mg; steady state]	0.153	–

[a] High-dose level in the fertility and early embryonic development study (U06-2047);
[b] High-dose level in the pre-/postnatal development study (U07-1558)

Fertility and early embryonic development were unaffected in rats when both males and females were treated with ≤240 mg/kg/day PO linagliptin (ER_{AUC}, ~1000). Linagliptin crossed the placenta in rats and rabbits, with significant exposure in the fetus. Placental transfer of the major metabolite, CD1790, was demonstrated in the rabbit. In the definitive embryofetal development studies, increased post implantation loss was observed in both species at the highest dose levels tested (240 mg/kg/day PO in the rat and 150 mg/kg/day PO in the rabbit), with an increase in runts and a slight increase in the incidence of fetal visceral variations also observed at this dose in the rabbit. There was no evidence of teratogenicity in these studies and the effects that were observed occurred in the context of significant maternotoxicity (signified by 19–75% inhibition of maternal body weight gain). Delayed ossification and malformations were observed in fetuses of rats and rabbits treated at higher doses in pilot studies (600 and 300 mg/kg/day PO in the respective species); given that there was severe concomitant maternotoxicity, this is unlikely to represent a

direct teratogenic effect. NOELs for embryofetal development were 30 mg/kg/day PO in the rat (ER_{AUC}, 50) and 25 mg/kg/day PO in the rabbit (ER_{AUC}, 78).

Lactating rats were found to readily excrete linagliptin in milk. Peak and overall exposure to ^{14}C-linagliptin derived radioactivity (that is, C_{max} and $AUC_{0-24\,h}$ values; ≥90% as unchanged drug) were 4 and 7 times higher for milk than for plasma. In a pre/postnatal development study in rats, pups from dams that had been treated with 300 mg/kg/day PO linagliptin from gestation day 6 and throughout lactation displayed reduced postnatal body weight gain (by 12% up to weaning; NOEL, 30 mg/kg/day PO; ER_{AUC}, 46). Apart from growth, postnatal survival, pup reproductive function and other developmental parameters were unaffected by maternal treatment with linagliptin (≤300 mg/kg/day PO; ER_{AUC}, ≤1261). Reduced postnatal pup weights were observed with other DPP-4 inhibitors (sitagliptin, vildagliptin and saxagliptin; Sitagliptin EPAR, 2007; Vildagliptin AusPAR, 2010; Saxagliptin EPAR, 2009) and rats deficient in DPP-4 had lower body weights than wild type animals (Karl *et al.*, 2003[13]), suggesting this may be a pharmacological effect.

Overall, no adverse effects on male or female fertility, embryofetal or postnatal development are predicted at clinically-relevant exposures.

Pregnancy classification

The sponsor has proposed Pregnancy Category B2. This category is for drugs where there were deficiencies in the embryofetal development studies in animals but the available data showed no evidence of an increased occurrence of fetal damage. Neither applies to linagliptin. Placement instead in Category B3 is considered appropriate given the increase in post implantation loss and other effects observed at high doses in the embryofetal studies. This pregnancy category is also consistent with that of other members of this class.

Local tolerance

Local tolerance studies were adequately conducted and revealed no irritation following topical dermal application or IM, IV or intra arterial injection in rabbits or following paravenous administration to rats. Haemocompatibility was demonstrated *in vitro* in assays with human blood (incubated with ≤0.5 mg/mL linagliptin).

Immunotoxicity

No specialised immunotoxicity studies were conducted as there was adequate information to assess immunotoxic potential from the general repeat dose toxicity studies. There were no haematological changes or treatment related signs to suggest altered immune function and histological changes in immune system tissues only occurred at doses beyond the maximum tolerated dose and are considered to reflect non-specific toxicity; see *Repeat-dose toxicity*). The T-cell dependent antibody response was unaffected in rats treated with linagliptin for 2 weeks at 1000 mg/kg/day PO (ER_{AUC}, 1915). Although DPP-4 (also designated CD26) is a co receptor with CD3 for T-cell activation and proliferation, there has been no indication that other DPP-4 inhibitors affect T cell function at therapeutic concentrations (Sitagliptin EPAR, 2007; Saxagliptin EPAR, 2009; Vildagliptin AusPAR, 2010). Based on the data, no significant immunotoxic risk is predicted for the clinical use of linagliptin.

[13] Karl, T., T. Hoffmann, R. Pabst and S. von Hörsten. (2003) Extreme reduction of dipeptidyl peptidase IV activity in F344 rat substrains is associated with various behavioural differences. *Physiol. Behav.* **80:** 123–134.

Paediatric use

Linagliptin is not proposed for paediatric use. Treatment in the 12 month repeat-dose toxicity study in monkeys coincided with puberty and did not indicate adverse effects on developing tissues.

Impurities

A number of impurities with specifications above those recommended in the relevant TGA adopted EU guideline[14] have been adequately qualified.

Nonclinical Summary

No nonclinical studies on pharmacokinetic or toxicological interactions with the proposed combination therapies were included in the current Australian submission.

In vitro, linagliptin inhibited dipeptidyl peptidase 4 (DPP-4) with nanomolar potency. This enzyme is responsible for the inactivation of the incretin hormones GLP-1 and GIP. *In vivo*, at subclinical exposures, orally administered linagliptin caused a marked and long-lasting decrease in plasma DPP-4 activity, increased the levels of the active form of GLP-1, improved plasma glucose clearance and increased plasma insulin levels in diabetic rats, consistent with the proposed pharmacological action. A metformin/linagliptin combination was more efficacious in improving glucose tolerance than monotherapy in diabetic mice.

There was no significant inhibition of nine non-DPP-4-related proteases, 50 receptors and/or ion channels at concentrations up to 10 μM of linagliptin. Some inhibition of FAP (fibroblast activation protein; a peptidase closely related to DPP-4) was observed but the IC_{50} (94 nM) is >7 times the peak plasma concentration of linagliptin expected in patients. No effect on wound healing in mice indicates a lack of biological relevance.

Safety pharmacology studies covered the CNS, cardiovascular, respiratory, renal and gastrointestinal systems. Moderate hypotension and tachycardia, coincident with pseudoallergic reactions and increased plasma histamine levels, were observed in dogs at very high plasma concentrations (>380-times the clinical C_{max}). No significant inhibition of the hERG K^+ channel was observed *in vitro* and no ECG abnormalities were seen in linagliptin-treated animals. The other systems were unaffected in rodents and/or dogs apart from slight inhibition of gastrointestinal transit in rats.

Overall, the pharmacokinetic profile in animals was qualitatively similar to that of humans. Linagliptin was rapidly absorbed following oral administration in all species. Plasma half-lives were long. Saturable binding to DPP-4 influenced the pharmacokinetics of linagliptin. Plasma protein binding by linagliptin was moderate to high and concentration dependent. Tissue distribution of linagliptin was wide. Unchanged linagliptin was the dominant circulating species in animals and humans. The only significant metabolite, CD1790, was pharmacologically inactive. Drug related material was excreted primarily *via* the faeces. Biliary excretion was indicated.

Linagliptin was shown to be a mechanism based (irreversible) inhibitor of CYP3A4 but clinical relevance is likely limited based on the kinetic parameters for the inhibition and the nanomolar circulating levels of the drug in patients. There was no clinically relevant inhibition of other human CYP450 isozymes (CYP1A1/2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 4A11), P-glycoprotein or human renal transporters (OATP-B, OCT2, OAT1, OAT3, OAT4, OCTN2, OATP2, OATP8, OCTN1, OCT1 and OATP2). CYP induction was not observed

[14] ICH Q3A (R). Impurities testing guideline: Impurities in new drug substances. http://www.tga.gov.au/pdf/euguide/ich273799en.pdf

in vitro (CYP1A2, 2B6 and 3A4 in human hepatocytes) or *in vivo* (CYP1A, 2B, 2E1, 3A and 4A in rats). Linagliptin is a substrate for P-glycoprotein. As such, co administration of an inhibitor or inducer of this transporter may affect linagliptin exposure.

Linagliptin displayed a low order of acute oral toxicity in tested animal species.

Repeat dose toxicity studies were performed in mice, rats, dogs and cynomolgus monkeys using the clinical route (PO) and in some species the IV route with very high multiples of the anticipated clinical exposure to linagliptin achieved. Pivotal studies were of 26 weeks duration in rats and 52 weeks in monkeys. The primary target organs for toxicity were the liver (mice, rats, dogs and monkeys), kidneys (mice, rats and dogs), gastrointestinal tract (mice, rats and monkeys) and lungs (rats only). Animal: human exposure ratios at the NOELs for hepatic, renal, gastrointestinal and pulmonary findings are at least 31 and frequently much higher. Linagliptin was not overtly immunotoxic.

The potential genotoxicity of linagliptin was investigated in the standard battery of tests. All assays returned negative results. No treatment related increase in tumour incidence was observed in mice or rats in 2 year oral carcinogenicity studies at very high exposure margins (~300–400).

Fertility and early embryonic development were unaffected in rats when both males and females were treated with linagliptin at doses resulting in exposures >1000 times the clinical exposure. Placental transfer of linagliptin was demonstrated in rats and rabbits. An increase in postimplantation loss (in rats and rabbits) and an increase in runts and the incidence of fetal visceral variations (rabbits) were observed in the definitive embryofetal development studies. Adverse effects on embryofetal development were only observed in the context of maternotoxicity and at very high exposure margins. Linagliptin and/or its metabolites were readily excreted in milk and decreased postnatal body weight gain was observed in rats.

Eight impurities with specifications above the TGA adopted EU guidelines have been adequately qualified.

Conclusions and Recommendations

- Primary pharmacology studies are supportive of the drug's use as an oral agent for the treatment of Type 2 diabetes mellitus.
- Secondary and safety pharmacology studies identify no clinically relevant hazards.
- Effects on the liver, kidney, gastrointestinal tract and lungs observed in the repeat dose toxicity studies, as well as adverse effects seen in the reproductive/developmental toxicity studies, occurred only at exposure margins sufficiently high to be not of particular concern. Additional primary targets that have been identified for other DPP-4 inhibitors in animals (such as skin and teeth) were not targets of linagliptin.
- Linagliptin is not considered to pose a genotoxic or carcinogenic hazard.
- There are no objections on nonclinical grounds to the registration of Trajenta as monotherapy for the proposed indication. In the absence of nonclinical data regarding linagliptin in combination with metformin, thiazolidinedione or a sulfonylurea, the safety of the proposed combinations will need to be addressed by clinical data alone.

IV. Clinical Findings

Introduction

The submission contained pharmacokinetic (PK) data from 25 studies. There were ten PK studies conducted in healthy volunteers, nine drug interaction studies conducted in healthy volunteers, one mass balance study, three PK studies in subjects with Type 2 diabetes, one PK study in subjects with renal impairment (RI) and one PK study in subjects with hepatic impairment.

There were ten studies that provided data on the main pharmacodynamic measure, inhibition of DPP-4. There was one study of QT[15] prolongation.

Pharmacokinetics

Pharmacokinetics in healthy volunteers is summarised below under *Evaluator's overall conclusions on pharmacokinetics*.

Pharmacokinetic studies in subjects with Type 2 diabetes

Study 1218.2 – U06-1139 was a single centre, randomised, placebo controlled, double blind within dose groups, multiple rising doses, in male patients with Type 2 diabetes mellitus to investigate safety, tolerability, pharmacokinetics and pharmacodynamics of linagliptin after oral administration of multiple rising doses. Subjects were male, with Type 2 diabetes mellitus, aged ≥21 and ≤65 years and with a BMI in the range of ≥18.5 and ≤35 kg/m^2. The study treatments were linagliptin solution (powder reconstituted with 0.1% tartaric acid) at 1 mg, 2.5 mg, 5 mg and 10 mg. The control was placebo solution (powder reconstituted with 0.1% tartaric acid). Treatments were taken once daily, orally, fasted for 12 days. Prior to commencing the treatment period there was a 14 day washout period of previous anti diabetic medication. There were a total of 48 subjects: nine subjects randomised to active treatment and three subjects randomised to placebo for each dose level. One subject in the 5 mg dose level withdrew prior to dosing on Day 1. The analysis included 47 male subjects aged 36 to 65 years. As noted in the PK studies performed in healthy subjects, AUC and C_{max} were not proportional to dose. The PK parameters are presented in Table 4.

[15] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated.

Table 4. Geometric mean (gMean) and geometric coefficient of variation (gCV) of pharmacokinetic parameters of BI 1356 BS after oral administration of 1 and 2.5 mg BI 1356 BS once daily for 12 days.

		1 mg		2.5 mg	
		gMean	gCV [%]	gMean	gCV [%]
AUC_{0-24}	[ng·h/mL]	19.0	39.7	40.3	22.7
$AUC_{\tau,ss}$	[ng·h/mL]	38.6	28.3	55.1	16.3
$AUC_{0-24,norm}$	[(ng·h/mL)/m	19.0	39.7	16.1	22.7
$AUC_{\tau,ss,norm}$	[(ng·h/mL)/m	38.6	28.3	22.0	16.3
C_{max}	[ng/mL]	1.48	43.2	2.48	24.5
t_{max}[1]	[h]	1.50	1.00-3.00	2.00	1.00-3.00
$C_{max,ss}$	[ng/mL]	2.14	29.0	3.11	23.0
$t_{max,ss}$[1]	[h]	1.48	1.00-3.00	1.42	1.00-3.00
$C_{max,norm}$	[(ng/mL)/mg]	1.48	43.2	0.993	24.5
$C_{max,ss,norm}$	[(ng/mL)/mg]	2.14	29.0	1.24	23.0
$t_{½,ss}$	[h]	121	21.3	113	10.2
$MRT_{po,ss}$	[h]	143	17.1	134	9.10
$CL/F_{,ss}$	[mL/min]	431	28.3	757	16.3
$V_z/F_{,ss}$	[L]	4510	32.1	7400	13.1
$CL_{R,0-24}$	[mL/min]	---	---	1.42	46.2
$CL_{R,ss}$	[mL/min]	14.0	24.2	23.1	39.3
fe_{0-24}	[%]	---	---	0.139	51.2
$fe_{\tau,ss}$	[%]	3.34	38.3	3.06	45.1
$R_{A,Cmax}$		1.44	25.6	1.25	10.6
$R_{A,AUC}$		2.03	30.7	1.37	8.19

Study 1218.3 – U06-1822 was a single centre, randomised, double blind within dose group, placebo controlled, multiple dose study in male and postmenopausal female subjects with Type 2 diabetes mellitus to investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of linagliptin during 4 week treatment. The study included male and female patients with Type 2 diabetes, male patients aged ≥21 and age ≤70 years and female postmenopausal patients aged ≥60 but ≤70 years with a BMI in the range of ≥18.5 and ≤35 kg/m^2. The study treatments were linagliptin tablet at 2.5 mg, 5 mg and 10 mg; and the control drug was placebo tablet. The treatments were administered once daily, orally, taken fasted. There was a 14 day washout period of previous antidiabetic medication, followed by 28 days of once daily dosing at each dose level. The study included 77 subjects: 26 in the 2.5 mg group, 16 subjects in the 5 mg group, 19 subjects in the 10 mg group and 16 subjects in the placebo group. There were 72 (95.5%) males, five (6.5%) females and the age range was 40 to 69 years. The PK of linagliptin were dose dependent, with a less than expected increase in AUC and C_{max} with increasing dose and an increase in apparent clearance with increasing dose (Table 5).

Table 5. Geometric mean (gMean) and geometric coefficient of variation (%gCV) of single dose and steady state pharmacokinetic parameters of BI 1356 BS after oral administration of 2.5, 5 and 10 mg BI 1356 BS once daily for 28 days.

		2.5 mg (N=26)		5 mg (N=15)		10 mg (N=19)	
		gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
Single dose (day 1)							
AUC_{0-24}	[nM·h]	93.1	27.5	124	20.4	188	32.5
$AUC_{0-24,norm}$	[(nM·h)/mg]	37.2	27.5	24.8	20.4	18.8	32.5
C_{max}	[nM]	6.09	42.0	9.55	39.3	18.8	64.5
$C_{max,norm}$	[(nM)/mg]	2.44	42.0	1.91	39.3	1.88	64.5
t_{max} [1]	[h]	1.50	0.50-8.00	2.00	0.983-6.20	1.50	1.00-8.00
Steady state (day 28)							
$AUC_{\tau,ss}$	[nM·h]	116	20.7	148	19.1	207	26.8
$AUC_{\tau,ss,norm}$	[(nM·h)/mg]	46.5	20.7	29.7	19.1	20.7	26.8
$C_{max,ss}$	[nM]	7.41	27.9	12.3	40.4	18.6	56.3
$C_{max,ss,norm}$	[(nM)/mg]	2.96	27.9	2.47	40.4	1.86	56.3
$t_{max,ss}$ [1]	[h]	1.00	0.500-3.00	1.00	0.500-4.02	1.00	0.45-6.00
$t_{½,ss}$	[h]	183	20.9	194	15.1	203	16.4
$MRT_{po,ss}$	[h]	164	16.9	145	20.3	130	23.2
$CL/F_{,ss}$	[mL/min]	785	20.7	1190	19.1	1700	26.8
$V_z/F_{,ss}$	[L]	12000	28.0	20000	28.5	30000	24.7
$R_{A,Cmax}$		1.22	34.1	1.29	40.5	0.991	87.3
$R_{A,AUC}$		1.25	19.2	1.20	19.9	1.10	29.6

Study 1218.12 – U08-3212-01 was a multicentre, randomised, double blind, placebo controlled, parallel-group, multiple dose study in Japanese patients with Type 2 diabetes mellitus to evaluate the safety, tolerability, PK and PD of linagliptin 0.5 mg, 2.5 mg and 10 mg. Although the study was listed as a Phase II study, it would be better categorized as a PK and PD study. The study included Japanese patients with a diagnosis of Type 2 diabetes mellitus treated with diet and/or exercise only or with one or two oral anti diabetic treatment (OAD) except glitazones; the glycosylated hemoglobin (HbA1c) was ≤8.5% for patients treated with diet and/or exercise and/or one OAD, or ≤8.0% for patients treated with two OAD; the age was ≥21 but ≤70 years; BMI was in the ≥17.6 and ≤35 kg/m^2 range. The study treatments were: linagliptin tablets at 0.5 mg, 2.5 mg and 10 mg and placebo tablet. Treatments were administered once daily, orally, fasted. There was a 14 day washout period of previous antidiabetic medication followed by 28 days of once daily dosing at each dose level. The study included 72 subjects: 19 in the linagliptin 0.5 mg group, 18 in the linagliptin 2.5 mg group, 18 in the linagliptin 10 mg group: and 17 in the placebo group. There were 72 subjects included in the PK and PD analyses: 55 (76.4%) male, 17 (23.6%) female and the age range was 29 to 69 years. In Japanese subjects linagliptin also displayed nonlinear pharmacokinetics with increased clearance with increasing dose. This is reflected in a less than proportional increase in C_{max} and AUC with

both single dose and multiple dosing (Table 6). There was also a greater than proportional increase in production of the metabolite CD 1750 (Table 7).

Table 6. Pharmacokinetic parameters of linagliptin after multiple oral administration of 0.5, 2.5 or 10 mg of BI 1356 BS once daily for 28 days.

Multiple, BI 1356 BS			0.5 mg	2.5 mg	10 mg
Day			gMean (gCV %)	gMean (gCV %)	gMean (gCV %)
1	N		19	18	18
	$AUC_{\tau,1}$	[nmol·h/L]	29.9 (45.7)	129 (23.7)	323 (32.6)
	$AUC_{\tau,1,norm}$	[(nmol·h/L)/mg]	59.7 (45.7)	51.8 (23.7)	32.3 (32.6)
	$C_{max,1}$	[nmol/L]	2.81 (55.4)	8.84 (35.1)	35.1 (80.1)
	$C_{max,1,norm}$	[(nmol/L)/mg]	5.62 (55.4)	3.54 (35.1)	3.51 (80.1)
	$t_{max,1}$ [a)]	[h]	1.50 (1.00-2.00)	1.50 (0.500-8.00)	1.50 (0.500-12.0)
	$fe_{0-24,1}$	[%]	---	0.227 (145)	4.08 (94.7)
	$CL_{R,0-24,1}$	[mL/min]	---	1.54 (120)	44.6 (59.2)
28	N		17	17	18
	$AUC_{\tau,ss}$	[nmol·h/L]	89.4 (27.2)	164 (23.4)	373 (33.5)
	$AUC_{\tau,ss,norm}$	[(nmol·h/L)/mg]	179 (27.2)	65.6 (23.4)	37.3 (33.5)
	$C_{max,ss}$	[nmol/L]	5.02 (33.9)	11.0 (40.9)	44.0 (80.4)
	$C_{max,ss,norm}$	[(nmol/L)/mg]	10.0 (33.9)	4.40 (40.9)	4.40 (80.4)
	$t_{max,ss}$ [a)]	[h]	1.50 (1.00-8.00)	1.50 (0.500-4.00)	1.25 (0.500-2.00)
	$t_{1/2,ss}$	[h]	240 (33.1)	223 (23.0) [b)]	260 (32.3)
	$MRT_{po,ss}$	[h]	214 (16.9)	178 (17.5) [b)]	119 (39.6)
	$CL/F_{,ss}$	[mL/min]	197 (27.2)	537 (23.4)	945 (33.5)
	$V_z/F_{,ss}$	[L]	4090 (45.0)	10400 (31.2) [b)]	21200 (55.5)
	$fe_{0-24,ss}$	[%]	2.26 (93.1) [b)]	4.25 (72.4) [b)]	6.79 (51.6) [c)]
	$CL_{R,ss}$	[mL/min]	4.50 (76.6) [b)]	22.8 (54.7) [b)]	65.0 (30.0) [c)]
	$R_{A,AUC}$		2.88 (28.3)	1.27 (21.4)	1.16 (27.8)
	$R_{A,Cmax}$		1.71 (35.8)	1.23 (40.4)	1.25 (78.0)

Table 7. Pharmacokinetic parameters of CD 1750 XX after multiple oral administration of 0.5, 2.5 or 10 mg of BI 1356 BS once daily for 28 days.

Multiple, CD 1750 XX Day			0.5 mg gMean (gCV %)	2.5 mg gMean (gCV %)	10 mg gMean (gCV %)
1	N		18	18	18
	$AUC_{\tau,1}$	[nmol·h/L]	---	10.4 (54.6)	81.2 (53.2)
	$AUC_{\tau,1,norm}$	[(nmol·h/L)/mg]	---	4.17 (54.6)	8.12 (53.2)
	$C_{max,1}$	[nmol/L]	0.220 (74.6)	1.61 (73.2)	12.2 (89.6)
	$C_{max,1,norm}$	[(nmol/L)/mg]	0.441 (74.6)	0.643 (73.2)	1.22 (89.6)
	$t_{max,1}$ [a)]	[h]	1.50 (0.917-2.00)	1.50 (1.00-2.00)	1.51 (0.917-12.0)
	$fe_{0-24,1}$	[%]	---	---	0.0588 (80.5)
	$CL_{R,0-24,1}$	[mL/min]	---	---	2.55 (47.3)
28	N		18	17	18
	$AUC_{\tau,ss}$	[nmol·h/L]	---	14.3 (55.1)	85.7 (48.8)
	$AUC_{\tau,ss,norm}$	[(nmol·h/L)/mg]	---	5.72 (55.1)	8.57 (48.8)
	$C_{max,ss}$	[nmol/L]	0.347 (81.3)[b)]	1.82 (95.7)	12.6 (73.9)
	$C_{max,ss,norm}$	[(nmol/L)/mg]	0.694 (81.3)[b)]	0.727 (95.7)	1.26 (73.9)
	$t_{max,ss}$ [a)]	[h]	1.50 (0.500-2.00)[b)]	1.50 (1.50-4.00)	1.50 (1.00-2.00)
	$t_{1/2,ss}$	[h]	---	18.4 (33.8)[c)]	15.9 (26.5)[d)]
	$MRT_{po,ss}$	[h]	---	18.7 (37.5)[c)]	15.7 (24.5)[d)]
	$fe_{0-24,ss}$	[%]	---	---	0.0758 (74.0)[d)]
	$CL_{R,ss}$	[mL/min]	---	---	3.23 (38.6)[d)]
	$R_{A,AUC}$		---	1.34 (69.1)	1.06 (59.4)
	$R_{A,Cmax}$		1.53 (94.8)[b)]	1.10 (100)	1.03 (97.8)

Studies in subjects with renal impairment

Study 1218.26 – U10-1467-02 was a single centre, open label, parallel group study, in male and female subjects and Type 2 diabetic subjects with or without renal impairment (RI). The study included otherwise healthy subjects with normal renal function or with renal impairment (RI); subjects with Type 2 diabetes mellitus with or without RI; male or female; aged 18 to 80 years, with a BMI in the 18 to 40 kg/m^2 range. RI was classified by creatinine clearance as: none (>80 mL/min); mild (>50 to ≤80 mL/min); moderate (>30 to ≤50 mL/min); and severe (≤30 mL/min or requiring haemodialysis). The study was performed to assess the effect of different degrees of RI on the safety, pharmacokinetics and pharmacodynamics of linagliptin administered orally. There were seven treatment groups:

- Group 1: subjects with normal renal function
- Group 2: subjects with mild RI
- Group 3: subjects with moderate RI
- Group 4: subjects with severe RI
- Group 5: subjects with end-stage renal disease; ESRD
- Group 6: subjects with severe RI and Type 2 diabetes mellitus

- Group 7 subjects with normal renal function and Type 2 diabetes mellitus (T2DM): CrCl>80 mL/min

The study treatment was linagliptin tablet 5 mg. The treatment regimens were:

- Groups 1 to 3, once daily, orally, taken fasted, multiple doses for 7 days
- Groups 4 and 5: single dose, orally, taken fasted
- Group 6 and 7: once daily, orally, taken fasted, multiple doses for 10 days

There was no randomisation.

The study included 51 subjects: Group 1: six; Group 2: six; Group 3: six, Group 4: six; Group 5: six; Group 6: ten; and Group 7: eleven. There were 30 (58.8%) males, 21 (41.2%) females and the age range was 30 to 72 years. With single doses, mild renal failure increased C_{max} and AUC by around 25% and all other severities of renal failure resulted in increases of around 50% (Table 8). With multiple doses moderate renal impairment increased exposure to linagliptin by 40% to 70% (Table 9). Exposure to CD 1750 was also around 50% greater in subjects with renal failure compared to those with normal renal function.

Table 8. Geometric mean ratio and 90% confidence intervals for the pharmacokinetic endpoints AUC0-24 and Cmax of linagliptin (measured on Day 1).

Parameter	Test	Reference	Inter-indiv. gCV (%)	Adjusted gMean Ratio (Test/Reference) (%)	2-sided 90 % Confidence Interval	
				Lower limit [%]	Upper limit [%]	
C_{max} [nmol/L]	Mild RI	Normal RF	44.7	125.6	80.4	196.3
	Moderate RI	Normal RF	76.2	157.2	77.4	319.2
	Severe RI	Normal RF	58.9	147.2	83.2	260.7
	ESRD	Normal RF	47.7	150.2	93.5	241.4
	Severe RI +T2DM	Normal RF +T2DM	58.0	122.5	81.5	184.0
AUC_{0-24} [nmol·h/L]	Mild RI	Normal RF	24.1	129.1	100.7	165.7
	Moderate RI	Normal RF	38.8	156.4	105.8	231.5
	Severe RI	Normal RF	29.6	140.6	103.9	190.5
	ESRD	Normal RF	25.8	153.7	117.9	200.4
	Severe RI +T2DM	Normal RF +T2DM	38.7	121.9	92.0	161.6

Table 9. Geometric mean ratio and 90% confidence intervals for the pharmacokinetic endpoints AUCτ,ss and Cmax,ss of linagliptin (measured on Day 7 for Groups 1 to 5 and on Day 10 for Groups 6 and 7)

Parameter	Test	Reference	Inter-indiv. gCV (%)	Adjusted gMean Ratio (Test/Reference) (%)	2 sided 90 % Confidence Interval	
					Lower limit [%]	Upper limit [%]
$C_{max,ss}$ [nmol/L]	Mild RI	Normal RF	32.3	97.7	70.2	138.9
	Moderate RI	Normal RF	40.1	146.2	97.6	218.9
	Severe RI +T2DM	Normal RF +T2DM	47.1	135.6	96.6	190.1
$AUC_{\tau,ss}$ [nmol·h/L]	Mild RI	Normal RF	16.6	107.9	90.8	128.3
	Moderate RI)	Normal RF	23.5	170.8	134.1	217.7
	Severe RI +T2DM	Normal RF +T2DM	34.1	141.8	110.4	182.1

Studies in subjects with hepatic impairment

Study 1218.27 – U10-1219-01 was a single centre, open label, parallel group study, in male and female subjects with hepatic impairment classified as mild (Child-Pugh class A, score 6 points, Group 2), moderate (Child-Pugh class B, score 7 to 9 points, Group 3) or severe (Child-Pugh class C, score 10 to 15 points. Group 4) and healthy males and females (Group 1) conducted in order to investigate the pharmacokinetics and pharmacodynamics of linagliptin 5 mg once daily in hepatic impairment. The study included healthy subjects and subjects with hepatic impairment matched for age, weight and sex. The study treatment was linagliptin tablet 5 mg. once daily, orally, taken fasted. In Groups 1 to 3 treatment was for 7 days (multiple doses) and in Group 4 treatment was for 1 day (single dose). There was no randomisation. The study included 33 subjects: eight healthy; eight with mild hepatic impairment, nine with moderate hepatic impairment and eight severe with hepatic impairment. There were 20 (60.6%) males, 13 (39.4%) females and the age range was 41 to 66 years. After a single dose the AUC and C_{max} of linagliptin appeared to be decreased in subjects with mild and moderate hepatic impairment (by around 30% for C_{max} and around 20% for AUC) (Table 10). After multiple dosing, the exposure to linagliptin, as assessed by AUC, was decreased by approximately 25% by hepatic failure (Tables 11 and 12). Reported separately, the plasma protein binding of radioactive hydrogen labeled [^{3}H] linagliptin did not seem to be altered in patients with different degrees of hepatic impairment (reported in Study U09-2250-01). The AUC for CD 1750 was decreased in subjects with hepatic impairment (Table 13).

Table 10. Adjusted gMean ratio and their 90% confidence intervals of the PK parameters AUC0-24 and Cmax of linagliptin between patients with different degrees of hepatic impairment and healthy subjects (Day 1) – treated set.

Parameter	Test	Reference	Inter-individual gCV [%]	Adjusted gMean ratio (test/reference) [%]	Two sided 90 % confidence interval	
					Lower limit [%]	Upper limit [%]
C_{max} [nmol/L]	Mild (N=7)	Healthy (N=8)	51.7	68.8	44.0	107.4
AUC_{0-24} [nmol·h/L]	Mild (N=7)	Healthy (N=8)	30.4	86.8	66.1	114.0
C_{max} [nmol/L]	Moderate (N=9)	Healthy (N=8)	44.5	70.0	48.7	100.5
AUC_{0-24} [nmol·h/L]	Moderate (N=9)	Healthy (N=8)	24.5	78.2	63.6	96.0
C_{max} [nmol/L]	Severe (N=8)	Healthy (N=8)	67.7	77.0	44.9	132.3
AUC_{0-24} [nmol·h/L]	Severe (N=8)	Healthy (N=8)	34.0	100.4	75.0	134.3

Table 11. Steady state non-compartmental PK parameters of linagliptin after multiple oral doses of 5 mg linagliptin to patients with mild or moderate hepatic impairment compared with healthy subjects

	Steady state non-compartmental PK parameters of linagliptin					
	Healthy		Mild		Moderate	
	gMean	gCV	gMean	gCV	gMean	gCV
N	8		8		8 (6)	
$AUC_{\tau,ss}$ [nmol·h/L]	254	18.9	191	27.2	217 (207)	26.0 (25.2)
$C_{max,ss}$ [nmol/L]	20.8	38.6	13.4	55.8	19.2 (17.9)	52.5 (54.2)
$t_{max,ss}$* [h]	1.50	0.500-2.00	1.00	0.500-3.00	0.625 (0.625)	0.250-2.00 (0.250-2.00)
$C_{24,ss}$ [nmol/L]	8.41	18.2	6.75	28.2	7.85 (7.92)	18.8 (13.7)
$t_{1/2,ss}$ [h]	77.7	32.6	95.0	18.0	96.1 (113)	54.7 (36.9)
Accumulation, $t_{1/2}$ [h]	10.9	66.2	8.11[1]	86.8	13.1 (10.8)	61.7 (55.7)
$CL/F_{,ss}$ [mL/min]	696	18.9	922	27.2	813 (852)	26.0 (25.2)
$Vz/F_{,ss}$ [L]	4680	35.7	7580	38.4	6760 (8350)	65.3 (53.0)
$MRT_{po,ss}$ [h]	95.4	23.2	109	27.0	119 (146)	58.9 (41.2)
$fe_{0-24,ss}$ [%]	7.12	50.3	4.84[1]	57.8	6.13 (7.10)	51.2(36.8)
$CL_{R,0-24,ss}$ [mL/min]	49.5	40.8	44.7[1]	40.1	49.8 (60.6)	50.8 (34.3)
$R_{A,AUC0-24}$	1.34	22.2	1.25[1]	23.9	1.46 (1.33)	28.4 (25.3)
$R_{A,Cmax}$	1.20	53.9	1.22[1]	64.3	1.53 (1.43)	65.8 (68.8)

* for $t_{max,ss}$, the median and range (min-max) is given

Table 12. Adjusted gMean ratio and their 90% confidence intervals of AUC0-24 and Cmax of linagliptin between patients with different degrees of hepatic disease and healthy subjects (Day 7) – treated set.

Parameter	Test	Reference	Inter-individual gCV [%]	Adjusted gMean ratio (Test/Reference) [%]	Two-sided 90 % confidence interval	
					Lower limit [%]	Upper limit [%]
$C_{max,ss}$ [nmol/L]	Mild (N=8)	Healthy (N=8)	47.7	64.4	43.2	96.0
$AUC_{\tau,ss}$ [nmol·h/L]	Mild (N=8)	Healthy (N=8)	23.4	75.5	61.6	92.5
$C_{max,ss}$ [nmol/L]	Moderate (N=8)	Healthy (N=8)	45.9	92.3	62.8	135.6
$AUC_{\tau,ss}$ [nmol·h/L]	Moderate (N=8)	Healthy (N=8)	22.7	85.5	70.2	104.2

Table 13. Non-compartmental PK parameters of CD 1750 after single and/or multiple oral administration of 5 mg linagliptin.

	Non-compartmental parameters of CD 1750							
	Healthy		Mild		Moderate		Severe	
	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
N	8		8		9		8	
AUC_{0-24} [nmol·h/L]	26.2	69.3	16.6[1]	54.4	9.78	65.8	11.3	124
C_{max} [nmol/L]	4.15	108	2.78[1]	111	1.62	71.3	1.34	128
t_{max}* [h]	1.50	1.00-2.00	2.00[1]	1.00-4.00	1.50	0.750-3.00	1.50	1.00-4.00
C_{24} [nmol/L]	0.382	36.4	0.224[1]	91.7	0.183[2]	53.5	0.266[3]	65.8
fe_{0-24} [%]	0.0301	31.6	0.0325[3]	37.4	---	---	---	---
$CL_{R,0-24}$ [mL/min]	2.03	49.5	3.49[3]	38.4	---	---	---	---
$RC_{max,Met}$ [%]	24.0	46.2	23.4[1]	63.8	13.4	50.3	10.1	50.3
$RAUC_{0-24,Met}$ [%]	13.8	49.2	10.1[1]	30.4	6.61	59.7	5.95	74.1
$AUC_{\tau,ss}$ [nmol·h/L]	34.8	59.2	21.6	52.4	17.4[2]	88.4	---	---
$C_{max,ss}$ [nmol/L]	4.29	94.9	2.17	91.6	2.27[2]	88.3	---	---
$t_{max,ss}$* [h]	1.50	1.00-3.00	2.50	1.00-4.00	1.25[2]	0.750-4.00	---	---
$C_{24,ss}$ [nmol/L]	0.764	35.1	0.490	55.9	0.331[2]	128	---	---
$t_{1/2,ss}$ [h]	18.2	34.8	14.4	26.3	18.7[2]	33.5	---	---
$fe_{0-24,ss}$ [%]	0.0503	58.3	0.0382[1]	32.3	0.0375[1]	114	---	---
$CL_{R,0-24,ss}$ [mL/min]	2.55	50.9	2.96[1]	29.5	3.11[1]	88.2	---	---
$RC_{max,ss,Met}$ [%]	20.7	57.2	16.3	39.8	11.9[2]	35.1	---	---
$RAUC_{\tau,ss,Met}$ [%]	13.7	48.6	11.3	36.9	8.01[2]	63.1	---	---

For t_{max} and $t_{max,ss}$, the median and range (min-max) is given.

Evaluator's overall conclusions on pharmacokinetics

Linagliptin displays nonlinear kinetics with an apparent increase in clearance with increasing dose up to 100 mg (single oral dose). Linagliptin showed nonlinear pharmacokinetics after IV infusion of 0.5 to 10 mg, with a less than proportional increase in exposure (Study 1218.10-U07-1800-01). There was a less than proportional increase in exposure to linagliptin as the dose increased in the range 1 to 5 mg (Study 1218.33-U10-1139-01). In Japanese subjects, linagliptin had a less than dose proportional increase in AUC and C_{max} for both single and multiple dosing (Study 1218.11-U07-3116). Linagliptin had linear kinetics at dose levels above 100 mg (Study 1218.1-U05-2072).

There was a greater than proportional increase in AUC for the metabolite CD 1750 with increasing dose (Study 1218.33-U10-1139-01 –). In the dose range 5 mg to 100 mg, there was a less than expected increase in C_{max} and AUC for linagliptin and a greater than expected increase in the C_{max} and AUC for the metabolite CD 1750 (Study 1218.32 – U09-1067-01). The pharmacokinetics can be explained by saturable protein binding, resulting in higher free fraction and increased clearance.
The PK parameters were similar for once daily and multiple dosing (Study 1218.58 – U10-3113-02).

Food had no significant effect upon AUC following a 1 mg or a 10 mg dose. C_{max} was reduced by 15% to 25% at a 5 mg to 10 mg dose level but there was no effect following a 1 mg dose (Study 1218.8-U06-1316 –, Study 1218.34 – U09-1628-03)

Absolute bioavailability was estimated to be 29.5% and showed a high inter individual variability of 46.7% (Study 1218.10-U07-1800-01 –).

There was no PK advantage in dosing twice daily with 2.5 mg compared to once daily with 5 mg (Study 1218.45 – U08-2123-01).

Linagliptin delayed the absorption of metformin with a resulting increase in T_{max} and decrease in C_{max} but there was no significant difference in AUC. However, for linagliptin in combination with metformin, there was a 20% increase in AUC (Study 1218.4 – U06-3414). There was a 30% increase in the AUC values for simvastatin and simvastatin acid when linagliptin was co administered. This was interpreted as indicating weak inhibition of CYP3A4 by linagliptin (Study 1218.9 – U06-1584). The $AUC_{\tau,ss}$ for linagliptin was increased by 13% in combination with pioglitazone: geometric mean ratio but there were no significant effects upon the PK of pioglitazone or its major metabolites in combination with linagliptin (Study 1218.13 – U07-1996). Linagliptin had no significant effects upon the PK or PD or warfarin (Study 1218.28 – U09-1674-04). There was no significant effect of linagliptin on digoxin PK (Study 1218.29 – U09-1618-01). There was no significant effect for glyburide on the PK of linagliptin but linagliptin decreased AUC and C_{max} for glyburide by approximately 14% (Study 1218.30 – U09-1247-01). Ritonavir (P-gp and CYP3A4) inhibition resulted in a two fold increase in AUC and a three fold increase in the C_{max} for linagliptin. There was a decrease in clearance of approximately 41% and a decrease in the formation of the CD1750 metabolite (Study 1218.31 – U09-1077-01). Linagliptin did not affect the PK of either ethinyloestradiol (EE) or levonorgestrel (LNG) (Study 1218.44 – U09-1393-01). The AUC and the C_{max} for linagliptin was decreased by 40% around 45%, respectively, when rifampicin was given concurrently (Study 1218.67 – U10-1328-01).

Most of the elimination of linagliptin was hepatic (Study 1218.7 – U08-1363-01).

In subjects with Type 2 diabetes, AUC and C_{max} were also not proportional to dose (Study 1218.2 – U06-1139). There was a less than expected increase in AUC and C_{max} with increasing dose and an increase in apparent clearance with increasing dose (Study 1218.3 – U06-1822). In Japanese subjects, linagliptin also displayed nonlinear pharmacokinetics with increased clearance with increasing dose. There was also a greater than proportional increase in production of the metabolite CD 1750 (Study 1218.12 – U08-3212-01).

With single doses, mild renal failure increased the C_{max} and the AUC by around 25%. All other severities of renal failure resulted in increases in exposure of around 50%. With multiple doses, moderate renal impairment increased exposure to linagliptin by 40% to 70%. Exposure to CD 1750 was also around 50% greater in subjects with renal failure compared to those with normal renal function (Study 1218.26 – U10-1467-02),

After a single dose, the AUC and C_{max} of linagliptin appeared to be decreased in subjects with mild and moderate hepatic impairment (by around 30% for C_{max} and around 20% for AUC). After multiple dosing, the exposure to linagliptin, as assessed by AUC, was also decreased by approximately 25% by hepatic failure. The plasma protein binding of linagliptin did not seem to be altered in patients with different degrees of hepatic impairment (reported in U09-2250-01). The AUC for CD 1750 was decreased in subjects with hepatic impairment (Study 1218.27 – U10-1219-01).

Pharmacodynamics

Effect on DPP-4

In *Study 1218.1 -U05-2072*, all doses of linagliptin resulted in an inhibition of DPP-4 activity in plasma. After administration of 2.5 mg linagliptin, plasma DPP-4 activity was reduced to 27.3%. Doses above 25 mg resulted in a reduction of plasma DPP-4 activity to less than 5% relative to baseline activity. The time to achieve maximum inhibition shifted with increasing doses from 3 h in the 2.5 mg dose group to less than 0.7 h in dose groups given 200 mg and above. The effect of linagliptin on plasma DPP-4 activity was prolonged compared to the plasma concentration and DPP-4 activity had not returned to baseline 96 h after drug administration. Inter individual variability in plasma DPP-4 activity was low.

In *Study 1218.10–U07-1800-01*, DPP-4 activity in plasma was plotted against plasma concentration of linagliptin. The 50% inhibitory concentration (IC_{50}) was approximately 2-4 nmol/L and the 80% inhibitory concentration (IC_{80}) was approximately 4-6 nmol/L. Maximum inhibition effect (I_{max}) can be taken to be 100% inhibition of DPP-4.

*Study 1218.11-U07-3116*showed that inhibition of DPP-4 was similar following single and multiple dosing. The plasma concentration effect relationship was similar to that demonstrated in Study U07-1800-01. Effect on DPP-4 persisted for 24 hours. The increase in GLP-1 concentrations plateaued with the 5 mg dose, both following single and multiple dosing.

In *Study 1218.25-U07-2003*, 24 hours after drug administration, the geometric mean DPP-4 activity was 26.4% for TF IIb (30.5% gCV), 27.8% for TF II (27.4% gCV) and 27.5% for iFF (intended formulation for marketing) (30.0% gCV).

In Study 1218.45 – U08-2123-01 both a 5 mg morning dose regimen and a 2.5 mg twice daily regimen resulted in a similar and sufficient DPP-4 inhibition over the whole dosing interval.

Study 1218.4 – U06-3414 showed that administration of metformin in combination with linagliptin did not have any interactive effect upon DPP-IV activity.

In *Study 1218.67 – U10-1328-01,* concurrent treatment with rifampicin resulted in a decrease in linagliptin plasma concentrations which resulted in a mean decrease in DPP-4 inhibition of 21%.

Study 1218.2 – U06-1139 showed that at Day 12 there was no significant difference between linagliptin 5 mg and 10 mg with respect to inhibition of DPP-4. Similarly, there was little difference between the 5 mg and 10 mg dose groups in plasma glucose concentrations over time. The mean (standard deviation (SD)) change from baseline to Day 13 in GLP-1 concentrations was 2.78 (3.88), 5.11 (6.29), 14.0 (18.4), 12.4 (9.04) and 12.4 (13.9) pmol/L for placebo, 1 mg, 2.5 mg, 5 mg and 10 mg linagliptin respectively. The greatest decrease in area under the concentration effect curve (AUCEC) at Day 13 was in the 10 mg linagliptin group.

In *Study 1218.3 – U06-1822*, DPP-4 inhibition was greatest in the 10 mg dosing group but there was no significant difference between the 5 mg and 10 mg dosing groups. However,

the greatest change in AUCEC from baseline was in the 5 mg dosing group. At Day 29, the mean (95% CI) placebo corrected change from baseline in HbA1c was -0.31% (-0.56% to -0.05%) for 2.5 mg, -0.37% (-0.67% to -0.08%) for 5 mg and -0.28 (-0.56% to -0.01%). Postprandial GLP-1 concentrations increased in all three active treatment groups compared to placebo. Postprandial glucagon concentrations also decreased in the active treatment groups relative to placebo but to a greater extent in the linagliptin 5 mg group. Hence, the optimal linagliptin treatment dose appeared to be 5 mg.

In *Study 1218.26 – U10-1467-02* inhibition of DPP-4 was slightly higher (approximately 10%) in the subjects with renal impairment compared to subjects with normal renal function.

Study 1218.27 – U10-1219-01 there was no clinically significant change in inhibition of DPP-4 by linagliptin 5 mg due to the presence of hepatic impairment.

In *Study 1218.12 – U08-3212-01* there was an increase in effect for each increase in linagliptin dose level up to 10 mg. DPP inhibition was greatest with the 10 mg dose. The mean (SD) change in fasting plasma glucose (FPG) from baseline to Day 28 was 1.4 (26.3) mg/dL for placebo, −12.8 (24.1) mg/dL for 0.5 mg, −6.6 (21.8) mg/dL for 2.5 mg and −18.9 (12.7) mg/dL for 10 mg. The mean (SD) change in AUC for 7 point glucose profile from baseline to Day 29 was 12.9 (358.9) mg•h/dL for placebo; −158.8 (283.0) mg•h/dL for 0.5 mg; −477.1 (409.3) mg•h/dL for 2.5 mg; and −418.3 (401.7) mg•h/dL for 10 mg. The mean (SD) change from baseline for area under the effect curve from 0 to 3 h postdosing (AUEC0-3) during a meal tolerance test was −2.6 (27.0) mg•h/dL for placebo; −16.8 (18.9) mg•h/dL for 0.5 mg; −17.6 (36.0) mg•h/dL for 2.5 mg; and −37.8 (28.9) mg•h/dL for 10 mg. The mean (SD) change from baseline in HbA1c was 0.04(0.55) % for placebo, −0.31 (0.19) % for 0.5 mg; −0.20 (0.39) % for 2.5 mg; and −0.44 (0.28) % for 10 mg. The mean (SD) reduction from baseline in GLP-1 was 2.2 (1.7) nmol/L for placebo; 5.1 (4.3) nmol/L for linagliptin 0.5 mg; 7.0 (4.1) for 2.5 mg; and 10.1 (7.2) nmol/L for 10 mg.

Effect on QT interval

In *Study 1218.32 – U09-1067-01* there was a decrease from baseline in QT in both linagliptin groups relative to placebo and an increase in the moxifloxacin group. The mean (90% CI) difference in change from baseline compared to placebo was −1.12 (−2.72 to 0.48) ms for linagliptin 5 mg, −2.49 (−4.07 to −0.90) ms for linagliptin 100 mg and 6.94 (5.35 to 8.52) ms for moxifloxacin. An increase in QTcB from baseline of >30 ms was reported in two (4.5%) subjects given placebo, five (11.4%) with linagliptin 100 mg and six (13.6%) with moxifloxacin. No subjects given linagliptin 5 mg showed an increase in QTcB.

Evaluator's overall conclusions on pharmacodynamics

The pharmacodynamic relationship of linagliptin plasma concentration to inhibition of DPP-4 was well characterised and generally supported the selection of the 5 mg dose. The IC_{50} was approximately 2-4 nmol/L, the IC_{80} was approximately 4-6 nmol/L and I_{max} can be taken to be 100% inhibition of DPP-4 (Study 1218.10–U07-1800-01). Effect on DPP-4 persisted for 24 hours (Study U07-2003; U07-3116 – 1218.11). DPP-4 activity had not returned to baseline 96 h after drug administration (Study 1218.1 -U05-2072).

There was no significant difference between the two doses of linagliptin 5 mg and 10 mg with respect to the inhibition of DPP-4 with (Study 1218.2 – U06-1139; Study 1218.3 – U06-1822). However, inhibition of DPP-4 was greatest with the 10 mg dose (Study 1218.3 – U06-1822; Study 1218.12 – U08-3212-01). The 5 mg morning dose regimen and the 2.5 mg twice daily regimen resulted in similar and sufficient DPP-4 inhibition over the whole dosing interval (Study 1218.45 – U08-2123-01). The increase in GLP-1 concentrations

plateaued with the 5 mg dose, both following single and multiple dosing (Study U07-3116 – 1218.11)

Linagliptin did not exhibit any prolonging effects on the QT interval (Study 1218.32 – U09-1067-01).

Efficacy

Dose Finding (Phase II) Studies

Study 1218.5-1218.5-U08-3761-02 was a multicentre, randomised, double blind, placebo controlled, parallel group, dose finding study in subjects with Type 2 diabetes mellitus. The study included male and female patients, aged ≥21 and ≤75 years, with a diagnosis of Type 2 diabetes treated only with diet and exercise (drug naïve) or with one or two oral hypoglycemic agents; glycosylated hemoglobin (HbA1c) of 7.5% to 10.0% at Visit 3 (beginning of the 2 week placebo run in period); BMI ≥25.0 and ≤40 kg/m^2. The study treatments were:

1. Linagliptin 0.5 mg
2. Linagliptin 2.5 mg
3. Linagliptin 5 mg
4. Placebo
5. Open label metformin treatment: 500 mg for 4 weeks then 1000 mg for 8 weeks.

Linagliptin and placebo were taken orally once daily and metformin was taken twice daily orally. There was a 6 week washout period followed by a 12 week treatment period and then a 2 week follow up period. The outcome measures for efficacy were: HbA1c, fasting plasma glucose (FPG), HbA1c ≤7%, DPP-4 inhibition and plasma linagliptin concentrations. The outcome measures for safety were AEs, physical examination, electrocardiogram (ECG), vital signs and laboratory parameters.

There were 302 subjects: 58 in the linagliptin 0.5 mg group, 57 in the 2.5 mg group and 55 in the 5 mg group. Some 67 subjects were given placebo and 65 subjects were treated with metformin. There were 175 (57.9%) males, 127 (42.1%) females and the age range was 25 to 75 years. The treatment groups were mismatched in gender distribution but similar in baseline disease characteristics.

There appeared to be a plateau in effect at the level of the linagliptin 2.5 mg dose. Compared to placebo the adjusted mean (95% CI) change from baseline in HbA1c was -0.14 (-0.41 to 0.14) % for 0.5 mg, -0.42 (-0.69 to -0.14) % for 2.5 mg, -0.46 (-0.74 to -0.18) % for 5 mg (Table 14) and -0.85 (-1.1 to -0.59) % for metformin. The results were not influenced by gender. The proportion of subjects achieving a HbA1c ≤7% was 10.5% for 0.5 mg, 7.25% for 2.5 mg and 11.1% for 5 mg. Compared to placebo, the adjusted mean (95% CI) change from baseline in FPG was 2.45 (-10 to 15.1) mg/dL for 0.5 mg, -19.4 (-32 to -6.6) mg/dL for 2.5 mg and -13.3 (-26 to -0.50) mg/dL for 5 mg. Mean (SD) DPP-4 inhibition at Week 12 was -4.63 (16.63) % for placebo, 40.58 (17.43) % for 0.5 mg, 64.90 (26.03) % for 2.5 mg and 62.58 (38.74) % for 5 mg.

Table 14. Comparison of treatments for change of HbA1c from baseline at Week 12 – FAS.

	Placebo	BI 1356 0.5mg	BI 1356 2.5 mg	BI 1356 5 mg
Number of patients	63	57	55	54
HbA1C [%]				
Adjusted Mean (SE)	0.18 (.10)	0.04 (.10)	-0.24 (.10)	-0.28 (.10)
HbA1C difference to Placebo [%]				
Adjusted Mean (SE)		-0.14 (.14)	-0.42 (.14)	-0.46 (.14)
95% CI		(-0.41, 0.14)	(-0.69, -0.14)	(-0.74, -0.18)
P-value		0.3271	0.0032	0.0012

Note: The above results are based on analysis that includes BI 1356 doses, Metformin and Placebo data

Study – 1218.6-U08-1056-03 was a multicentre, randomised, double blind, placebo controlled, parallel group study with an additional open label arm (active comparator: glimepiride) in patients with Type 2 diabetes mellitus and insufficient glycaemic control despite treatment with metformin. The study compares three linagliptin doses. The study was conducted at 47 centres in France, Germany, Slovakia, Sweden, Ukraine and UK. The study included male and female subjects with a diagnosis of Type 2 diabetes mellitus for at least 3 months; previously treated with metformin alone or with metformin and one other OAD other than rosiglitazone or pioglitazone; HbA1c 7.0 to 9.0% for patients treated with metformin and one other OAD, or HbA1c 7.5 to 10.0% for patients treated with metformin alone. Patients were ≥21 and <75 years old and had a BMI in the ≥25 and ≤40 kg/m^2 range.

The study treatments were:

1. Linagliptin tablets 1mg
2. Linagliptin tablets 5 mg
3. Linagliptin tablets 10 mg
4. Placebo tablet
5. Open-label glimepiride tablet (forced titration from 1 mg to maximum of 3 mg) once daily before breakfast.

All treatments were administered once daily. Subjects were randomised to treatment in the ratio 1:1:1:1:1.

The efficacy outcome measures were: change in HbA1c from baseline to Week 12; FPG and proportion of subjects achieving HbA1c≤7%. Hypothesis tests were performed using analysis of co variance (ANCOVA). The safety outcome measures were: AEs, ECGs, vital signs and laboratory parameters.

The study included 333 subjects: 65 in the linagliptin 1mg group, 66 in the 5 mg group, 66 in the 10 mg group, 71 in the placebo group and 65 in the glimepiride group. A total of 47 (14.1%) subjects discontinued, 14 (4.2%) because of AE. There were 193 (58.0%) male subjects, 140 (42.0%) females and the age range was 31 to 78 years. The treatment groups were similar in demographic, baseline characteristics and antidiabetic therapies at screening.

There was a clinically and statistically significant improvement in HbA1c from baseline for all the linagliptin groups compared with placebo: mean (95% CI) difference -0.40 (-0.68 to -0.12) % for linagliptin 1 mg; -0.73 (-1.01 to -0.44) % for linagliptin 5 mg and -0.67 (-0.95 to -0.39) % for linagliptin 10 mg (Table 15).

Table 15. Adjusted means for HbA1c change from baseline at Week 12 (FAS LOCF),

HbA1c (%)	Placebo	BI 1356 1 mg	BI 1356 5 mg	BI 1356 10 mg
Number of patients	70	64	62	66
Adjusted mean change from baseline (SE)	0.25 (0.10)	–0.15 (0.10)	–0.48 (0.11)	–0.42 (0.10)
Difference to placebo (SE) 95% CI p-value		–0.40 (0.14) (–0.68, –0.12) 0.0055	–0.73 (0.14) (–1.01, –0.44) <.0001	–0.67 (0.14) (–0.95, –0.39) <.0001

LOCF=last observation carried forward

The corresponding improvement in the glimepiride group was -0.90 (-1.16 to -0.64) %. The 5 mg and 10 mg groups had similar responses that were greater than the 1 mg response. In the linagliptin groups, the response was greater in those subjects on lower doses of metformin (Table 16).

Table 16. Descriptive statistics of the HbA1c change from baseline at week 12 by subgroups (FAS-LOCF).

	Placebo		BI 1356 1 mg		BI 1356 5 mg		BI 1356 10 mg	
	N	HbA1c change [%], mean (SD)	N	HbA1c change [%], mean (SD)	N	HbA1c change [%], mean (SD)	N	HbA1c change [%], mean (SD)
All patients	70	0.24 (0.74)	64	–0.14 (0.92)	62	–0.50 (0.81)	66	–0.42 (0.87)
ATS*								
No	46	0.12 (0.62)	45	–0.33 (0.76)	37	–0.70 (0.62)	37	–0.64 (0.75)
Yes	24	0.48 (0.90)	19	0.31 (1.11)	25	–0.19 (0.97)	29	–0.15 (0.94)
HbA1c baseline group								
<8%	20	0.07 (0.45)	27	0.15 (1.04)	21	–0.12 (0.80)	21	–0.39 (0.66)
8 to 9%	35	0.51 (0.62)	26	–0.48 (0.61)	26	–0.58 (0.73)	31	–0.43 (0.72)
≥9%	15	–0.17 (1.05)	11	–0.05 (1.02)	15	–0.87 (0.80)	14	–0.46 (1.37)
Gender								
Male	43	0.31 (0.80)	36	–0.26 (0.95)	33	–0.42 (0.77)	35	–0.57 (0.81)
Female	27	0.13 (0.64)	28	0.01 (0.87)	29	–0.58 (0.86)	31	–0.25 (0.91)
Age group								
<65 years	40	0.28 (0.68)	40	–0.12 (0.96)	42	–0.49 (0.75)	37	–0.39 (0.89)
≥65 years	30	0.19 (0.82)	24	–0.18 (0.86)	20	–0.51 (0.95)	29	–0.46 (0.85)
BMI group								
<30 kg/m^2	20	0.15 (0.77)	23	–0.26 (0.78)	22	–0.64 (0.63)	21	–0.36 (0.98)
30 to 35	34	0.26 (0.72)	22	–0.18 (0.85)	23	–0.30 (0.98)	28	–0.67 (0.85)
≥35 kg/m^2	16	0.31 (0.78)	19	0.04 (1.14)	17	–0.58 (0.75)	17	–0.11 (0.64)
Metformin dose group								
<1500 mg	17	0.12 (0.79)	13	–0.25 (0.55)	11	–0.80 (0.69)	21	–0.49 (0.76)
≥1500 mg	53	0.28 (0.73)	51	–0.11 (0.99)	51	–0.43 (0.83)	45	–0.40 (0.92)

The results for FPG were similar to those for HbA1c: adjusted mean (95% CI) difference to placebo in change from baseline -19.2 (-31.3 to -7.1) mg/dL for linagliptin 1 mg; -34.7 (-

46.8 to -22.5) mg/dL for linagliptin 5 mg and -29.0 (-41.0 to -17.1) mg/dL for linagliptin 10 mg (Table 17).

Table 17. Adjusted means for change in fasting plasma glucose from baseline at Week 12 (FAS-LOCF)

Fasting plasma glucose (mg/dL)	Placebo	BI 1356 1 mg	BI 1356 5 mg	BI 1356 10 mg
Number of patients	68	63	62	66
Adjusted mean change from baseline (SE)	12.7 (4.3)	–6.5 (4.4)	–22.0 (4.5)	–16.3 (4.3)
Difference to placebo (SE)		–19.2 (6.1)	–34.7 (6.2)	–29.0 (6.1)
95% CI		(–31.3, –7.1)	(–46.8, –22.5)	(–41.0, –17.1)
p-value		0.0020	<.0001	<.0001

Means are adjusted based on a model with baseline fasting plasma glucose, treatment

The proportion of subjects achieving HbA1c ≤7 % was 1.4% for placebo, 15.6% for linagliptin 1 mg, 14.5% for linagliptin 5 mg and 21.2% for linagliptin 10 mg. Body weight decreased (compared to baseline) in the linagliptin groups but increased in the glimepiride group (Table 18). Homeostasis model assessment–insulin resistance (HOMA-IR) decreased in all the active treatment groups (Table 19). HOMA insulin secretion (HOMA-S) increased in the linagliptin groups and decreased in the glimepiride.

Table 18. Body weight change from baseline to week 12 (FAS- LOCF)

	Placebo	BI 1356 1 mg	BI 1356 5 mg	BI 1356 10 mg	Glimepiride
Baseline					
Number of patients	70	64	62	66	64
Body weight (kg), mean (SD)	93.20 (16.93)	92.35 (17.00)	89.89 (13.47)	89.92 (16.27)	90.81 (14.96)
Week 12					
Number of patients	63	52	53	55	60
Body weight change from baseline (kg), mean (SD)	–0.84 (2.51)	–0.15 (2.26)	–0.57 (1.61)	–1.27 (2.65)	0.73 (3.20)

Table 19. Change from baseline in proinsulin/insulin ratio and HOMA indices at Week 12 (PPS-observed case).

	Placebo	BI 1356 1mg	BI 1356 5mg	BI 1356 10mg	Glimepiride
Proinsulin/insulin ratio					
Number of patients	44	43	43	45	18
Mean change from baseline (SD)	0.0 (0.1)	–0.0 (0.1)	–0.0 (0.1)	–0.0 (0.1)	–0.0 (0.0)
HOMA index for insulin resistance					
Number of patients	43	40	42	44	18
Mean change from baseline (SD)	0.5 (4.1)	–0.8 (4.0)	–1.3 (5.1)	–1.3 (2.5)	–1.7 (3.8)
HOMA index for insulin secretion					
Number of patients	43	40	42	44	18
Mean change from baseline (SD)	–2.5 (31.5)	3.4 (23.5)	8.1 (34.5)	7.9 (19.5)	–20.1 (210.7)

Study 1218.37-U09-2397-02 was a multicentre, randomised, double blind, double dummy, placebo controlled, parallel group study in subjects with Type 2 diabetes mellitus to compare the effect of linagliptin 5 mg and sitagliptin 100 mg on 24 h glucose control. The study was conducted at three centres in Germany. The study included subjects with Type 2

diabetes mellitus aged ≥ 18 and ≤ 80 years who were treatment naïve or had had previous monotherapy with oral anti-diabetic agents and HbA1c ≥6.5% to ≤10.0% at start of run in period with a BMI ≤ 40 kg/m^2 at the screening visit. The study treatments were:

1. Linagliptin tablet 5 mg once daily, orally
2. Sitagliptin 100 mg capsule, once daily orally
3. Placebo

There were matching placebos for each treatment. The study was designed with a 2 week wash out (only patients already treated with one oral antidiabetic medication), followed by 2 week placebo run in phase, followed by 4 week double blind treatment, followed by 2 week follow up phase.

The outcome measures were:

- change from baseline in weighted mean glucose (WMG);
- change from baseline in the $AUEC_{0\text{-}2h}$ of GLP-1 after a meal tolerance test; and
- PD responses to study drug administration for plasma glucose: active GLP-1, active and total GIP, insulin, C-peptide, glucagon, HbA1c, fructosamine, 1,5 anhydroglucitol and the inhibition of plasma DPP-4 activity.

The safety outcome measures were: AEs, vital signs, ECG, physical examination and laboratory safety tests.

Hypothesis tests were performed using analysis of variance (ANOVA) using a level of significance of 0.05. Superiority was tested using the change in WMG from baseline to Day 28; and change in GLP-1 $AUEC_{0\text{-}2h}$ following an MTT, from baseline to Day 28, sequentially using a closed stepwise procedure. The sample size calculation was based on both of the primary endpoints.

The study included 121 subjects: 40 in the linagliptin group, 41 in the sitagliptin group and 40 subjects given placebo. There were 86 (71.1%) males, 35 (28.9%) females and the age range was 28 to 76 years. The treatment groups were similar in demographic and baseline characteristics.

For the efficacy outcome variables, linagliptin was superior to placebo for weighted mean glucose, GLP-1 AUC, FPG and plasma glucose AUEC (Table 20). In comparison with sitagliptin, there were no significant differences. The adjusted mean (95% CI) difference in change from baseline in GLP-1 was 18.24 (12.72 to 23.77) for linagliptin – placebo; 15.46 (9.94 to 20.99) for sitagliptin – placebo; and 2.78 (-2.65 to 8.21) for linagliptin – sitagliptin. The adjusted mean (95% CI) difference in change from baseline in FPG was -10.74 (-19.44 to -2.03) for linagliptin – placebo; -15.98 (-24.73 to -7.23) for sitagliptin-placebo and 5.24 (-3.32 to 13.81) for linagliptin – sitagliptin. The adjusted mean (95% CI) difference in change from baseline in AUEC was -106.19 (-143.77 to -68.61) for linagliptin – placebo; -128.94 (-166.69 to -91.18) for sitagliptin – placebo and 22.75 (-14.03 to 59.53) for linagliptin – sitagliptin.

Table 20. Adjusted mean change from baseline for outcome variables.

Weighted mean glucose 24 h [mg/dL]	Placebo	BI 1356
Number of patients with endpoint data	38	39
Baseline (Day -1) mean (SE)	190.8 (5.8)	188.8 (6.9)
Adjusted mean change from baseline (SE)	0.1 (3.0)	−19.8 (2.9)
Comparison vs. placebo		
Adjusted mean (SE)		−19.9 (4.0)
(95% CI)		(−28.0, −11.9)
p-value		<0.0001
GLP-1 $AUEC_{0-2h}$ [pmol*h/L]	Placebo	BI 1356
Number of patients with endpoint data	38	39
Baseline (day −1) mean (SE)	15.0 (1.9)	17.4 (1.8)
Adjusted mean change from baseline (SE)	0.4 (2.1)	18.5 (2.1)
Comparison vs. placebo		
mean (SE)		18.1 (2.9)
(95% CI)		(12.4, 23.9)
p-value		<0.0001
Fasting plasma glucose [mg/dL]	Placebo	BI 1356
Number of patients with endpoint data	38	39
Baseline (day −1) mean (SE)	169.6 (4.2)	166.6 (4.5)
Adjusted mean change from baseline (SE)	−0.1 (3.6)	−10.9 (3.5)
Comparison vs. placebo		
mean (SE)		−10.8 (4.8)
(95% CI)		(−20.4, −1.2)
p-value		0.0283
Plasma glucose $AUEC_{0-3h}$ [mg*h/dL]	Placebo	BI 1356
Number of patients with endpoint data	38	39
Baseline (day −1) mean (SE)	722.0 (22.5)	728.4 (25.0)
Adjusted mean change from baseline (SE)	8.1 (15.1)	−98.4 (14.7)
Comparison vs. placebo		
mean (SE)		−106.5 (20.3)
(95% CI)		(−147.0, −66.0)
p-value		<0.0001

In comparison with placebo, there were decreases in AUCs for insulin and C-peptide (Table 21), a decrease in glucagon (Table 22), a decrease in total GIP (Table 23) and an increase in active GIP with linagliptin.

Table 21. Placebo corrected adjusted means (SE) of the peak and the AUEC0-2h of insulin and C-peptide–PPS completers (BI–Pbo).

	BI 1356 – Placebo			
	Insulin		C-peptide	
Endpoint	Peak [mU/L]	$AUEC_{0-2h}$ [mU·h/L]	Peak [pmol/L]	$AUEC_{0-2h}$ [pmol·h/L]
Mean baseline (Pbo / BI 1356)*	72.1 / 78.8	87.6 / 102.4	3201.8 / 3574.2	4515.0 / 5161.4
Day 1 – adj. mean (SE)	0.5 (6.0)	−4.3 (7.4)	−167.6 (127.7)	−322.3 (181.6)
Day 28 – adj. mean (SE)	2.2 (6.7)	−8.0 (7.2)	−7.3 (148.0)	−24.8 (210.7)
Day 29 – adj. mean (SE)	−1.6 (6.6)	−9.8 (7.6)	−49.0 (155.1)	−43.6 (255.1)
Day 30 – adj. mean (SE)	−4.7 (9.2)	−6.8 (9.6)	−9.2 (165.2)	−152.8 (235.3)

Note: The number of patients with endpoints varies between endpoints, groups and days, ranging from 33 to 38 patients

Table 22. Placebo corrected adjusted means (SE) of the peak and the AUEC0-2h of glucagon–PPS completers (BI–Pbo).

	BI 1356 – Placebo	
Parameter	Glucagon	
Endpoint	Peak [pg/mL]	$AUEC_{0-2h}$ [pg*h/mL]
Mean baseline (Pbo / BI 1356)*	109.2 / 110.0	183.0 / 182.1
Day 1 – adj. mean (SE)	−14.4 (5.9)	−23.4 (6.7)
Day 28 – adj. mean (SE)	−16.8 (6.0)	−18.7 (9.2)
Day 29 – adj. mean (SE)	−19.4 (6.6)	−18.8 (10.0)
Day 30 – adj. mean (SE)	−15.2 (6.6)	−17.5 (8.9)

Note: The number of patients with endpoints varies between endpoints, groups and days, ranging from 36 to 39 patients.
* The baseline value refers to patients with endpoints on day 28.

Table 23. Placebo-corrected adjusted means (SE) of the peak and the AUEC0-2h of the active and total GIP–PPS completers (BI–Pbo).

	BI 1356 – Placebo			
Parameter	Active GIP		Total GIP	
Endpoint	Peak [pM]	$AUEC_{0-2h}$ [pM·h]	Peak [pM]	$AUEC_{0-2h}$ [pM·h]
Mean baseline (Pbo / BI 1356)*	73.4 / 92.9	105.2 / 129.9	168.9 / 214.1	239.6 / 301.4
Day 1 – adj. mean (SE)	21.1 (11.3)	40.7 (13.4)	−102.4 (25.6)	−133.3 (26.7)
Day 28 – adj. mean (SE)	51.1 (9.5)	91.4 (12.2)	−80.3 (15.8)	−106.7 (20.7)
Day 29 – adj. mean (SE)	41.6 (13.2)	86.1 (17.4)	−91.4 (25.1)	−100.7 (25.7)
Day 30 – adj. mean (SE)	35.2 (11.4)	66.0 (15.3)	−71.5 (17.5)	−92.4 (21.0)

Note: The number of patients with endpoints varies between endpoints, groups and days, ranging from 36 to 39 patients.
* The baseline value refers to patients with endpoints on day 28.

There was an improvement in HbA1c at Day 28: mean (95% CI) difference in change from baseline was-0.22 (-0.35 to -0.08) % p=0.0021. There was an improvement in serum fructosamine: mean (95% CI) difference in change from baseline was -9.0 (-17.9 to -0.2) mmol/L p=0.0446. There was a relative increase in serum 1,5-anhydroglucitol concentrations: mean (95% CI) difference in change from baseline was 1.8 (1.0 to 2.5) mg/mL p<0.0001. There was no significant change in either HOMA-S or HOMA-IR. At Day 28, 23 (58.975) subjects in the linagliptin group and four (9.76%) subjects in the sitagliptin group had a DPP-4 inhibition ≥80%.

Pivotal Placebo Controlled Studies

1. Study 1218.15-U09-2519-01 was a multicentre, randomised, double blind, placebo controlled, parallel group comparison in patients with Type 2 diabetes mellitus and insufficient glycaemic control to evaluate efficacy and safety of 5 mg linagliptin with 30 mg pioglitazone in comparison with placebo with 30 mg pioglitazone. The study was conducted at 43 centres in seven countries: Austria, Greece, Hungary, Japan, Portugal, Romania and Spain.

The inclusion criteria included:

- Male and female patients with Type 2 diabetes mellitus and treatment naïve or previously treated with any oral hypoglycaemic agent.
- HbA1c at screening
    - Patients undergoing washout of previous antidiabetic medication: 7.0%≤ HbA1c ≤9.5%
    - Patients not undergoing washout of previous antidiabetic medication: 7.5%≤ HbA1c ≤11.0%
- HbA1c at start of run in: 7.5%≤ HbA1c ≤11.0%
- Age ≥18 and ≤80 years
- BMI ≤40 kg/m2

The exclusion criteria included:

- Myocardial infarction (MI), stroke, or transient ischaemic attack (TIA) within 6 months
- Impaired hepatic function, defined as serum levels of either ALT, AST or ALP above 3 x ULN
- Treatment with GLP-1 analogues/agonists, insulin, or anti obesity drugs (such as sibutramine, rimonabant, orlistat) within 3 months
- Alcohol or drug abuse within 3 months
- Premenopausal women who were nursing or pregnant or were of child bearing potential and were not practicing an acceptable method of birth control
- Treatment with systemic steroids or change in dosage of thyroid hormones within 6 weeks
- Fasting blood glucose (FBG) >13.3 mmol/L
- Heart failure NYHA Class III-IV[16] or history of heart failure
- Diabetic ketoacidosis within 6 months
- Haemodialysis patients

The study treatments were:

1. Linagliptin tablet 5 mg plus pioglitazone 30 mg as initial combination, once daily orally
2. Placebo tablet plus pioglitazone 30 mg as initial combination, once daily orally

Assignment to treatment group was by Interactive voice response and Web Response Services (IVRS)/IWRS.

[16] The New York Heart Association (NYHA) Functional Classification provides a simple way of classifying the extent of heart failure. It places patients in one of four categories based on how much they are limited during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and or angina pain. The classifications range from Class I (No symptoms and no limitation in ordinary physical activity, e.g. shortness of breath when walking, climbing stairs) to Class IV (Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients).

The primary efficacy outcome measure was the change from baseline in HbA1c after 24 weeks of treatment.

The secondary efficacy outcome measures were:

- HbA1c on treatment <7.0% or <6.5% after 24 weeks of treatment
- HbA1c lowering by at least 0.5% after 24 weeks of treatment
- Reduction from baseline in HbA1c by visit over time
- Change from baseline in FPG after 24 weeks of treatment
- Change from baseline in FPG by visit over time

Other endpoints included:

- Use of rescue therapy
- HOMA-IR and HOMA-S
- Disposition index ([DI]; derived from the indices for insulin sensitivity and β-cell function) at baseline and after 24 weeks of treatment
- Change from baseline in body weight after 24 weeks of treatment
- Change from baseline in waist circumference after 24 weeks of treatment
- Change from baseline in lipid parameters after 24 weeks of treatment
- EQ-5D[17]
- Health care resource utilization

Safety outcome measures were: AEs, vital signs, ECGs and clinical laboratory measures.

Statistical Issues

Hypothesis tests were performed using ANCOVA with 'treatment' and 'prior use of antidiabetic agents' as fixed classification effects and 'HbA1c baseline' as a linear covariate.

Using a SD of 1.6% for the change in HbA1c from baseline, from previous studies of pioglitazone, a total number of 83 patients in the placebo group and 166 in the linagliptin group were required to achieve a power of 90% to detect a 0.7% difference in HbA1c change from baseline. With 125 patients in the placebo group and 250 in the linagliptin group the power increased to 97%.

Results

A total of 707 subjects were enrolled and 389 were assigned to treatment: 259 to linagliptin 5 mg and 259 to placebo. A total of 252 subjects in the linagliptin group and 128 in the placebo were analysed for the primary endpoint. There were 237 (60.9%) males, 152 (39.1%) females and the age range was 29 to 75 years. The treatment groups were similar in demographic and baseline characteristics. The treatment groups were similar in diabetes characteristics and baseline biomarker measures.

The primary efficacy outcome measure demonstrated superior efficacy for linagliptin-pioglitazone in comparison with placebo-pioglitazone: adjusted mean (95% CI) difference -0.51 (-0.71 to -0.30) %, p<0.0001. Superior efficacy was demonstrated from Week 6 to Week 24. Baseline covariates did not influence efficacy. There was a greater decrease in

[17] EQ-5D™ is a standardised instrument developed by the EuroQol Group for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status.

FPG in the linagliptin-pioglitazone group: adjusted mean (95% CI) difference -14.2 (-21.1 to -7.3) mg/dL, p<0.0001.

Of the subjects with HbA1c values ≥7.0% at baseline, 108 (42.9%) subjects in the linagliptin + pioglitazone group and 39 (30.5%) subjects in the placebo + pioglitazone group achieved HbA1c <7.0% at 24 weeks (p=0.0051). Of the subjects with baseline HbA1c ≥6.5%, 44 (17.5%) subjects in the linagliptin + pioglitazone group and 18 (14.1%) subjects in the placebo + pioglitazone group reached the target of HbA1c <6.5% at 24 weeks, (p=0.3547). A total of 189 (75.0%) subjects in the linagliptin + pioglitazone group and 65 (50.8%) subjects in the placebo + pioglitazone group and achieved an HbA1c reduction by 0.5% or more at 24 weeks (p<0.0001). Twenty (7.9%) subjects in the linagliptin + pioglitazone group and 18 (14.1%) subjects in the placebo + pioglitazone group required rescue therapy (p=0.0352). There was a mean (SD) weight increase of 2.4 (3.7) kg in the linagliptin + pioglitazone group and 1.2 (3.9) kg in the placebo + pioglitazone group. There was a mean (SD) increase in waist circumference of 1.0 (8.9) cm in the linagliptin + pioglitazone group and a decrease of 0.2 (9.4) cm in the placebo + pioglitazone group. The results of the EQ-5D did not indicate any significant differences between the groups. There was no significant difference between the groups in HOMA-IR or HOMA-S but the Disposition Index increased in the linagliptin + pioglitazone group: adjusted mean (95% CI) difference 2.69 (0.65 to 4.74) mmol/L x mmol/L.

2. Study 1218.16-U10-1103-03 –was a multicentre, randomised, double blind, placebo controlled, parallel group study in subjects with Type 2 diabetes mellitus and insufficient glycaemic control to evaluate efficacy and safety of 5 mg linagliptin in comparison with placebo as monotherapy. The study was conducted at 66 centres in eleven countries: Croatia, India, Italy, Israel, Malaysia, Poland, Romania, Slovakia, Ukraine, Thailand and the Netherlands.

The inclusion criteria included:

- Male and female patients with Type 2 diabetes mellitus who were either treatment naïve or who had been treated with not more than one OAD. Antidiabetic therapy had to be unchanged for 10 weeks.
- HbA1c at screening for subjects undergoing washout of previous antidiabetic medication: 6.5%≤ HbA1c ≤9.0%; and for those not undergoing washout of previous antidiabetic medication: 7.0%≤ HbA1c ≤10%
- HbA1c at start of run in: ≥7.0% to ≤10.0%
- Age: 18 years to ≤80 years
- BMI: ≤40 kg/m^2

The exclusion criteria included:

- MI, stroke or TIA within 6 months
- Impaired hepatic function defined as serum levels of either ALT, AST or ALP 3 times the upper limit of normal (ULN)
- Treatment with more than one antidiabetic agent within 10 weeks
- Treatment with rosiglitazone, pioglitazone, GLP-1 analogues, insulin or anti-obesity drugs (such as sibutramine, rimonabant, orlistat) within 3 months
- Alcohol abuse within 3 months or drug abuse
- Premenopausal women who were nursing or pregnant or were of child bearing potential and were not practicing an acceptable method of birth control

- Current treatment with systemic steroids or change in dosage of thyroid hormones within 6 weeks

The study treatments were:

1. Linagliptin tablet 5 mg
2. Placebo

Treatments were administered orally once daily. There was a 6 week washout period including a 2 week open label placebo run in (subjects pre-treated with an OAD) or 2 week open label placebo run in (patients not pretreated with an OAD) followed by a 24 week treatment period. Assignment to treatment was by IVRS/IWRS.

The primary efficacy outcome measure was the change from baseline in HbA1c after 24 weeks of treatment. Secondary efficacy outcome measures were:

- HbA1c on treatment <7.0% or <6.5% after 24 weeks of treatment
- HbA1c lowering by at least 0.5% after 24 weeks of treatment
- Reduction from baseline in HbA1c by visit over time
- Change from baseline in FPG after 24 weeks of treatment
- MTT: 2 h post-prandial glucose (2hPPG) change from baseline after 24 weeks of treatment

Other efficacy outcome measures were:

- Use of rescue therapy
- HOMA at baseline and after 24 weeks of treatment
- Disposition index ([DI] at baseline and after 24 weeks of treatment
- Change from baseline in body weight after 24 weeks of treatment
- Change from baseline in waist circumference after 24 weeks of treatment
- Change from baseline in lipid parameters after 24 weeks of treatment
- EQ-5D and Health Care Resource Utilisation (HCRU) questionnaires at baseline (Visit 3) and Visits 4, 5 and 7
- MTT: glucose AUC, insulin AUC, C-peptide AUC and insulin AUC to glucose AUC ratio change from baseline after 24 weeks of treatment
- Change in plasma proinsulin/insulin ratio by visit over time
- Plasma DPP-4 inhibition after 12 and 24 weeks)

The safety outcome measures were: AEs, physical examination, vital signs, ECG and clinical laboratory tests.

Statistical Issues

Hypothesis tests were performed using an ANCOVA model comparing the change from baseline in HbA1c after 24 weeks of treatment; with 'treatment' and 'prior use of antidiabetic agents' as fixed classification effects and 'HbA1c baseline' as a linear covariate; and using the FAS and last observation carried forward (LOCF.

The sample size calculation was based on the primary efficacy outcome variable, assumed a standard deviation of 1.0% for HbA1c for change from baseline at 24 weeks. A sample size of 150 patients in the placebo group and 300 patients in the linagliptin was determined to be sufficient to detect a 0.7% difference between the treatment groups with a power of more than 95%.

Results

A total of 935 subjects were enrolled in the study and 503 were randomised to treatment: 336 in the linagliptin group and 167 in the placebo. A total of 318 (94.6%) subjects in the linagliptin group and 152 (91.0%) in the placebo completed the study. Five (1.5%) subjects in the linagliptin group and four (2.4%) in the placebo were withdrawn because of an AE. The FAS data included 333 (99.1%) subjects in the linagliptin group and 163 (97.6%) in the placebo. There were 260 (51.7%) females and 243 (48.3%) males and the age range was 24 to 79 years. The treatment groups were similar in demographic and baseline characteristics. The treatment groups were similar in time since diagnosis of diabetes, concomitant diagnoses related to diabetes and baseline biomarkers.

Linagliptin was superior to placebo by the primary efficacy outcome measure. The adjusted mean (95% CI) difference in change from baseline in HbA1c for linagliptin–placebo treatment was: -0.69 (-0.85 to -0.53) %, p<0.0001. The treatment difference was apparent from Week 6 through to Week 24. Treatment effect was greater in subjects with higher HbA1c at baseline. FPG decreased to a greater extent in the linagliptin group: adjusted mean (95% CI) change from baseline, linagliptin – placebo: -23.3 (-30.4 to -16.3) mg/dL, p<0.0001. Among patients with baseline HbA1c ≥7.0%, 77 (25.2%) subjects in the linagliptin group and 17 (11.6%) subjects in the placebo group achieved HbA1c <7.0%, p=0.0006. Among patients with baseline HbA1c ≥6.5%, 35 (10.6%) subjects in the linagliptin group and eight (4.9%) subjects in the placebo group achieved HbA1c <6.5% p=0.0323. Reduction from baseline in HbA1c of ≥0.5% was achieved by 157 (47.1%) subjects in the linagliptin group and 31 (19.0%) subjects in the placebo group, p<0.0001. PPG was lower post MTT in the linagliptin group: adjusted mean (95% CI) change from baseline: -58.38 (-82.33 to -34.43) mg/dL, p<0.0001.

There was no significant change in mean weight or waist circumference. Mean (SD) change in body weight was 0.0 (2.1) kg for linagliptin and -0.3 (2.0) kg for placebo. Mean (SD) change in waist circumference was 0.4 (9.0) cm for linagliptin and -0.6 (4.5) cm for placebo. There was no apparent difference between the groups in EQ-5D. Analysis of DPP-4 activity was only performed in the linagliptin subjects and the median inhibition at trough was 84.18% at Week 12 and 82.81% at Week 24. Relative to placebo, proinsulin/insulin ratio decreased and HOMA-%B and DI increased in the linagliptin group. The total glucose AUC following a MTT decreased in the linagliptin group relative to placebo: adjusted mean (95% CI) -3.326 (-5.35 to -1.17) mmol•h/L, p =0.0026.

3. *Study 1218.17-U09-2533-02* was a multicentre, randomised, double blind, placebo controlled, parallel group study in subjects with Type 2 diabetes mellitus and insufficient glycaemic control despite treatment with metformin. The study evaluated the efficacy and safety of 5 mg linagliptin as add on therapy to metformin. The study was conducted at 82 centres in ten countries: Czech Republic, Finland, Greece, India, Israel, Mexico, New Zealand, Russia, Sweden and USA.

The inclusion criteria included:

- Male and female patients with Type 2 diabetes and previously treated with metformin and not more than one other OAD. Antidiabetic therapy had to be unchanged for 10 weeks
- A dose of ≥1500 mg/day metformin, or maximum tolerated dose of metformin, stable for at least 12 weeks before randomisation
- HbA1c at screening for subjects undergoing washout of previous antidiabetic medication: HbA1c ≥6.5 to ≤9.0%; and for subjects not undergoing washout: HbA1c ≥7.0 to ≤10.0%

- HbA1c at start of run in: ≥7.0 to ≤10.0%
- Age: ≥18 and <80 years
- BMI ≤40 kg/m^2

The exclusion criteria were the same as for Study 1218.16-U10-1103-03but with the additional exclusion criteria of:

- Renal failure or renal impairment (serum creatinine ≥1.5 mg/dL)
- 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

The study treatments were:

1. Linagliptin tablet 5 mg
2. Placebo

Treatments were administered orally once daily. Treatment allocation was by IVRS/IWRS. Subjects continued to take metformin during the study at the baseline dosage.

The primary efficacy outcome measure was the change from baseline in HbA1c after 24 weeks of treatment. The secondary efficacy outcome measures were:

- HbA1c on treatment <7.0% after 24 weeks of treatment
- HbA1c lowering by at least 0.5% after 24 weeks of treatment
- Reduction from baseline in HbA1c by visit over time
- Change from baseline in FPG after 24 weeks of treatment
- Change from baseline in FPG by visit over time
- MTT: 2 h post-prandial glucose (2hPPG) change from baseline after 24 weeks of treatment
- 2hPPG increment over FPG at week 24
- HbA1c under treatment of <6.5% after 24 weeks of treatment

Other efficacy outcome measures were:

- Use and time to start of rescue therapy
- HOMA indices for insulin resistance/insulin secretion
- DI after 24 weeks of treatment
- Change from baseline in body weight after 24 weeks of treatment
- Change from baseline in waist circumference after 24 weeks of treatment
- Change from baseline in lipid parameters after 24 weeks of treatment
- EQ-5D, Health Care Resource Utilisation (HCRU) and Diabetes Treatment Satisfaction Questionnaire, status version (DTSQs) questionnaires
- MTT: glucose AUC, insulin AUC, C-peptide AUC and insulin AUC to glucose AUC ratio change from baseline after 24 weeks of treatment

The safety outcome measures were: AEs, physical examination, vital signs, ECG and clinical laboratory assessments.

Statistical Issues

Hypothesis tests were performed using ANCOVA models comparing the change from baseline in HbA1c after 24 weeks of treatment; including 'treatment' and ‘prior use of antidiabetic agents’ as fixed classification effects and 'HbA1c baseline' as a linear

covariate. For patients who received rescue therapy, another antidiabetic agent, or prior to change/increase of metformin dose, the last available HbA1c value prior to these interventions (LOCF) was used for the analysis.

Based on prior data from studies of thiazolinedinediones a median standard deviation of 1.6% for the difference of HbA1c from baseline was used to calculate a sample size of 450 patients on linagliptin and 150 patients on placebo to obtain a power of was >95%. However, the treatment effect used to determine the sample size was not stated in the report or in the statistical analysis plan.

Results

A total of 1268 subjects were enrolled and 701 were randomised to treatment: 524 to linagliptin and 177 to placebo. One subject in the linagliptin group did not receive treatment. A total of 484 (92.5%) subjects in the linagliptin group and 163 (92.1%) in the placebo completed the study. Nine (1.7%) subjects in the linagliptin group and three (1.7%) subjects in the placebo group discontinued because of AEs. The FAS included 513 (97.9%) subjects from the linagliptin group and 175 (98.9%) from the placebo. There were 379 (54.1%) males, 321 (45.9%) females and the age range was 21 to 79 years. The treatment groups were similar in demographic characteristics, baseline variables, time since diagnosis of diabetes, concomitant diagnoses and baseline biomarkers. Metformin dose was <1500 mg/day for 37 (7.2%) subjects in the linagliptin group and twelve (6.9%) subjects in the placebo group.

For the primary efficacy outcome measure, linagliptin + metformin (MET) was superior to placebo + MET: adjusted mean (95% CI) difference -0.64 (-0.78 to -0.50) %, p<0.0001. The treatment effect was apparent from Week 6 through to Week 24. Treatment effect was greater in subjects with higher HbA1c at baseline. There was a decrease in FPG in the linagliptin + MET group relative to placebo + MET: adjusted mean (95% CI) difference -21.1 (-27.3 to -15.0) mg/dL, p<0.0001. Of subjects with a baseline HbA1c ≥7.0%, 127 (26.1%) subjects in the linagliptin group and 15 (9.2%) subjects in the placebo group achieved a HbA1c below 7.0% after 24 weeks, p<0.0001. Of subjects with baseline HbA1c ≥6.5%, 53 (10.4%) subjects in the linagliptin group and four (2.3%) subjects in the placebo group achieved HbA1c <6.5% after 24 weeks, p=0.0016. A HbA1c reduction of at least 0.5% at 24 weeks was achieved by 255 (49.7%) subjects in the linagliptin group and 38 (21.7%) subjects in the placebo group, p<0.0001. Following a MTT, the 2hPPG decreased in the linagliptin + MET group relative to placebo + MET: adjusted mean (95% CI) difference -67.1 (-94.7 to -39.6) mg/dL, p<0.0001. Rescue medication was required by 40 (7.8%) subjects in the linagliptin group and 33 (18.9%) subjects given placebo, p<0.0001. There was no significant difference between the treatment groups in body weight change from baseline: mean (SD) -0.4 (3.3) kg for linagliptin + MET and -0.5 (3.3) kg for placebo. There was no significant difference between the treatment groups in waist circumference change from baseline: mean (SD) -0.1 (8.2) cm for linagliptin + MET and -1.4 (4.5) cm for placebo. There were no apparent differences reported in EQ-5D, HCRU and DTSQ. There were no significant differences in HOMA-IR, HOMA-%B or DI. Total glucose AUC following MTT decreased in the linagliptin + MET group relative to placebo + MET: adjusted mean (95% CI) difference -5.35 (-7.67 to -3.04) p<0.0001 (Table 24).

Table 24. Adjusted mean change from baseline in MTT parameters at Week 24 - MTT set (OC).

	Placebo	Linagliptin
Total glucose AUC [mmol*h/L]		
Number of patients	21	77
Baseline, mean (SE)	28.03 (1.29)	26.34 (0.62)
Adjusted mean change from baseline (SE)	1.57 (1.08)	−3.79 (0.61)
Comparison vs. placebo		
Adjusted mean (SE)		−5.35 (1.17)
95% Confidence interval		(−7.67, -3.04)
p-value		<0.0001
Total insulin AUC [pmol*h/L]		
Number of patients	13	46
Baseline, mean (SE)	457.05 (90.55)	511.92 (44.91)
Adjusted mean change from baseline (SE)	104.66 (79.15)	85.09 (49.51)
Comparison vs. placebo		
Adjusted mean (SE)		−19.58 (88.81)
95% Confidence interval		(−197.6, 158.5)
p-value		0.8264
Total C-peptide AUC [pmol*h/L]		
Number of patients	14	57
Baseline, mean (SE)	3369.10 (391.4)	3473.62 (175.0)
Adjusted mean change from baseline (SE)	906.50 (314.3)	563.83 (181.7)
Comparison vs. placebo		
Adjusted mean (SE)		−342.67 (351.3)
95% Confidence interval		(−1044, 358.72)
p-value		0.3329
Total insulin AUC/total glucose AUC ratio [pmol/mmol]		
Number of patients	13	45
Baseline, mean (SE)	18.37 (3.59)	21.02 (1.95)
Adjusted mean change from baseline (SE)	3.87 (3.24)	5.98 (2.02)
Comparison vs. placebo		
Adjusted mean (SE)		2.11 (3.64)
95% Confidence interval		(−5.19, 9.41)
p-value		0.5643
Total insulin AUC/total C-peptide AUC ratio		
Number of patients	11	40
Baseline, mean (SE)	0.12 (0.01)	0.14 (0.01)
Adjusted mean change from baseline (SE)	0.01 (0.01)	−0.01 (0.01)
Comparison vs. placebo		
Adjusted mean (SE)		−0.01 (0.01)
95% Confidence interval		(−0.04, 0.01)
p-value		0.2872
Total glucose AUC / (total insulin AUC/total C-peptide AUC ratio) [mmol*h/L]		
Number of patients	11	39
Baseline, mean (SE)	254.44 (33.02)	219.10 (25.25)
Adjusted mean change from baseline (SE)	4.44 (29.58)	−43.01 (18.08)
Comparison vs. placebo		
Adjusted mean (SE)		−47.45 (33.17)
95% Confidence interval		(−114.3, 19.36)
p-value		0.1595

4. Study 1218.18-U09-2458-02 was a multicentre, randomised, double blind, placebo controlled, parallel group study in patients with Type 2 diabetes mellitus and insufficient glycaemic control despite treatment with metformin in combination with a sulphonyluera (SU) as add on therapy to metformin. The study was conducted at 100 trial centres in 11 countries: Argentina, Belgium, Canada, China, Germany, Korea, Philippines, Russia, Taiwan, Turkey and the UK.

The inclusion criteria included:

- Male and female patients with a diagnosis of Type 2 diabetes mellitus, who had been treated only with a stable total daily dose of preferably ≥ 1500 mg metformin and a dose of a SU drug that had been documented by the Investigator to be the individual maximum tolerated dose of that SU drug. Both the dose and dosing regimen of metformin and the SU had to be stable (unchanged) for 10 weeks prior to informed consent and was not to be changed for the duration of the trial.
- HbA1c ≥7.0% and ≤10.0%
- Age ≥18 years and ≤80 years
- BMI ≤40 kg/m^2

The exclusion criteria were similar to those for Study 1218.17-U09-2533-02 .

The treatment groups were:

1. Linagliptin tablet 5 mg, once a day orally in combination with SU and MET (dose unchanged from baseline)
2. Placebo, once a day orally in combination with SU and MET (dose unchanged from baseline)

Assignment to treatment was by IVRS/IWRS. There was a 2 week open label placebo run in followed by a 24 week treatment period with linagliptin 5 mg or placebo as add on therapy to metformin in combination with an SU.

The primary efficacy outcome measure was the change from baseline in HbA1c after 24 weeks of treatment. The secondary efficacy outcome measures were:

- HbA1c on treatment <7.0% or <6.5% after 24 weeks of treatment
- HbA1c lowering by at least 0.5% after 24 weeks of treatment
- Reduction from baseline in HbA1c by visit over time
- Change from baseline in FPG after 24 weeks of treatment
- Change from baseline in FPG by visit over time

Other efficacy outcome measures were:

- Use of rescue therapy
- HOMA-IR, HOMA-%B and DI after 24 weeks of treatment
- Change from baseline in body weight after 24 weeks of treatment
- Change from baseline in waist circumference after 24 weeks of treatment
- Change from baseline in lipid parameters after 24 weeks of treatment
- EQ-5D, Health Care Resource Utilisation (HCRU) and DTSQs questionnaires

The safety outcome measures were AEs, vital signs, ECG and clinical laboratory tests.

Statistical Issues

Hypothesis tests were performed using ANCOVA models comparing the change from baseline in HbA1c after 24 weeks of treatment. The models included 'treatment' as fixed classification effect and 'HbA1c baseline' as linear covariate. For patients who received rescue therapy, another antidiabetic agent, or a change in metformin or SU dose, the last available HbA1c value prior to these interventions was used for the analysis (LOCF). The FAS consisted of all randomised patients who were treated with at least one dose of study medication, had a baseline HbA1c measurement and had at least one HbA1c measurement during treatment.

The sample size calculation assumed a SD of 1.2%, used a difference in means of 0.7%, an α of 0.05, a dropout rate of 5% and calculated a sample size of 800 subjects (600 subjects randomised to linagliptin and 200 to placebo (3:1 randomisation)) with a power >99%.

Results

A total of 1598 subjects were enrolled and 1058 were randomised to treatment: 793 to linagliptin and 265 to placebo. A total of 793 subjects in the linagliptin group and 263 subjects in the placebo group received treatment; 734 in the linagliptin group and 242 in the placebo group completed the study and 778 in the linagliptin group and 262 in the placebo were included in the analysis (Table 25). There were 557 (52.8%) females, 498 (47.2%) males and the age range was 23 to 79 years. The treatment groups were similar in demographic characteristics, baseline efficacy variables, time since diagnosis of diabetes, concomitant diagnoses related to diabetes and biomarkers at baseline.

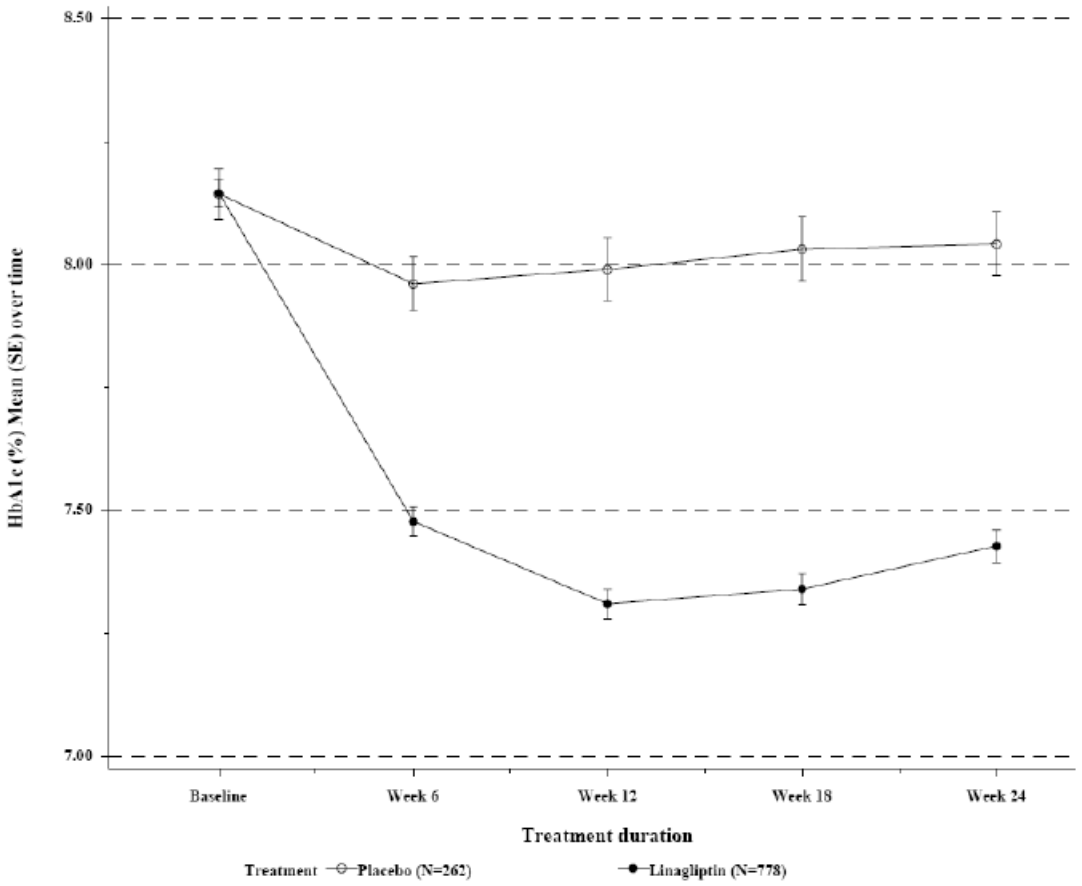
Table 25. Disposition of randomised patients.

	Placebo N (%)	Linagliptin N (%)	Total N (%)
Enrolled			1598
Randomised	265	793	1058
Treated[1]	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)
Study disease worsening	1 (0.4)	3 (0.4)	4 (0.4)
Other disease worsening	1 (0.4)	4 (0.5)	5 (0.5)
Other AE	3 (1.1)	16 (2.0)	19 (1.8)
Lack of efficacy [2]	4 (1.5)	2 (0.3)	6 (0.6)
Non-compliance to protocol	4 (1.5)	19 (2.4)	23 (2.2)
Refused to continue trial medication	8 (3.0)	14 (1.8)	22 (2.1)

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

For the primary efficacy outcome variable, linagliptin + MET + SU was superior to placebo + MET + SU: adjusted mean (95% CI) difference from baseline in HbA1c -0.62 (-0.73 to -0.50), p<0.0001. The treatment effect was evident from Week 6 through to Week 24 (Figure 2). The effect size was greater in subjects with higher baseline HbA1c. FPG decreased to a greater extent in the linagliptin + MET + SU group: adjusted mean (95% CI) difference from baseline -12.7 (-18.1 to -7.3) p<0.0001. Of subjects with baseline HbA1c ≥7.0%, 217 (29.2%) subjects in the linagliptin + MET + SU group and 20 (8.1%) subjects in the placebo + MET + SU group achieved HbA1c <7.0%, p<0.0001. Of subjects with baseline HbA1c ≥6.5%, 102 (13.1%) subjects in the linagliptin + MET + SU group and eleven (4.2%) subjects in the placebo + MET + SU group achieved HbA1c <6.5%, p< 0.0001. A higher frequency of subjects in the linagliptin + MET + SU group had a HbA1c reduction of at least 0.5%: 453 (58.2%) compared with 79 (30.2%) subjects in the placebo + MET + SU group. Rescue medication was required by 42 (5.4%) subjects in the linagliptin + MET + SU group and 34 (13.0%) subjects in the placebo group, p<0.0001. There was no significant difference between the treatment groups in body weight change from baseline: mean (SD) change of 0.3 (2.4) kg for linagliptin + MET + SU and -0.1 (2.5) for placebo + MET + SU. There was no significant difference between the treatment groups in waist circumference change from baseline: mean (SD) change of -0.2 (4.3) cm for linagliptin + MET + SU and 0.0 (4.0) for placebo + MET + SU. There were no differences reported between the treatment groups with respect to EQ-5D, HCRU or DTSQs. HOMA-IR and HOMA-%B both increased in the linagliptin + MET + SU group relative to placebo + MET + SU but there was no significant change in DI.

Figure 2. Mean HbA1c (%) and SE over time – FAS (LOCF).



Comparator Controlled Studies

1. *Study 1218.20-U10-1465-01* was an interim report from 52 weeks of a multicentre, randomised, double blind, double dummy, active controlled, parallel group study in subjects with Type 2 diabetes mellitus and insufficient glycaemic control despite treatment with MET to evaluate linagliptin 5 mg in comparison with glimepiride as add on therapy to MET. The study was conducted at 209 trial sites in 16 countries: Bulgaria, Denmark, France, Germany, Hong Kong, Hungary, India, Ireland, Italy, Netherlands, Norway, Poland, South Africa, Sweden, UK and the USA.

The inclusion criteria included:

- Male and female patients with Type 2 Diabetes Mellitus (T2DM) and previously treated with metformin monotherapy or metformin plus not more than one other OAD.
- Antidiabetic therapy unchanged for 10 weeks
- Stable daily dose of ≥1500 mg metformin or ≤1500 mg metformin only if the investigator considered this was the patient's maximum tolerated dose of metformin; and the dose of metformin had to remain unchanged during the course of the trial
- HbA1c at screening for subjects undergoing washout of previous antidiabetic medication: HbA1c ≤ 6.0% to ≤9.0%; and for subjects not undergoing washout of previous antidiabetic medication: ≤6.5% to ≤10.0%
- HbA1c at start of run in: ≤6.5% to ≤10.0%
- Age: ≥18 years and ≤80 years
- BMI ≤40 kg/m^2 (for patients in the Netherlands: ≤25 kg/m^2 to ≤40 kg/m^2)

The exclusion criteria were similar to those for Study 1218.17-U09-2533-02.

The study treatments were:

1. Linagliptin 5 mg once a day orally
2. Glimepiride tablet, forced titration from 1 mg to a maximum of 4 mg, once daily orally

MET was continued at the same dose as at baseline. There was an 8 week washout including a 2 week open label placebo run in (subjects pretreated with MET and an additional OAD) or 2 week open label placebo run in (subjects pretreated with MET only), followed by a 104 week treatment period. The interim report was for subjects that had completed 52 weeks.

The primary efficacy outcome measure was the change in HbA1c from baseline after 52 weeks of treatment. Secondary efficacy outcome measures were:

- Change in body weight from baseline to Week 52
- Hypoglycaemic events up to 52 weeks
- Change from baseline in FPG after 52 weeks of treatment
- Change from baseline in FPG by visit over time
- HbA1c on treatment <7.0% or <6.5% after 52 weeks of treatment
- HbA1c reduction from baseline by visit over time
- MTT: area under the glucose AUC, change in 2h PPG from baseline after 52 weeks of treatment and 2h PPG increment over FPG at Week 52.

Other efficacy outcome measures were:

- Use of rescue therapy
- HOMA-IR, HOMA-S and DI after 52 weeks of treatment
- Change from baseline in waist circumference after 52 weeks of treatment
- Change from baseline in lipid parameters after 52 weeks of treatment
- Plasma concentration of linagliptin at trough after 28 and 52 weeks of treatment
- Plasma DPP-4 inhibition after 28 and 52 weeks of treatment
- Change from baseline in C-peptide, plasma proinsulin, insulin and proinsulin / insulin ratio by visit over time after MTT

The safety outcome measures were AEs, vital signs, ECGs and clinical laboratory tests.

Statistical Issues

The primary outcome analyses were:

1. Non inferiority of linagliptin versus glimepiride with respect to HbA1c change from baseline
2. Superiority of linagliptin versus glimepiride with respect to body weight change from baseline
3. Superiority of linagliptin versus glimepiride with respect to occurrence of hypoglycaemic events

The analysis was performed as an interim analysis with the three confirmatory hypotheses ordered hierarchically and tested in a fixed sequence at the level of α=0.025.

The margin for non inferiority was 0.35 % for the difference in HbA1c. Non inferiority was concluded if the 97.5% CI did not include 0.35%. Hypothesis tests were performed using ANCOVA models comparing the change from baseline in HbA1c after 52 weeks of treatment; with 'treatment' and prior use of antidiabetic agents as fixed classification effects and 'HbA1c baseline' as a linear covariate. For patients who received rescue therapy, another antidiabetic agent or an increase in the metformin dose, the last available

HbA1c value prior to these interventions was used for the analysis (LOCF). The primary analysis was performed on the FAS.

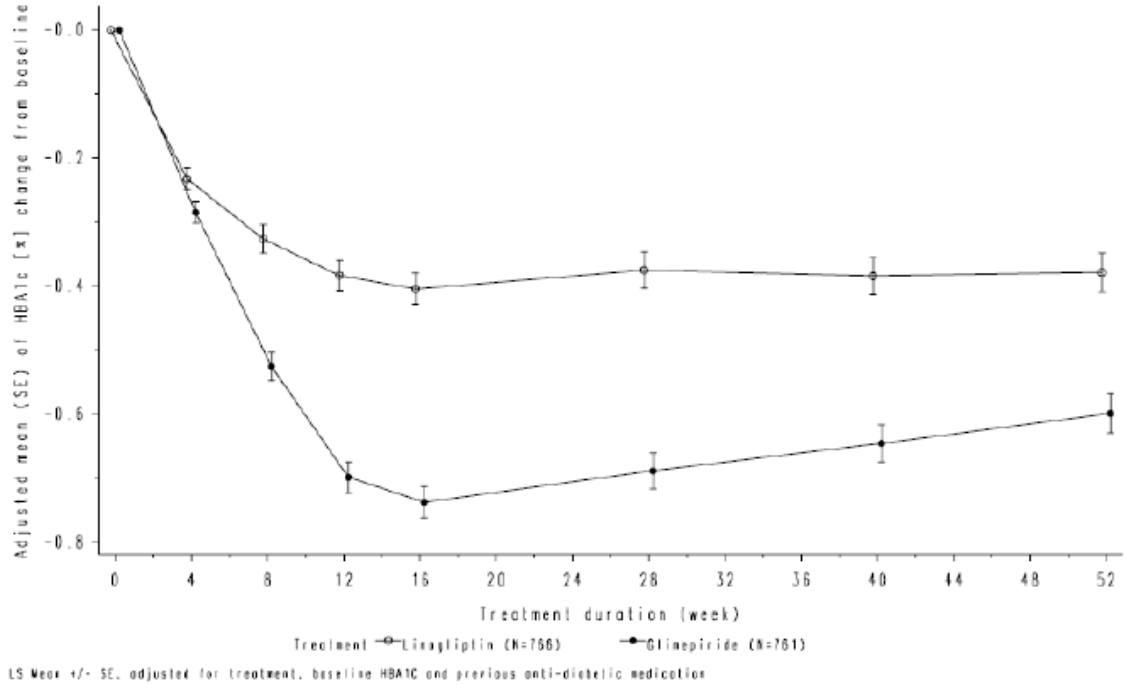
The original sample size calculation was for 570 subjects per treatment group to achieve 90% power to rule out a difference of 0.35% in HbA1c; assuming a difference in HbA1c reduction of 0.1% or less between linagliptin and glimepiride after treatment over 104 weeks. This was increased to 707 patients per treatment group to take into account the interim analysis at Week 52.

Results

A total of 2300 subjects were enrolled in the study and 1560 were randomised to treatment: 779 to linagliptin + MET and 781 to glimepiride and MET. There were 638 (82.0%) subjects in the linagliptin + MET group and 636 (81.4%) subjects in the glimepiride + MET group that completed the study. AEs resulted in discontinuation for 45 (5.8%) subjects in the linagliptin + MET group and 77 (9.9%) subjects in the glimepiride + MET group. The FAS included 766 (98.3%) subjects in the linagliptin + MET group and 761 (97.4%) subjects in the glimepiride + MET group. There were 939 (60.2%) males, 620 (39.8%) females and the age range was 28 to 80 years. The treatment groups were similar in demographic characteristics, baseline efficacy variables, time since diagnosis of diabetes, concomitant diagnoses related to diabetes and baseline biomarkers.

Glimepiride + MET was superior to linagliptin + MET by the primary efficacy outcome measure: adjusted mean (97.5% CI) difference in change from baseline for HbA1c 0.22 (0.13 to 0.31) % p<0.0001. Although the sponsor's predefined criteria for non inferiority were met, the non-inferiority analysis was superseded by the test of superiority. A greater decrease in HbA1c with glimepiride + MET was apparent from Week 8 through to Week 52 (Figure 3). Treatment effect was greater in subjects with higher HbA1c at baseline for both treatment groups. There was weight loss in the linagliptin + MET group compared with weight gain in the glimepiride + MET: adjusted mean (97.5% CI) difference -2.49 (-2.92 to -2.06) kg p<0.0001. For both treatments there was a decrease in FPG from baseline to Week 52 but the decrease was greater in the glimepiride + MET group: adjusted mean (95% CI) difference 7.61 (4.33 to 10.90) mg/dL p<0.0001. For subjects with baseline HbA1c ≥7.0%, 175 (29.6%) subjects in the linagliptin + MET group and 233 (38.9%) subjects in the glimepiride + MET group achieved HbA1c <7.0% at Week 52, p=0.0004. For subjects with baseline HbA1c ≥6.5%, 125 (16.9%) subjects in the linagliptin + MET group and 168 (22.7%) subjects in the glimepiride + MET group achieved HbA1c <6.5% at Week 52, p=0.0025. A lower frequency of subjects in the linagliptin + MET group had an HbA1c reduction of at least 0.5%: 303 (39.6%) subjects compared to 363 (47.7%) subjects, p=0.0015. There was no significant difference between the groups in the change in 2hPPG form baseline to Week 52: adjusted mean (95% CI) difference -2.13 (-15.31 to 11.04) mg/dL, p=0.7502. A higher proportion of subjects in the linagliptin + MET group required rescue therapy with pioglitazone: 125 (16.3%) subjects compared with 92 (12.1%) subjects, p=0.0113. The mean (SD) change from baseline to Week 52 in waist circumference was -1.0 (5.3) cm in the linagliptin + MET group compared with 0.6 (5.3) cm in the glimepiride + MET group. The proinsulin/insulin ratio and HOMA-%B decreased in the linagliptin +MET group relative to the glimepiride + MET.

Figure 3. Adjusted mean HbA1c (SE) over time – FAS (LOCF).



Supportive Studies

1. *Study 1218.35-U10-3206-01* was a multicentre, randomised, double blind, placebo controlled, parallel group study in subjects with Type 2 diabetes mellitus and insufficient glycaemic control despite treatment with a SU drug to evaluate linagliptin as add on therapy to a SU drug. The study was conducted at 45 centres in Asia, Europe, North America and South America.

The inclusion criteria included:

- Patients ≥18 and <80 years with Type 2 diabetes with insufficient glycaemic control (HbA1c ≥7.0% and ≤10%) despite therapy with a sulphonylurea drug.
- Sulphonylurea dose of at least one half the maximum dose (or less if documented as maximum tolerated dose of at least 12 weeks)
- BMI ≤40 kg/m^2

The study treatments were:

1. Linagliptin tablet 5 mg, orally once a day
2. Placebo

Subjects continued with their dose of SU and other OADs current at baseline. There was a 6 week washout including a 2 week open label placebo run in (patients pretreated with a SU drug and an additional OAD) or 2 week open label placebo run in (patients pretreated with a SU drug only), followed by a 18 week treatment period.

The primary efficacy outcome measure was the change from baseline in HbA1c after 18 weeks of treatment. The secondary efficacy outcome measures were:

- The occurrence of an HbA1c of <7.0% after 18 weeks of treatment
- Occurrence of HbA1c lowering by at least 0.5% after 18 weeks of treatment
- HbA1c change from baseline by each nominal week

- The change from baseline in FPG after 18 weeks of treatment
- The change from baseline in FPG by each nominal week
- The occurrence of an HbA1c under treatment of <6.5% after 18 weeks of treatment

Other efficacy outcome measures were:

- Use of rescue therapy
- HOMA and DI
- Change in body weight from baseline to Week 18
- Change in waist circumference from baseline to Week 18
- Changes from baseline in lipid parameters to Week 18
- The change in EQ-5D, HCRU and DTSQ questionnaires from baseline

The safety outcome measures were: AEs, physical examination, vital signs, ECGs and laboratory safety parameters.

Hypothesis tests were performed using ANCOVA models with 'treatment' and 'prior use of anti-diabetic agents' as fixed classification effects and 'HbA1c baseline' as a linear covariate. For patients who received rescue therapy, another anti-diabetic agent or a change of the sulphonylurea dose, the last available HbA1c value prior to these interventions was used for the analysis (LOCF).

The sample size calculation used a SD of 1.6%, a difference in HbA1c of 0.7% between treatments, a one sided level of significance of 0.025 and a power of 90% to determine a sample size of 170 subjects in the linagliptin group and 85 in the placebo.

A total of 471 subjects were enrolled and 245 of these were randomised to treatment: 161 subjects to linagliptin + SU and 84 subjects to placebo + SU. All randomised subjects received treatment. A total of 151 (93.8%) subjects in the linagliptin + SU groups and 77 (91.7%) subjects in the placebo + SU group completed the study. The FAS included 158 (98.1%) subjects in the linagliptin + SU group and 82 (97.6%) subjects in the placebo + SU group. There were 129 (52.7%) males, 116 (47.3%) females and the age range was 27 to 79 years. The treatment groups were similar in demographic characteristics. A total of 68 (28.3%) subjects received metformin plus sulphonylurea (45 [28.5%] in the linagliptin + SU and 23 [28.0%] in the placebo + SU) and 13 (5.4%) of patients received an alpha-glucosidase inhibitor plus sulphonylurea (nine [5.7%] in the linagliptin + SU and four [4.9%] in the placebo + SU). The treatment groups were similar in baseline efficacy variables, time since diagnosis of diabetes and concomitant diabetes related diagnoses.

For the primary efficacy outcome variable linagliptin + SU was superior to placebo + SU: adjusted mean (95% CI) difference in change from baseline in HbA1c -0.47 (-0.70 to -0.24) % p<0.0001. The treatment effect was apparent from Week 6 to Week 18. The treatment effect increased with increasing baseline HbA1c. There was no significant difference between the treatment groups for the change in FPG: adjusted mean (95% CI) difference (linagliptin – placebo): -6.4 (-17.2 to 4.3) p=0.2406. For subjects with baseline HbA1c ≥7.0%, 23 (14.7%) subjects in the linagliptin + SU group and three (3.7%) subjects in the placebo + SU group achieved HbA1c <7.0% p=0.0065. For subjects with HbA1c ≥6.5%, nine (5.7%) subjects in the linagliptin + SU and two (2.4%) subjects in the placebo + SU group achieved HbA1c <6.5% (not hypothesis tested). Ninety one (57.6%) subjects in the linagliptin + SU group and 18 (22.0%) subjects in the placebo + SU group achieved a reduction in HbA1c of ≥0.5% from baseline (not hypothesis tested). Twelve (7.6%) subjects in the linagliptin + SU and 13 (15.9%) subjects in the placebo + SU group required rescue medication. There was no significant difference in body weight or waist circumference between the treatment groups. The statistical analysis for EQ-5D, HCRU and DTSQ were not provided. HOMA-IR increased in the linagliptin + SU group relative to placebo + SU but there was no significant change in HOMA-%B or DI.

2. *Study 1218.50 – U10-1277-02* was a multicentre, randomised, double blind, placebo controlled study (Part 1) followed by active controlled (SU), parallel group comparison (Part 2) in patients with Type 2 diabetes mellitus and insufficient glycaemic control for whom metformin therapy was inappropriate. The report presented data for Part 1 only. The study was conducted at 53 trial sites in seven countries: Canada, Mexico, Philippines, Romania, Russia, Ukraine and the USA.

The inclusion criteria included:

- Patients ≥ 18 and ≤ 80 years with BMI ≤ 40 kg/m^2 and Type 2 diabetes with insufficient glycaemic control (washout of previous medication: HbA1c ≥ 6.5 to ≤ 9.0%, treatment naive patients: HbA1c ≥ 7.0 to ≤ 10.0 % for whom metformin therapy is inappropriate), intolerability or contraindication.
- Patients ineligible for metformin therapy due to contraindication according to the drug label for example:
    - Renal disease or renal dysfunction
    - Dehydration by clinical judgement of the investigator
    - Unstable or acute congestive heart failure
    - Acute or chronic metabolic acidosis
    - Hereditary galactose intolerance
- Patients ineligible for metformin therapy due to intolerable side effects attributed to metformin for example:
    - Nausea or vomiting
    - Diarrhoea
    - Intestinal gas
    - Severe abdominal discomfort

The study treatments were:

1. Linagliptin tablet 5 mg, once daily orally
2. Placebo for Part 1, Glimepiride 1 to 4 mg for Part 2, once daily orally

Part 1 of the study comprised a 6 week washout including a 2 week open label placebo run in (patients pretreated with an OAD) or 2 week open label placebo run in (patients not pretreated with an OAD), followed by a 18 week placebo period. Part 2 of the study was a 34 week active control period.

The primary efficacy outcome measure was the change from baseline in HbA1c after 18 weeks of treatment. The secondary efficacy outcome measures were:

- HbA1c of <7.0% after 18 weeks of treatment
- HbA1c lowering by a least 0.5% after 18 weeks of treatment
- HbA1c of <6.5% after 18 weeks of treatment
- Change from baseline in FPG after 18 weeks of treatment
- HbA1c reduction from baseline by visit over time
- The change from baseline in FPG by visit over time.

Other outcome measures

- Use of rescue therapy
- Change in body weight from baseline to Week 18
- Change in waist circumference from baseline to Week 18
- Changes from baseline in lipid parameters to Week 18
- Quality of life (EQ-5D) and health care resource utilisation (HCRU)

The safety outcome measures were: AEs, vital signs, ECG, changes in creatinine from baseline to Week 18 and clinical laboratory tests.

Hypothesis tests were performed using ANCOVA comparing the change from baseline in HbA1c after 18 weeks of treatment; with 'HbA1c baseline', 'prior use of anti-diabetes agents', 'reason ineligible for metformin' and 'treatment' as fixed classification effects and 'HbA1c baseline' as a linear covariate.

The sample size calculation used a SD of 1.25% for the difference of HbA1c from baseline, a 0.7% difference in means, 97% power, a two sided level of significance of 0.05, a 2:1 (linagliptin: placebo) randomisation and a 5% drop out rate. The estimated sample size was 225 patients: 150 randomised to linagliptin and 75 randomised to placebo.

A total of 571 subjects were enrolled and 227 were randomised to treatment: 151 to linagliptin and 76 to placebo. A total of 137 (90.7%) subjects in the linagliptin group and 64 (84.2%) in the placebo completed the 18 week placebo controlled phase. The FAS included 147 (97.4%) subjects in the linagliptin group and 73 (96.1%) subjects in the placebo group. There were 139 (61.2%) females, 88 (38.8%) males and the age range was 20 to 80 years. The treatment groups were similar in demographic characteristics, time since diagnosis of diabetes, concomitant diagnoses related to diabetes and baseline efficacy variables.

Linagliptin was superior to placebo by the primary efficacy outcome measure: adjusted mean (95% CI) difference in change in HbA1c from baseline -0.57 (-0.86 to -0.29) %, p<0.0001. The treatment effect was apparent from Week 6 through to Week 18. In the linagliptin group the effect size increased with increasing baseline HbA1c. FPG decreased in the linagliptin group and increased in the placebo: adjusted mean (95% CI) difference -20.5 (-31.1 to -9.9) mg/dL, p=0.0002. Of subjects with baseline HbA1c ≥7.0%, 32 (23.5%) subjects in the linagliptin group and eight (11.8%) subjects in the placebo group achieved HbA1c <7.0% at Week 18, p=0.0374. Of subjects with baseline HbA1c ≥6.5%, 13 (8.9%) in the linagliptin group and two (2.9%) subjects in the placebo group achieved HbA1c <6.5% at Week 18, p=0.1281. A reduction of ≥0.5% in HbA1c from baseline was achieved by 53 (36.1%) subjects in the linagliptin group and 13 (17.8%) subjects in the placebo group, p=0.0046. Rescue treatment was required by 17 (11.6%) subjects in the linagliptin group and 13 (17.8%) subjects in the placebo group, p=0.0764. There was no significant difference between the treatment groups in body weight or waist circumference. Statistical analysis was not presented for EQ-5D or HCRU.

3. *Study 1218.23-U10-1466-01* was a randomised, double blind, placebo controlled, voglibose referenced, parallel group study in Japanese patients with Type 2 diabetes mellitus and insufficient glycaemic control.

The inclusion criteria included:

- Japanese subjects with Type 2 diabetes mellitus
- age ≥20 and ≤80 years
- BMI ≤40 kg/m^2
- Insufficient glycaemic control despite being treated with diet and/or exercise only or with oral antidiabetic drugs

The study treatments were:

1. Linagliptin tablets 5 mg and 10 mg, once daily oral administration
2. Placebo tablet
3. Voglibose 0.2 mg three times daily

There was a 4 week washout including a 2 week open label placebo run in (patients pretreated with OAD) or 2 week open label placebo run in (patients not pretreated with OAD), followed by a 12 week treatment period with linagliptin 5 mg or 10 mg or placebo

or voglibose, followed by a 14 week treatment period with linagliptin 5 mg or 10 mg or voglibose, followed by a 26 week extension period with linagliptin 5 mg or 10 mg.

The primary efficacy outcome measure was change in HbA1c from baseline to Week 12 to compare the efficacy of linagliptin (5 mg or 10 mg) with placebo; and to Week 26 to compare efficacy with voglibose. The secondary efficacy outcome measures were:

- HbA1c under treatment of <7.0% and <6.5% after 12, 26 and 52 weeks of treatment
- HbA1c decrease by at least 0.5% after 12, 26 and 52 weeks of treatment
- HbA1c reduction from baseline by visit over time
- Change from baseline in FPG after 12, 26 and 52 weeks of treatment
- Change from baseline in FPG by visit over time

Other efficacy outcome measures were:

- Change from baseline in plasma proinsulin/insulin ratio by visit over time
- HOMA-IR, HOMA-%B and DI
- Change from baseline in glycosylated albumin levels by visit over time
- Change in body weight from baseline to Weeks 12, 26 and 52
- Change in BMI from baseline to Weeks 12, 26 and 52
- Change in waist circumference from baseline to Weeks 12, 26 and 52
- Pharmacokinetics/pharmacodynamics of linagliptin
- Plasma concentration of linagliptin at trough after 12 and 26 weeks of treatment
- Plasma DPP-4 inhibition at baseline and at trough after 12, 26 and 52 weeks of treatment
- Changes from baseline in lipid parameters to Weeks 12, 26 and 52
- DTSQ data at baseline (Visit 2) and Week 12, Week 26 and Week 52

Safety endpoints were AEs, physical examination, vital signs, ECG and clinical laboratory tests.

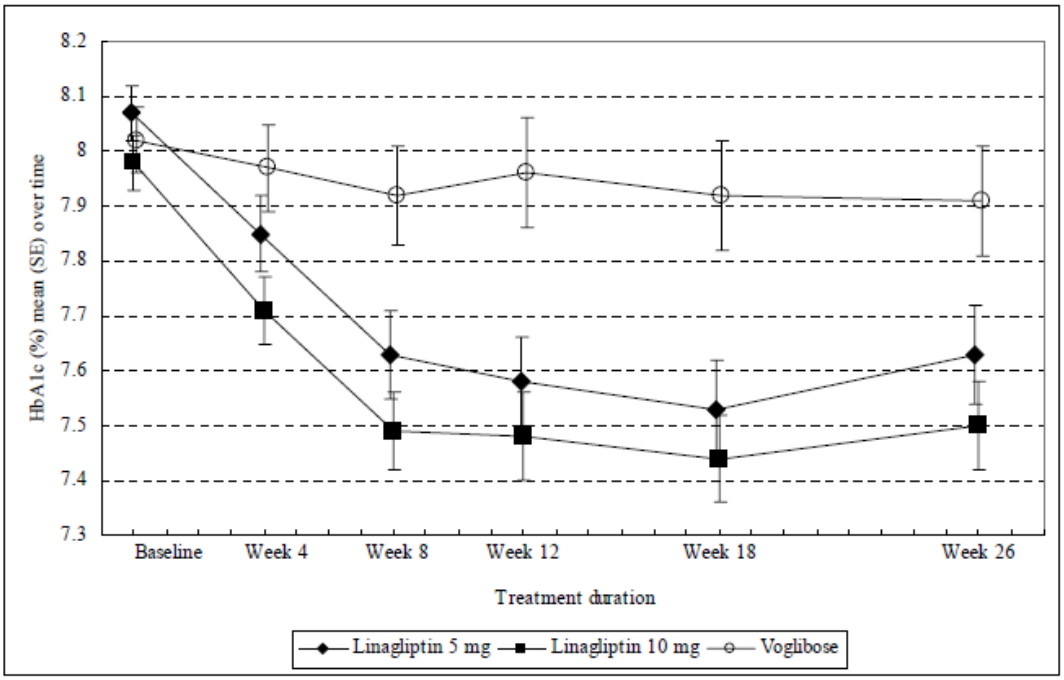
Hypothesis tests were performed using ANCOVA for HbA1c with placebo after 12 week treatment and ANCOVA for HbA1c with voglibose as an active control after 26 weeks of treatment were performed by using “treatment” and “previous antidiabetic therapy” as a fixed effect and baseline values in the observation phase as a covariate.

The samples size calculation for the comparison with placebo used a difference of 0.5% between both groups, a SD of 0.9%, a one sided level of significance of 0.025, a power of 90% and treatment allocation in the ratio placebo to linagliptin of 1:2 and determined a sample size of 52 subjects in the placebo group and 104 subjects in the linagliptin groups. The comparison with voglibose assumed a change in HbA1c from baseline after 26 weeks of treatment of 0.7% in the linagliptin group and 0.25% in the voglibose, giving a difference of 0.45% between the groups, a SD of 1.0%, a one sided level of significance of 0.025 and power of 90% and determined a sample size of 105 in each group. Allowing for a 15% drop out rate the overall sample size calculation was for 441 subjects.

A total of 700 subjects were enrolled and 561 were randomised to treatment: 80 to placebo, 159 to linagliptin 5 mg, 160 to linagliptin 10 mg and 162 to voglibose. At the beginning of the 26 week phase there were 192 subjects treated with linagliptin 5 mg, 193 treated with linagliptin 10 mg and 158 treated with voglibose. There were 395 (70.4%) males, 166 (29.6%) females and the age range was 30 to 80 years. The treatment groups were similar in baseline demographic characteristics and baseline efficacy variables.

In comparison with placebo both linagliptin treatments were superior with similar efficacy for HbA1c: mean (95% CI) treatment difference -0.87 (-1.04 to -0.70) % for 5 mg and -0.88 (-1.05 to -0.71) % for 10 mg. In comparison with voglibose, both linagliptin treatments were also superior with similar efficacy for HbA1c: mean (95% CI) treatment difference -0.32 (-0.49 to -0.15) % for 5 mg and -0.39 (-0.56 to -0.21) % for 10 mg. The benefit in comparison with placebo was apparent from Week 4 through to Week 12, with similar findings for the 5 mg and 10 mg dose levels. The benefit in comparison with voglibose was apparent from Week 8 through to Week 26, with similar findings for the 5 mg and 10 mg dose levels (Figure 4). At Week 12 the number (%) subjects with HbA1c level of <7.0% were 42 (26.4%) with linagliptin 5 mg, 56 (35.7%) with linagliptin 10 mg and eight (10.0%) patients with placebo ($p<0.01$); and the number of subjects with HbA1c level of <6.5% was 15 (9.4%) for linagliptin 5 mg, 18 (11.5%) for linagliptin 10 mg and 0 for placebo ($p<0.005$). The number (%) of subjects achieving HbA1c levels lowered by ≥0.5% were 91 (57.2%) with linagliptin 5 mg, 94 (59.9%) with linagliptin 10 mg and seven (8.8%) with placebo ($p<0.001$). There was a significant decrease in FPG for both linagliptin groups compared with placebo: mean (95% CI) difference -19.7 (-25.4 to -14.0) mg/dL for linagliptin 5 mg and -20.4 (-26.2 to -14.7) mg/dL for 10 mg. There was a significant decrease in FPG for both linagliptin groups compared with voglibose: mean (95% CI) difference -6.9 (-13.0 to -0.9) mg/dL for linagliptin 5 mg and -9.8 (-15.8 to -3.8) mg/dL for 10 mg. There were no significant differences in HOMA-IR, HOMA-S or DI. There was a greater decrease in glycosylated albumin for both linagliptin groups compared with placebo and voglibose. Proinsulin/insulin ratio decreased in the linagliptin groups relative to placebo and voglibose. Compared with placebo, there was no significant difference in body weight in the linagliptin groups. Compared with the linagliptin groups there was a decrease in body weight with voglibose: 0.88 (0.42 to 1.34) kg for linagliptin 5 mg compared to 1.03 (0.57 to 1.48) kg, $p<0.005$. Compared with placebo, there was no significant difference in waist circumference in the linagliptin groups. Compared with the linagliptin groups there was a decrease in waist circumference with voglibose: 0.92 (0.26 to 1.59) cm for linagliptin 5 mg compared to 1.02 (0.36 to 1.69) kg, $p<0.01$. There was no significant change in cholesterol over time in the linagliptin groups. There were no significant changes in DTSQ.

Figure 4. Mean HbA1c (%) and SE over time for 26-week treatment period - FAS26 (LOCF).



Evaluator's Overall Conclusions on Clinical Efficacy

The Phase II dose finding studies also supported the choice of the 5 mg dose form for further development. In Study 1218.5 – U08-3761-02 there appeared to be a plateau in effect at the level of the linagliptin 2.5 mg dose. In Study 1218.6 – U08-1056-03 there was similar efficacy for the 5 mg and 10 mg dose levels. Study 1218.37 – U09-2397-02 was a proof of concept study that supported the further development of linagliptin.

The data from the pivotal randomised placebo controlled studies demonstrated:

- Linagliptin in monotherapy was superior to placebo over a 24 week period: adjusted mean (95% CI) difference in change from baseline in HbA1c, linagliptin – placebo was: -0.69 (-0.85 to -0.53) %, p<0.0001 (Study 1218.16-U10-1103-03 –).
- Linagliptin-pioglitazone was superior to placebo-pioglitazone: adjusted mean (95% CI) difference -0.51 (-0.71 to -0.30) %, p<0.0001, (Study 1218.15-U09-2519-01 –).
- Linagliptin + MET was superior to placebo + MET: adjusted mean (95% CI) difference -0.64 (-0.78 to -0.50) %, p<0.0001 (Study 1218.17-U09-2533-02 –).
- Linagliptin + MET + SU was superior to placebo + MET + SU: adjusted mean (95% CI) difference from baseline in HbA1c -0.62 (-0.73 to -0.50), p<0.0001 (Study 1218.18-U09-2458-02).

The effect sizes were clinically significant as well as statistically significant. For all of the studies the secondary outcome measures supported the primary. Treatment effect was greater in subjects with higher HbA1c at baseline. Efficacy was demonstrated for up to 52 weeks.

Glimepiride + MET was superior to linagliptin + MET: adjusted mean (97.5% CI) difference in change from baseline for HbA1c was 0.22 (0.13 to 0.31) % p<0.0001 (Study 1218.20 – U10-1465-01). The secondary outcome measures supported the primary outcome measure. However, there was a mean weight loss of 2.49 kg in the linagliptin + MET group compared with SU + MET. This amount of weight loss is not clinically significant in obese

patients. In this particular study there was forced titration of glimepiride dose which might explain the high rate of hypoglycaemia in the glimepiride + MET group and it might also have influenced the relative efficacy. Although in the study design the margin for non inferiority was sufficiently robust (0.35 % for the difference in HbA1c) the study results demonstrated inferiority for the linagliptin + MET combination.

In the supportive studies

- Linagliptin + SU was superior to placebo + SU over 18 weeks: adjusted mean (95% CI) difference in change from baseline in HbA1c was -0.47 (-0.70 to -0.24) % p<0.0001 (Study 1218.35 – U10-3206-01)
- Linagliptin was superior to placebo over an 18 week period in subjects not suitable for treatment with MET: adjusted mean (95% CI) difference in change in HbA1c from baseline was -0.57 (-0.86 to -0.29) %, p<0.0001 (Study 1218.50 – U10-1277-02)
- In comparison with placebo, both 5 mg and 10 mg linagliptin were superior with similar efficacy for HbA1c: mean (95% CI) treatment difference was -0.87 (-1.04 to -0.70) % for 5 mg and -0.88 (-1.05 to -0.71) % for 10 mg (Study 1218.23 – U10-1466-01).
- In comparison with voglibose both linagliptin 5 mg and 10 mg were superior with similar efficacy for HbA1c: mean (95% CI) treatment difference was -0.32 (-0.49 to -0.15) % for 5 mg and -0.39 (-0.56 to -0.21) % for 10 mg (Study 1218.23 – U10-1466-01)

The effect sizes were clinically significant as well as statistically significant.

The effect of linagliptin on weight was variable. There was weight gain when in combination with pioglitazone, no effect on weight for linagliptin + MET in comparison with placebo + MET but weight loss in comparison with glimepiride + MET. There did not appear to be any significant effect of linagliptin on serum lipids.

The clinical development program included sufficient data from studies with generally accepted combinations in Australia. The doses of comparator drugs were within generally accepted dosing ranges for patients in Australia, excepting the forced titration of glimepiride in Study 1218.20 – U10-1465-01.

However, the clinical development program did not adequately investigate the optimal sequence of treatments. Hence, it is not clear at what stage linagliptin should be introduced and what combinations of drugs should include linagliptin.

Safety

Introduction

In addition to the studies submitted in support of pharmacodynamics, pharmacokinetics and efficacy there was one additional study submitted in support of safety. This study was an open label extension to the four pivotal placebo controlled trials.

Patient Exposure

Pharmacokinetic and pharmacodynamic studies

Study 1218.1 – U05-2072, 48 subjects were exposed to single doses of oral linagliptin of up to 600 mg.

In *Study 1218.8 – U06-1316,* 24 subjects were exposed to two doses of oral linagliptin of up to 10 mg.

In *Study 1218.10 – U07-1800-01,* 28 subjects were exposed to two doses of IV or oral linagliptin of up to 10 mg.

In *Study 1218.11 – U07-3116*, 24 subjects were exposed to single oral doses of up to 10 mg linagliptin and 18 subjects were exposed to daily doses of up to 10 mg for 12 days.

In *Study 1218.25 – U07-2003*, 24 subjects were exposed to three single doses of linagliptin 5 mg orally.

In *Study U10-1139-01 – 1218.33*, 12 subjects were exposed to oral linagliptin for 21 days at doses from 1 to 5 mg per day.

In *Study 1218.34 – U09-1628-03*, 32 subjects were treated with 5 mg linagliptin orally on two separate study days.

In *Study 1218.45 – U08-2123-01*, 16 subjects were exposed to 5 mg linagliptin per day for up to 14 days.

In *Study 1218.58 – U10-3113-02*, 12 Chinese subjects were exposed to linagliptin 5 mg daily, orally, for seven doses.

In *Study 1218.32 – U09-1067-01*, 44 subjects were exposed to single oral doses of linagliptin 5 mg and 100 mg.

In *Study 1218.4 – U06-3414*, 16 subjects were exposed to linagliptin 10 mg daily for 6 days and linagliptin 10 mg and metformin for 3 days.

In *Study 1218.9 – U06-1584*, 20 subjects were exposed to linagliptin in combination with simvastatin for 6 days.

In *Study 1218.13 – U07-1996*, 20 subjects were exposed to linagliptin for 5 days and linagliptin and pioglitazone for 7 days.

In *Study 1218.28 – U09-1674-04*, 18 subjects were exposed to linagliptin 5 mg once daily for 12 days, with a single dose of warfarin 10 mg.

In *Study 1218.29 – U09-1618-01*, 20 subjects were exposed to linagliptin 5 mg and digoxin for 11 days.

In *Study 1218.30 – U09-1247-01*, 20 subjects were exposed to linagliptin once daily for 5 days and combined with glyburide for one day.

In *Study 128.31 – U09-1077-01*, twelve subjects were exposed to a single dose of linagliptin 5 mg alone and in combination with ritonavir.

In *Study 1218.44 – U09-1393-01*, 18 women were exposed to linagliptin 5 mg in combination with Microgynon® (fixed dose combination of 30 µg EE and 150 µg LNG) daily for 21 days.

In *Study 1218.67 – U10-1328-01*, 16 subjects were treated with linagliptin and rifampicin for 6 days and linagliptin alone for 12 days.

In *Study 1218.7 – U08-1363-01*, six subjects were exposed to a single oral dose of 10 mg linagliptin and six subjects were exposed to a single IV dose of 5 mg.

In *Study 1218.2 – U06-1139*, nine subjects were exposed for 12 days to each of the 1 mg, 2.5 mg, 5 mg and 10 mg dose levels of linagliptin.

In *Study 1218.3 – U06-1822*, 26 subjects received 2.5 mg, 15 subjects received 5 mg and 19 subjects in the 10 mg group were treated once daily for 28 days.

In *Study 1218.26 – U10-1467-02*, 51 subjects were exposed to linagliptin 5 mg for 1 to 10 days.

Study 1218.27 – U10-1219-01, eight healthy subjects, eight with mild hepatic impairment and nine with moderate hepatic impairment were exposed to linagliptin 5 mg for 7 days. Eight subjects with severe hepatic impairment were exposed for a single dose.

In *Study 1218.12 – U08-3212-01*, 19 subjects were exposed to linagliptin 0.5 mg, 18 subjects to linagliptin 2.5 mg and 18 subjects to linagliptin 10 mg for up to 28 days.

Phase II studies

In *Study 1218.5 – U08-3761-02*, 58 subjects were exposed to linagliptin 0.5 mg, 31 for 12 weeks; 57 were exposed to 2.5 mg, 42 subjects for 12 weeks; 55 subjects were exposed to 5 mg, 39 subjects for 12 weeks.

In *Study 1218.6 – U08-1056-03*, 65 subjects were exposed to linagliptin 1mg (54 for more than 10 weeks), 66 subjects to 5 mg (57 for more than 10 weeks) and 66 subjects to 10 mg (61 for more than 10 weeks).

In *Study 1218.37 – U09-2397-02*, 39 subjects were exposed to linagliptin 5 mg and 38 subjects were exposed for 28 days.

Pivotal placebo controlled studies

In *Study 1218.15 – U09-2519-01*, 259 subjects were exposed to linagliptin + pioglitazone, 244 subjects for more than 20 weeks.

In *Study 1218.16 – U10-1103-03*, 336 subjects were exposed to linagliptin 5 mg once daily orally, with 321 (95.5%) subjects exposed for more than 20 weeks.

In *Study 1218.17 – U09-2533-02*, 523 subjects were exposed to linagliptin 5 mg in combination with metformin, 493 (94.3%) subjects for more than 20 weeks.

In *Study 1218.18 – U-09-2458-02*, 792 subjects were exposed to linagliptin + MET + SU, 742 subjects for more than 20 weeks.

Comparator controlled studies

In *Study 1218.20 – U10-1465-01*, 778 subjects were exposed to linagliptin + MET and 637 subjects were exposed for more than 52 weeks.

Supportive studies

In *Study 1218.35 – U10-3206-01*, 161 subjects were exposed to linagliptin + SU, 153 subjects for more than 14 weeks.

In *Study 1218.50 – U10-1277-02, 151* subjects were exposed to linagliptin 5 mg once daily and 142 subjects were exposed for more than 14 weeks.

In *Study 1218.23 – U10-1466-01*, 266 subjects were exposed to linagliptin 5 mg tablets, 152 subjects for more than 40 weeks; and 274 were exposed to linagliptin 10 mg tablets, 152 subjects for more than 40 weeks.

Additional safety studies

Study 1218.40 – U10-1468-01 was a multicentre, open label extension study in subjects who completed one of the four pivotal placebo controlled trials (1218.15-U09-2519-01, 1218.16-U10-1103-03, 1218.17-U09-2533-02 or 1218.18-U09-2458-02) to assess long term safety. Included in the study were:

- 342 subjects treated with linagliptin 5 mg plus 30 mg pioglitazone (from Study 1218.15-U09-2519-01)
- 443 subjects treated with linagliptin 5 mg (from Study 1218.16-U10-1103-03)
- 610 subjects treated with linagliptin 5 mg plus metformin (from Study 1218.17-U09-2533-02)
- 726 subjects treated with linagliptin 5 mg plus metformin and sulphonylurea (from Study 1218.18-U09-2458-02):

There were 1100 (51.9%) males, 1021 (48.1%) females and the age range was 21 to 80 years. A total of 533 subjects were exposed to linagliptin for more than 54 weeks.

Adverse Events

PK and PD studies

In *Study 1218.1-U05-2072*, treatment emergent adverse events (TEAEs) were reported in 2 (34%) subjects. The most frequent reported AEs were headache (19/35), influenza like illness (5/35) and nausea (3/35).

Study 1218.8-U06-1316, nine (37.5%) subjects reported EAEs. The AEs reported most frequently were: headache (5) and dizziness (3).

In *Study1218.10- U07-1800-01*, 21 TEAEs were reported in 15 (41.7%) subjects. The most commonly reported AEs were headache (9) and pharyngolaryngeal pain (2)

In *Study 1218.11-U07-3116* three AEs were reported.

In *Study 1218.25-U07-2003* sixteen TEAEs were reported in twelve subjects. The most commonly reported AEs were headache (5) and nasopharyngitis (3).

In *Study 1218.33-U10-1139-01* seven (58.3%) subjects reported a total of nine TEAEs during the trial. The most frequently reported AE was headache: four (33%) subjects.

In *Study 1218.34-U09-1628-03*, a total of 17 (53%) subjects reported TEAEs. Headache was reported in nine (28.1%) subjects, nasopharyngitis in four (12.5%) and vomiting in two (6.3%)

In *Study 1218.45-U08-2123-01*, six (37.5%) subjects reported TEAEs: headache was reported in two (12.5%) subjects.

In *Study 1218.4-U06-3414* two subjects reported TEAEs with linagliptin alone and two with linagliptin and metformin.

In *Study 1218.9-U06-1584*, 20 AEs were reported in 11 (55%) subjects: the most commonly reported AE was headache in 9 subjects.

In *Study 1218.19-U07-1996*, there were 27 AEs reported in 14 (70.0%) subjects: headache was reported in seven subjects, fatigue in six and diarrhoea in three.

In *Study 2118.28-U09-1674-04*, eight (44.4%) subjects reported AEs: headache in seven.

In *Study 1218.29-U09-1618-01*, a total of 17 (85%) subjects reported AEs: headache was reported in 13 subjects and nausea in six subjects.

In *Study 1218.30-U09-1247-01*, four (20%) subjects reported AEs with linagliptin alone, five (25%) with linagliptin and glyburide and four (20%) with glyburide alone: the most frequent AE was headache in five subjects.

In *Study 1218.31U09-1077-01*, nine (75%) subjects reported AEs. No individual AEs were reported in more than two subjects.

In *Study 1218.44-U09-1393-01*, a total of 15 (83%) subjects reported AEs. The most common AEs were headache in nine subjects and oropharyngeal pain in four.

In *Study 1218.67-U10-1328-01*, all 16 (100%) subjects reported AEs: chromaturia in 16 subjects and headache in nine subjects.

In *Study 1218.7-U08-1363-01*, six (50%) subjects reported AEs: headache in three subjects.

In Study *1218.32*-U09-1067-01, three (6.8%) subjects reported AEs during placebo, four (9.3%) subjects with linagliptin 5 mg, six (13.6%) subjects with linagliptin 100 mg and two (4.5%) subjects with moxifloxacin. Headache was reported by five (11.4%) subjects with linagliptin 100 mg and three (7.0%) subjects with linagliptin 5 mg.

In *Study 1218.2-U06-1139*, 31 AEs were reported in 19 (54.3%) subjects treated with linagliptin compared with 18 AEs reported in nine (75%) subjects treated with placebo.

In *Study 1218.3-U06-1822*, 21 (34.4%) subjects in the linagliptin groups and 5 (31.3%) subjects in the placebo reported AEs

In *Study 1218.26-U10-1467-02*, twelve (23.5%) subjects reported AEs during treatment with linagliptin: back pain in three subjects.

In *Study 1218.27-U10-1219-01*, AEs were reported in three (37.5%) subjects in the healthy group, one (12.5%) subjects in the mild liver impairment group, two (44.4%) subjects in the moderate liver impairment group and five (62.5%) subjects in the severe liver impairment group. Two subjects with liver impairment had prolongation of QT interval of <30 ms (not temporally related to dosing).

In *Study 1218.12-U08-3212-01*, TEAEs were reported in two (10.5%) subjects in the linagliptin 0.5 mg group, five (27.8%) subjects in the 2.5 mg, four (22.2%) subjects in the 10 mg. and six (35.3%) subjects in the placebo. The most frequently reported AE was

nasopharyngitis: four (7.3%) subjects in the linagliptin groups and two (11.8%) subjects in the placebo group.

In *Study 1218-58-U10-3113-02* there were no TEAEs reported.

Phase II studies

In *Study 1218.5-U08-3761-02*, TEAEs were reported for 35 (52.2%) subjects in the placebo group, 26 (44.8%) subjects in the 0.5 mg group, 22 (38.6%) subjects in the 2.5 mg group, 24 (43.6%) subjects in the 5 mg group and 27 (41.5%) subjects in the metformin group. The most commonly reported TEAEs were hyperglycaemia, nasopharyngitis and headache (Table 26).

In *Study 1218.6-U08-1056-03-U08-1056-03*, AEs were reported in 33 (46.5%) subjects in the placebo group, 25 (38.5%) subjects in the linagliptin 1 mg group, 32 (48.5%) subjects in the linagliptin 5 mg group, 30 (45.5%) subjects in the linagliptin 10 mg group and 29 (44.6%) subjects in the glimepiride group. Nausea appeared to be more common in the linagliptin 5 mg and 10 mg groups (Table 27).

In *Study 1218.37-U09-2397-02* TEAEs were reported in 12 (30%) subjects in the linagliptin 5 mg group, 18 (43.9%) subjects in the sitagliptin group and 13 (32.5%) subjects in the placebo group. The most commonly reported TEAE was headache: four (10%) subjects in the linagliptin group, five (12.2%) subjects in the sitagliptin group and three (7.5%) subjects in the placebo group.

Table 26. Most frequent AE in the treatment period occurring in 2% or more patients in each treatment group – TS.

	Double-blind				Open-label	
	Placebo	BI 1356 0.5 mg	BI 1356 2.5 mg	BI 1356 5 mg	Metformin	TOTAL
Number of patients	67 (100.0)	58 (100.0)	57 (100.0)	55 (100.0)	65 (100.0)	302 (100.0)
Total with adverse events	35 (52.2)	26 (44.8)	22 (38.6)	24 (43.6)	27 (41.5)	157 (52.0)
Hyperglycaemia	7 (10.4)	7 (12.1)	2 (3.5)	1 (1.8)	3 (4.6)	24 (7.9)
Nasopharyngitis	5 (7.5)	1 (1.7)	2 (3.5)	1 (1.8)	2 (3.1)	23 (7.6)
Headache	1 (1.5)	5 (8.6)	1 (1.8)	3 (5.5)	2 (3.1)	19 (6.3)
Diarrhoea	2 (3.0)	2 (3.4)	0 (0.0)	1 (1.8)	5 (7.7)	13 (4.3)
Influenza	1 (1.5)	1 (1.7)	3 (5.3)	1 (1.8)	0 (0.0)	11 (3.6)
Blood glucose increased	4 (6.0)	2 (3.4)	0 (0.0)	2 (3.6)	2 (3.1)	10 (3.3)
Urinary tract infection	0 (0.0)	1 (1.7)	0 (0.0)	1 (1.8)	0 (0.0)	9 (3.0)
Arthralgia	3 (4.5)	0 (0.0)	0 (0.0)	1 (1.8)	2 (3.1)	8 (2.6)
Upper respiratory tract infection	0 (0.0)	3 (5.2)	1 (1.8)	1 (1.8)	0 (0.0)	7 (2.3)
Hypertension	3 (4.5)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)	7 (2.3)
Nausea	0 (0.0)	1 (1.7)	1 (1.8)	2 (3.6)	1 (1.5)	7 (2.3)
Bronchitis	1 (1.5)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	7 (2.3)
Dizziness	3 (4.5)	1 (1.7)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.0)
Pharyngolaryngeal pain	0 (0.0)	2 (3.4)	0 (0.0)	1 (1.8)	1 (1.5)	6 (2.0)
Cough	0 (0.0)	2 (3.4)	0 (0.0)	2 (3.6)	0 (0.0)	5 (1.7)
Fatigue	1 (1.5)	1 (1.7)	0 (0.0)	2 (3.6)	0 (0.0)	5 (1.7)
Back pain	2 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.5)	5 (1.7)
Asthenia	1 (1.5)	0 (0.0)	0 (0.0)	2 (3.6)	0 (0.0)	4 (1.3)
Abdominal pain	0 (0.0)	2 (3.4)	1 (1.8)	0 (0.0)	1 (1.5)	4 (1.3)
Palpitations	0 (0.0)	2 (3.4)	0 (0.0)	1 (1.8)	0 (0.0)	4 (1.3)
Rhinitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	0 (0.0)	3 (1.0)
Oedema peripheral	0 (0.0)	2 (3.4)	0 (0.0)	0 (0.0)	1 (1.5)	3 (1.0)
Blood creatine phosphokinase increased	1 (1.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.1)	3 (1.0)
Lymphadenopathy	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	0 (0.0)	2 (0.7)
Sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	0 (0.0)	2 (0.7)
Vision blurred	0 (0.0)	2 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.7)

Table 27. Adverse events during the treatment period with an incidence of more than 2% in either treatment group on the preferred term level, sorted by overall incidence and SOC (TS)

SOC/ Preferred Term	Placebo N (%)	BI 1356 1 mg N (%)	BI 1356 5 mg N (%)	BI 1356 10 mg N (%)	Glimepiride N (%)
Infections and infestations					
Nasopharyngitis	7 (9.9)	4 (6.2)	5 (7.6)	5 (7.6)	4 (6.2)
Upper respiratory tract infection	3 (4.2)	1 (1.5)	0 (0.0)	0 (0.0)	1 (1.5)
Influenza	1 (1.4)	0 (0.0)	2 (3.0)	0 (0.0)	0 (0.0)
Urinary tract infection	1 (1.4)	0 (0.0)	0 (0.0)	2 (3.0)	0 (0.0)
Gastrointestinal disorders					
Diarrhoea	3 (4.2)	1 (1.5)	2 (3.0)	2 (3.0)	3 (4.6)
Nausea	3 (4.2)	0 (0.0)	4 (6.1)	3 (4.5)	0 (0.0)
Constipation	0 (0.0)	0 (0.0)	1 (1.5)	2 (3.0)	1 (1.5)
Dyspepsia	0 (0.0)	0 (0.0)	1 (1.5)	1 (1.5)	2 (3.1)
Investigations					
Blood glucose increased	2 (2.8)	2 (3.1)	0 (0.0)	1 (1.5)	1 (1.5)
Blood triglycerides increased	0 (0.0)	2 (3.1)	0 (0.0)	1 (1.5)	0 (0.0)
Musculoskeletal and connective tissue disorders					
Arthralgia	2 (2.8)	2 (3.1)	1 (1.5)	0 (0.0)	0 (0.0)
Musculoskeletal pain	1 (1.4)	0 (0.0)	2 (3.0)	1 (1.5)	0 (0.0)
Respiratory, thoracic and mediastinal disorders					
Cough	0 (0.0)	1 (1.5)	2 (3.0)	1 (1.5)	0 (0.0)
Asthma	0 (0.0)	2 (3.1)	0 (0.0)	0 (0.0)	1 (1.5)
Fatigue	0 (0.0)	1 (1.5)	1 (1.5)	2 (3.0)	0 (0.0)
Metabolism and nutrition disorders					
Hypoglycaemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (4.6)

Pivotal placebo controlled studies

In *Study 1218.15-U09-2519-01* TEAEs were reported in 136 (52.5%) subjects in the linagliptin + pioglitazone group and 69 (53.1%) subjects in the placebo + pioglitazone group. The most frequently reported TEAEs were nasopharyngitis and URTI (Table 28). Hypoglycaemia was reported in three (1.2%) subjects in the linagliptin + pioglitazone group and none in the placebo + pioglitazone group. No subject in the linagliptin + pioglitazone group was reported with renal failure.

Table 28. Frequency of patients with AEs occurring at an incidence of more than 2% of patients in either treatment group at the preferred term level, sorted by overall frequency and system organ class – Treated set.

System Organ Class/ Preferred Term	Pbo+pio N (%)	Lina+pio N (%)
Number of patients	130 (100.0)	259 (100.0)
Patients with any AE	69 (53.1)	136 (52.5)
Infections and infestations	32 (24.6)	54 (20.8)
Nasopharyngitis	11 (8.5)	24 (9.3)
Upper respiratory tract infection	10 (7.7)	9 (3.5)
Influenza	3 (2.3)	1 (0.4)
Gastrointestinal disorders	13 (10.0)	21 (8.1)
Constipation	4 (3.1)	5 (1.9)
Musculoskeletal and connective tissue disorders	12 (9.2)	25 (9.7)
Osteoarthritis	4 (3.1)	2 (0.8)
Arthralgia	3 (2.3)	3 (1.2)
Back pain	2 (1.5)	6 (2.3)
Metabolism and nutrition disorders	8 (6.2)	19 (7.3)
Hyperlipidaemia	1 (0.8)	7 (2.7)
Hyperglycaemia	3 (2.3)	0 (0.0)
Injury, poisoning and procedural complications	10 (7.7)	11 (4.2)
Contusion	3 (2.3)	2 (0.8)
Nervous system disorders	5 (3.8)	15 (5.8)
Headache	3 (2.3)	6 (2.3)
Vascular disorders	3 (2.3)	9 (3.5)
Hypertension	3 (2.3)	6 (2.3)
Investigations	2 (1.5)	10 (3.9)
Weight increased	1 (0.8)	6 (2.3)

Note that total numbers in the system organ class level correspond to all AEs, and not the total of AEs shown in the table.

In *Study 1218.16-U10-1103-03*, TEAEs were reported in 176 (52.4%) subjects in the linagliptin group and 98 (58.7%) subjects in the placebo group. TEAEs reported more frequently with linagliptin compared to placebo treatment: headache, nine (2.7%) subjects compared with two (1.2%) subjects, respectively, and hypertension, twelve (3.6%) subjects compared with two (1.2%) subjects, respectively (Table 29). There was one subject in each group reported with a hypoglycaemic AE. Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) increased slightly in the linagliptin group relative to placebo (Table 30).

Table 29. Frequency of patients with AEs occurring at an incidence of more than 2% in either treatment group on the preferred term level, sorted by overall frequency and system organ class – Treated set

	Placebo N (%)	Linagliptin N (%)
Number of patients	167 (100.0)	336 (100.0)
Number of patients with any AE	98 (58.7)	176 (52.4)
Infections and infestations	38 (22.8)	55 (16.4)
Nasopharyngitis	7 (4.2)	13 (3.9)
Upper respiratory tract infection	5 (3.0)	9 (2.7)
Respiratory tract infection	4 (2.4)	1 (0.3)
Viral infection	4 (2.4)	1 (0.3)
Metabolism and nutrition disorders	45 (26.9)	44 (13.1)
Hyperglycaemia	38 (22.8)	29 (8.6)
Dyslipidaemia	4 (2.4)	4 (1.2)
Nervous system disorders	4 (2.4)	15 (4.5)
Headache	2 (1.2)	9 (2.7)
Vascular disorders	2 (1.2)	17 (5.1)
Hypertension	2 (1.2)	12 (3.6)
Musculoskeletal and connective tissue disorders	10 (6.0)	32 (9.5)
Back pain	3 (1.8)	9 (2.7)
Investigations	11 (6.6)	21 (6.3)
Blood glucose increased	3 (1.8)	7 (2.1)

The number of patients in an SOC are based on all AEs within this SOC, not only on the most frequent AEs >2% shown here

Table 30. Mean changes in systolic and diastolic blood pressure from baseline over time - Treated set

	Placebo		Linagliptin	
SBP [mmHg]	N	Mean (SD)	N	Mean (SD)
Visit 3	167	129.01 (13.63)	336	129.81 (14.52)
Visit 4	161	127.09 (14.40)	332	129.93 (14.98)
Visit 5	157	128.58 (14.96)	329	130.91 (14.89)
Visit 6	154	128.85 (14.37)	324	130.59 (14.30)
Visit 7 / EoT	158	128.53 (13.73)	322	130.66 (14.33)
Change from Visit 3 to Visit 4	161	-2.09 (12.25)	332	0.18 (12.57)
Change from Visit 3 to Visit 5	157	-0.46 (13.44)	329	1.14 (13.36)
Change from Visit 3 to Visit 6	154	-0.30 (13.84)	324	0.75 (13.66)
Change from Visit 3 to Visit 7 / EoT	158	-0.83 (13.85)	322	0.63 (14.17)
DBP [mmHg]				
Visit 3	167	79.40 (8.74)	336	78.74 (7.76)
Visit 4	161	78.07 (8.25)	332	79.83 (7.88)
Visit 5	157	78.12 (7.89)	329	79.56 (7.23)
Visit 6	154	78.97 (7.79)	324	78.64 (7.74)
Visit 7 / EoT	158	77.88 (8.38)	322	79.48 (7.68)
Change from Visit 3 to Visit 4	161	-1.22 (8.40)	332	1.10 (7.58)
Change from Visit 3 to Visit 5	157	-1.12 (8.21)	329	0.78 (7.93)
Change from Visit 3 to Visit 6	154	-0.36 (8.73)	324	-0.18 (8.22)
Change from Visit 3 to Visit 7 / EoT	158	-1.42 (8.71)	322	0.87 (8.47)

In *Study 1218.17-U09-2533-02* TEAEs were reported in 276 (52.8%) subjects in the linagliptin + MET group and 98 (55.4%) subjects in the placebo + MET group. The most commonly reported AE was nasopharyngitis and the pattern of AEs was similar for the two treatment groups (Table 31). Hypoglycaemic episodes were reported in three (0.6%) subjects in the linagliptin + MET group and five (2.8%) subjects in the placebo + MET group. Acute renal failure was reported in one subject in the placebo + MET group.

Table 31. Frequency of patients with AEs occurring at an incidence of more than 2% of patients in either treatment group at the preferred term level, sorted by overall frequency and system organ class – Treated set

System Organ Class/ Preferred Term	Placebo N (%)	Linagliptin N (%)
Number of patients	177 (100.0)	523 (100.0)
Total with adverse events	98 (55.4)	276 (52.8)
Infections and infestations	38 (21.5)	112 (21.4)
Nasopharyngitis	9 (5.1)	27 (5.2)
Urinary tract infection	7 (4.0)	16 (3.1)
Influenza	5 (2.8)	18 (3.4)
Upper respiratory tract infection	4 (2.3)	15 (2.9)
Metabolism and nutrition disorders	38 (21.5)	47 (9.0)
Hyperglycaemia	26 (14.7)	27 (5.2)
Hypoglycaemia	5 (2.8)	3 (0.6)
Investigations	15 (8.5)	19 (3.6)
Blood glucose increased	7 (4.0)	5 (1.0)
Nervous system disorders	9 (5.1)	36 (6.9)
Headache	7 (4.0)	15 (2.9)
Vascular disorders	7 (4.0)	22 (4.2)
Hypertension	6 (3.4)	17 (3.3)
Gastrointestinal disorders	20 (11.3)	57 (10.9)
Diarrhoea	4 (2.3)	15 (2.9)
Abdominal pain	4 (2.3)	2 (0.4)
Musculoskeletal and connective tissue disorders	14 (7.9)	58 (11.1)
Back pain	5 (2.8)	12 (2.3)
Arthralgia	3 (1.7)	11 (2.1)
Respiratory, thoracic and mediastinal disorders	5 (2.8)	25 (4.8)
Cough	3 (1.7)	11 (2.1)

In Study 1218.18-U-09-2458-02, TEAEs were reported in 525 (66.3%) subjects in the linagliptin + MET + SU group and 157 (59.7%) subjects in the placebo + MET + SU group. Hypoglycaemia was reported as a TEAE more commonly in the linagliptin + MET + SU group: 180 (22.7%) subjects compared to 39 (14.8%) subjects placebo + MET + SU group (Table 32). Investigator defined hypoglycaemic events were reported in 188 (23.7%) subjects in the linagliptin + MET + SU group and 42 (16.0%) subjects in the placebo + MET + SU group. However, severe hypoglycaemic events were reported in five (0.6%) subjects in the linagliptin + MET + SU group compared to two (0.8%) subjects in the placebo + MET + SU group (Table 33). Cardiovascular/ischaemic AEs were rare and occurred at a similar frequency in both treatment groups.

Table 32. Frequency of patients with AEs occurring at an incidence of more than 2% in either treatment group on the preferred term level, sorted by overall frequency and system organ class – Treated set.

System Organ Class[1]/ Preferred Term	Placebo N (%)	Linagliptin N (%)
Number of patients, N(%)	263 (100.0)	792 (100.0)
Number of patients with any AE, N(%)	157 (59.7)	525 (66.3)
Metabolism and nutrition disorders	68 (25.9)	246 (31.1)
Hypoglycaemia	39 (14.8)	180 (22.7)
Hyperglycaemia	23 (8.7)	45 (5.7)
Infections and infestations	76 (28.9)	170 (21.5)
Upper respiratory tract infection	25 (9.5)	46 (5.8)
Urinary tract infection	14 (5.3)	26 (3.3)
Nasopharyngitis	12 (4.6)	41 (5.2)
Nervous system disorders	30 (11.4)	77 (9.7)
Headache	13 (4.9)	33 (4.2)
Dizziness	12 (4.6)	29 (3.7)
Gastrointestinal disorders	48 (18.3)	103 (13.0)
Diarrhoea	9 (3.4)	21 (2.7)
Abdominal pain upper	7 (2.7)	9 (1.1)
Nausea	6 (2.3)	10 (1.3)
Musculoskeletal and connective tissue disorders	24 (9.1)	97 (12.2)
Back pain	8 (3.0)	13 (1.6)
Arthralgia	4 (1.5)	21 (2.7)
General disorders and administration site conditions	19 (7.2)	61 (7.7)
Asthenia	5 (1.9)	19 (2.4)
Respiratory, thoracic and mediastinal disorders	7 (2.7)	33 (4.2)
Cough	3 (1.1)	19 (2.4)
Vascular disorders	6 (2.3)	34 (4.3)
Hypertension	5 (1.9)	19 (2.4)
Psychiatric disorders	9 (3.4)	18 (2.3)
Insomnia	6 (2.3)	5 (0.6)

[1] Totals in SOC are based on the total of all PTs within the SOC and not only on the most frequent PTs >2% shown here

Table 33. Frequency of patients with investigator-defined hypoglycaemia by treatment–Treated set.

	Placebo	Linagliptin
Number of patients, N(%)	263 (100.0)	792 (100.0)
Number of patients with any investigator-defined hypoglycaemia, N(% of patients treated)	42 (16.0)	188 (23.7)
Number of patients with any investigator-defined hypoglycaemia, N(%)[1]	42 (100.0)	188 (100.0)
Any asymptomatic hypoglycaemia, N(% of patients with hypoglycaemia)[2]	15 (35.7)	83 (44.1)
Any documented symptomatic hypoglycaemia and measured plasma glucose ≥54 mg/dL and ≤70 mg/dL, N(% of patients with hypoglycaemia)[3]	15 (35.7)	76 (40.4)
Any documented symptomatic hypoglycaemia and measured plasma glucose <54 mg/dL, N(% of patients with hypoglycaemia)[4]	10 (23.8)	51 (27.1)
Any severe hypoglycaemic episode, N(% of patients with hypoglycaemia)[5]	2 (4.8)	5 (2.7)
Number of hypoglycaemic episodes per patient, N(% of patients with hypoglycaemia)		
1	23 (54.8)	71 (37.8)
2 to 3	11 (26.2)	61 (32.4)
≥4	8 (19.0)	56 (29.8)

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

Comparator controlled studies

In *Study 1218.20-U10-1465-01*, TEAEs were reported in 611 (78.5%) subjects in the linagliptin + MET group and 662 (84.8%) subjects in the glimepiride + MET group. Hyperglycaemia was reported more frequently in the linagliptin + MET group (31 [94.0%] subjects compared to 17 [2.2%]) but hypoglycaemia was reported more frequently in the glimepiride + MET (237 [30.3%] subjects compared to 41 [5.3%]). Dizziness was also reported more frequently in the glimepiride + MET group (37 (4.7%) subjects compared to 19 (2.4%) subjects). Investigator defined hypoglycaemia was more frequent in the glimepiride + MET group: 248 (31.8%) subjects compared to 42 (5.4%) subjects in the linagliptin + MET group. Severe hypoglycaemic events were more common in the glimepiride + MET group: nine (1.2%) subjects compared with one (0.1%) subject. A greater proportion of subjects in the glimepiride + MET group were reported with cardiovascular death, MI, stroke or unstable angina: 20 (2.6%) subjects compared to three (0.4%) subjects (Table 34). Hepatic TEAEs were reported in eight (1.0%) subjects in the linagliptin + MET group and nine (1.2%) subjects in the glimepiride + MET group. Renal TEAEs were reported in two (0.3%) subjects in the linagliptin + MET group and four (0.5%) subjects in the glimepiride + MET group Mean values for vital signs were similar for the two treatment groups.

Table 34. Adjudication results: Frequency of patients with CEC-confirmed events by treatment – Treated set

	Linagliptin N (%)		Glimepiride N (%)	
Number of patients	778	(100.0)	781	(100.0)
Patients with TIA	1	(0.1)	3	(0.4)
Patients with non-fatal stroke	0	(0.0)	10	(1.3)
Patients with ischaemic stroke	0	(0.0)	9	(1.2)
Patients with haemorrhagic stroke	0	(0.0)	1	(0.1)
Patients with non-fatal MI	2	(0.3)	6	(0.8)
Patients with STEMI	1	(0.1)	5	(0.6)
Patients with NSTEMI	1	(0.1)	1	(0.1)
Patients with other myocardial ischaemia	7	(0.9)	5	(0.6)
Patients with stable angina	7	(0.9)	3	(0.4)
Patients with unstable angina	0	(0.0)	2	(0.3)
Patients with cardiovascular death (including fatal stroke)	1	(0.1)	2	(0.3)
Patients with sudden death	1	(0.1)	2	(0.3)
Number of patients with cardio-vascular death, MI, stroke or unstable angina	3	(0.4)	20	(2.6)

Supportive studies

In *Study 1218.35-U10-3206-01*, TEAEs were reported in 68 (42.2%) subjects in the linagliptin + SU group and 36 (42.9%) subjects in the placebo + SU group. Infections occurred in a higher proportion of subjects in the linagliptin + SU group: 20 (12.4%) subjects compared to four (4.8%) subjects. Investigator defined hypoglycaemia was reported for nine (5.6%) subjects in the linagliptin + SU group and four (4.8%) subjects in the placebo + SU group. There were no severe hypoglycaemic episodes. Two subjects in the linagliptin + SU group had renal AEs: acute renal failure (1) and renal impairment (1). There were no significant differences between the groups in vital signs.

In *Study 1218.50-U10-1277-02*, TEAEs were reported in 61 (40.4%) subjects in the linagliptin group and 37 (48.7%) i subjects n the placebo group. The higher rate of TEAEs in the placebo group might be due to an excess of hyperglycaemia reported as an AE: 11 (14.5%) subjects compared with ten (6.6%) subjects in the linagliptin group. Two (1.3%) subjects in the linagliptin group (but none in the placebo group) had hypoglycaemia reported as a TEAE. One subject in each treatment group was reported with a nonfatal myocardial infarction. One subject in the placebo group had a hepatic AE. There were no clinically relevant changes in vital signs.

In *Study 1218.23-U10-1466-01*, in the first 12 week treatment period, 89 (56.0%) of the 159 patients administered linagliptin 5 mg, 85 (53.1%) of the 160 patients administered linagliptin 10 mg, 45 (56.3%) of the 80 patients given placebo experienced an AE. There was one hypoglycaemic episode reported in each of the linagliptin groups during the full 52 week treatment period. During the 26 week treatment period, 115 (72.3%) of the 159 patients administered linagliptin 5 mg, 124 (77.5%) of the 160 patients administered linagliptin 10 mg and 116 (71.6%) of the 162 patients administered voglibose experienced an AE. Over the entire 52 week study period, 204 (76.7%) subjects in the linagliptin 5 mg group and 224 (81.8%) subjects in the 10 mg group reported TEAEs. There do not appear to be any TEAEs related to dose.

Additional Safety Studies

In *Study 1218.40 – U10-1468-01*, TEAEs were reported in 1403 (66.1%) subjects. The most common TEAEs were hyperglycaemia (reported in 345 [16.3%] subjects) and hypoglycaemia (reported in 205 [9.7%]). The pattern of AEs of special interest was as would be expected in the subject group included in the study. HbA1c and FPG were recorded during the study but did not undergo hypothesis testing.

Serious Adverse Events and Deaths

SAEs in PK and PD studies

In *Study U09-1067-01*, there was one SAE: breast cancer.

In *Study U06-1822* there were no SAEs during treatment but one subject in the 10 mg group had a myocardial infarction 23 days after treatment period ended.

There were no SAEs reported in Studies 1218.1-U05-2072, 1218.8-U06-1316, 1218.10-U07-1800-01, 1218.11-U07-3116, 1218.25-U07-2003, 1218.33-U10-1139-01, 1218.34-U09-1628-03, 1218.45-U08-2123-01, 1218.58-U10-3113-02, 1218.4-U06-3414, 1218.39-U06-1584, 1218.13-U07-1996, 1218.28-U09-1674-04, 1218.29-U09-1618-01, 1218.30-U09-1247-01, 1218.31-U09-1077-01, 1218.44-U09-1393-01, Study 1218.67-U10-1328-01, 1218.7-U08-1363-01, 1218.2-U06-1139, 1218.26-U10-1467-02, 1218.27-U10-1219-01 or U1218.12-08-3212-01.

There were no deaths in Studies 1218.1-U05-2072, 1218.8-U06-1316, 1218.10-U07-1800-01, 1218.11-U07-3116, 1218.25-U07-2003, 1218.33-U10-1139-01, 1218.34-U09-1628-03, 1218.45-U08-2123-01, 1218.58-U10-3113-02, 1218.4-U06-3414, 1218.9-U06-1584, 1218.13-U07-1996, 1218.28-U09-1674-04, 1218.29-U09-1618-01, 1218.30-U09-1247-01, 1218.31-U09-1077-01, 1218.44-U09-1393-01, 1218.67-U10-1328-01, 1218.7-U08-1363-01, 1218.32-U09-1067-01, 1218.2-U06-1139, 1218.3-U06-1822, 1218.26-U10-1467-02, 1218.27-U10-1219-01 or 1218.12-U08-3212-01.

SAEs in Phase II studies

In *Study 1218.5-U08-3761-02* SAEs were reported for one (1.5%) subject in the placebo group (chronic bronchitis), one (1.7%) subject in the 0.5 mg group (coronary ischaemia), two (3.5%) subjects in the 2.5 mg group (renal colic; post-injection abscess), none in the 5 mg group and one (1.5%) subject in the metformin group (worsening schizoaffective disorder).

In *Study 1218.6-U08-1056-03* SAEs were reported in one (1.4%) subject in the placebo group, three (4.6%) subjects in the linagliptin 1 mg group, one (1.5%) subject in the linagliptin 5 mg group, four (6.1%) subjects in the linagliptin 10 mg group and one (1.5%) subject in the glimepiride group. There was no apparent pattern to the SAEs.

In *Study 1218.37-U09-2397-0* no SAEs were reported during or following the treatment period.

In *Study 1218.5-U08-3761-02* and *Study 1218.37-U09-2397-02* there were no deaths reported.

In *Study 1218.6-U08-1056-03* there were no deaths in treated subjects.

SAEs in Pivotal Placebo Controlled Studies

In *Study 1218.15-U09-2519-01* SAEs were reported in 8 (3.1%) subjects in the linagliptin + pioglitazone group and 3 (2.3%) subjects in the placebo + pioglitazone group (Table 35).

Table 35. Frequency of patients with SAEs by treatment, system organ class and preferred term – Treated set.

Age [years] /gender	AE preferred term	Start day	Duration [days]	Intensity	Drug related	Action taken	Outcome
Treatment at onset: Placebo (pbo) + pioglitazone (pio)							
52/M	Glaucoma	3	104	Mod	No	Disc	Rcver
56/M	Cholecistitis acute	137	14	Mod	No	Rein	Rcver
	Cholelithiasis	137	14	Mod	No	Rein	Rcver
58/M	Tendonitis	25	1	Sev	No	Cont	Rcver
t at onset: Lina+pio							
67/M	Acute coronary syndrome	1	9	Mod	No	Disc	Rcver
64/M	Abdominal pain upper	41	5	Mild	No	Cont	Rcver
	Vomiting	41	5	Mild	No	Cont	Rcver
62/M	Colonic polyp	105	37	Mild	No	Cont	Rcver
68/F	Cholelithiasis	168	32	Mod	No	Cont	Rcver
67/M	Carotid artery stenosis	52	61	Mod	No	Cont	Rcver
43/F	Hypoesthesia	2	8	Sev	Yes	Disc	Rcver
60/M	Meniscus removal	123	1	Mod	No	Cont	Rcver
48/M	Varicose vein	153	2	Mod	No	Cont	Rcver
F: female; Mod: moderate; Sev: severe; Cont: continued study medication; Rein: reinitiated; Rcver: recovered							
52/M	Glaucoma	3	104	Mod	No	Disc	Rcver
56/M	Cholecistitis acute	137	14	Mod	No	Rein	Rcver
	Cholelithiasis	137	14	Mod	No	Rein	Rcver
58/M	Tendonitis	25	1	Sev	No	Cont	Rcver
t at onset: Lina+pio							
67/M	Acute coronary syndrome	1	9	Mod	No	Disc	Rcver
64/M	Abdominal pain upper	41	5	Mild	No	Cont	Rcver
	Vomiting	41	5	Mild	No	Cont	Rcver
62/M	Colonic polyp	105	37	Mild	No	Cont	Rcver
68/F	Cholelithiasis	168	32	Mod	No	Cont	Rcver
67/M	Carotid artery stenosis	52	61	Mod	No	Cont	Rcver
43/F	Hypoesthesia	2	8	Sev	Yes	Disc	Rcver
60/M	Meniscus removal	123	1	Mod	No	Cont	Rcver
48/M	Varicose vein	153	2	Mod	No	Cont	Rcver
F: female; Mod: moderate; Sev: severe; Cont: continued study medication; Rein: reinitiated; Rcver: recovered							

In *Study 1218.16-U10-1103-03* SAEs were reported in ten (3.0%) subjects in the linagliptin group and seven (4.2%) subjects in the placebo group. There was no apparent pattern to the SAEs.

In *Study 1218.17-U09-2533-02* SAEs were reported in 18 (3.4%) subjects in the linagliptin + MET group and four (2.3%) subjects in the placebo + MET group. There was no apparent pattern in the SAEs.

In *Study 1218.18-U-09-2458-02*, SAEs were reported in 25 (3.2%) subjects in the linagliptin + MET + SU group and ten (3.8%) subjects in the placebo + MET + SU group. The SAEs did not appear to follow a pattern and reflected the age group in the study.

In *Studies 1218.15-U09-2519-01, 1218.16-U10-1103-03 1218.17-U09-2533-02 and 1218.18-U09-2458-02* there were no deaths reported.

SAEs in Comparator Controlled Studies

In *Study 1218.20-U10-1465-01* SAEs were reported in 93 (12.0%) subjects in the linagliptin + MET group and 114 (14.6%) subjects in the glimepiride + MET group. The frequency and pattern of SAEs was similar for the two treatment groups (Table 36).

In *Study 1218.20-U10-1465-01*there were two (0.3%) deaths in the linagliptin + MET group (cardio respiratory arrest; sudden cardiac death) and three (0.4%) subjects in the glimepride + MET group (abdominal infection; sudden cardiac death; myocardial infarction).

Table 36. Frequency of patients with SAEs occurring at an incidence of >2 patients in either treatment group at the preferred term level, sorted by system organ class and preferred term – Treated set.

System Organ Class/ Preferred Term	Linagliptin N (%)	Glimepiride N (%)
Number of patients, N (%)	778 (100.0)	781 (100.0)
Number of patients with SAEs, N (%)	93 (12.0)	114 (14.6)
Infections and infestations	11 (1.4)	15 (1.9)
Pneumonia	3 (0.4)	1 (0.1)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	13 (1.7)	10 (1.3)
Prostate cancer	5 (0.6)	1 (0.1)
Nervous system disorders	6 (0.8)	19 (2.4)
Cerebrovascular accident	0 (0.0)	5 (0.6)
Cerebral infarction	0 (0.0)	3 (0.4)
Transient ischaemic attack	1 (0.1)	3 (0.4)
Cardiac disorders	17 (2.2)	18 (2.3)
Myocardial infarction	3 (0.4)	5 (0.6)
Coronary artery disease	4 (0.5)	2 (0.3)
Angina pectoris	1 (0.1)	3 (0.4)
Cardiac failure	3 (0.4)	0 (0.0)
Hepatobiliary disorders	5 (0.6)	3 (0.4)
Cholelithiasis	3 (0.4)	2 (0.3)
Musculoskeletal and connective tissue disorders	11 (1.4)	14 (1.8)
Osteoarthritis	3 (0.4)	5 (0.6)
Renal and urinary disorders	4 (0.5)	10 (1.3)
Nephrolithiasis	2 (0.3)	3 (0.4)
Renal colic	1 (0.1)	3 (0.4)

SAEs in Supportive Studies

In *Study 1218.35-U10-3206-01-U10-3206-01*, SAEs were reported in five (3.1%) subjects in the linagliptin + SU and one (1.2%) subject in the placebo + SU group.

In *Study 1218.50-U10-1277-02-U10-1277-02*, SAEs were reported in one (0.7%) subject in the linagliptin group and one (1.3%) subject in the placebo group (both were acute myocardial infarctions).

In *Study 1218.23-U10-1466-01* during the 12 week placebo controlled period, SAEs were reported in one (0.6%) subject in the linagliptin 5 mg group, four (2.5%) subjects in the

linagliptin 10 mg group and one (1.3%) subject in the placebo group. During the 26 week comparator controlled period, SAEs were reported in five (3.1%) subjects in the linagliptin 5 mg group, eight (5.0%) subjects in the linagliptin 10 mg group and seven (4.3%) subjects in the voglibose group.

In *Study 1218.35-U10-3206-01*there was one death in the linagliptin + SU group (cardio respiratory arrest). In Study 1218.50-U10-1277-02, there was one death 3 weeks after discontinuing linagliptin. In Study 1218.23-U10-1466-01there were no deaths reported.

SAEs in Additional Safety Studies

In *Study 1218.40 – U10-1468-01* SAEs were recorded in 133 (6.3%) subjects. The pattern of SAEs was to be expected in the subject group included in the study (Table 37).

Table 37. Serious adverse events in the treatment period by SOC and PT (overall incidence of at least 3 patients on PT or SOC level, sorted by overall frequency)/TS.

	Old lina		New lina		Total	
Number of patients [n (%)]	1532	(100.0)	589	(100.0)	2121	(100.0)
Patients with any SAEs	100	(6.5)	33	(5.6)	133	(6.3)
Cardiac disorders	13	(0.8)	12	(2.0)	25	(1.2)
Myocardial infarction	2	(0.1)	3	(0.5)	5	(0.2)
Unstable angina	3	(0.2)	0		3	(0.1)
Infections and infestations	17	(1.1)	5	(0.8)	22	(1.0)
Gastroenteritis	3	(0.2)	0		3	(0.1)
Pneumonia	2	(0.1)	1	(0.2)	3	(0.1)
Neoplasms benign, malignant and unspecified	17	(1.1)	2	(0.3)	19	(0.9)
Prostate cancer	5	(0.3)	0		5	(0.2)
Injury, poisoning and procedural complications	12	(0.8)	5	(0.8)	17	(0.8)
Road traffic accident	2	(0.1)	1	(0.2)	3	(0.1)
Musculoskeletal and connective tissue disorders	10	(0.7)	2	(0.3)	12	(0.6)
Osteoarthritis	2	(0.1)	1	(0.2)	3	(0.1)
General disorders and administration site conditions	6	(0.4)	4	(0.7)	10	(0.5)
Chest pain	4	(0.3)	0		4	(0.2)
Nervous system disorders	8	(0.5)	1	(0.2)	9	(0.4)
Gastrointestinal disorders	7	(0.5)	1	(0.2)	8	(0.4)
Vascular disorders	4	(0.3)	2	(0.3)	6	(0.3)
Hepatobiliary disorders	5	(0.3)	0		5	(0.2)
Renal and urinary disorders	5	(0.3)	0		5	(0.2)
Nephrolithiasis	3	(0.2)	0		3	(0.1)
Respiratory, thoracic and mediastinal disorders	4	(0.3)	1	(0.2)	5	(0.2)
Metabolism and nutrition system disorders	3	(0.2)	1	(0.2)	4	(0.2)
Eye disorders	2	(0.1)	1	(0.2)	3	(0.1)
Reproductive system and breast disorders	2	(0.1)	1	(0.2)	3	(0.1)

Old lina = originally randomised to linagliptin; New lina = originally randomised to placebo

In *Study 1218.40 – U10-1468-01* there were three (0.1%) deaths during treatment (cardio respiratory arrest; pulmonary embolism; infectious endocarditis) and another two that occurred after treatment was ceased (metastatic pulmonary carcinoma; cardio respiratory arrest).

Laboratory Findings

In *Study U06-1822*, one subject had an elevation of AST on Day 19 to 187 U/L and concurrently an increase in creatinine kinase (13414 U/L) and CK-MB (142 U/L). These abnormalities resolved.

In *Study 1218.5-U08-3761-02*, a higher proportion of subjects in the linagliptin 0.5 mg group had elevations in plasma triglycerides. Except for this abnormality there did not appear to be a pattern in laboratory parameter abnormalities.

In *Study 1218.6-U08-1056-03* a possibly clinically significant increases in amylase levels occurred in 8 subjects: three (4.8%) subjects in the linagliptin 5 mg group, three (4.6%) subjects in the 10 mg group, one (1.5%) subject in the glimepiride group and one (1.4%) subject in the placebo group.

In *Study 1218.37-U09-2397-02* there were no clinically significant abnormalities in safety laboratory tests, ECGs or vital signs.

In *Study 1218.15-U09-2519-01* there were few significant laboratory abnormalities in either treatment group.

In *Study 1218.16-U10-1103-03*, one subject in the placebo group had elevated ALT and AST as an AE. Serum amylase was increased nine (2.7%) subjects in the linagliptin group and in two (1.2%) subjects in the placebo group.

In *Study 1218.17-U09-2533-02*, two subjects in the linagliptin + MET group and one subject in the placebo + MET group had elevations in AST and ALT. Clinically significant abnormalities in clinical laboratory tests were uncommon and there was a similar pattern for the two treatment groups.

In *Study 1218.18-U-09-2458-02*, clinically significant laboratory abnormalities were uncommon and occurred at a similar frequency in both treatment groups.

In *Study 1218.20-U10-1465-01*the frequency and pattern of clinically significant abnormalities in laboratory tests was similar for the two treatment groups.

In *Study 1218.35-U10-3206-01*one subject in the linagliptin + SU group had elevations of liver enzymes resulting in discontinuation: AST 131 U/L, ALT 231, ALP 89 U/L, GGT 215 U/L, LDH 256 U/L and total bilirubin 10.3 umol. Seven (4.4%) subjects in the linagliptin +SU group had elevations in creatinine compared with two (2.5%) subjects in the placebo + SU group. Sixteen (10.1%) subjects in the linagliptin +SU group had elevations in plasma triglycerides compared with three (3.7%) subjects in the placebo + SU group.

In *Study 1218.50-U10-1277-02*- the pattern of significant clinical laboratory test abnormalities was similar for the two groups except for six (4.7%) subjects with raised uric acid and two (1.6%) subjects with raised creatinine in the linagliptin group compared with none in the placebo group.

In Study 1218.40 – U10-1468-01, an unexpectedly high number of subjects had elevations in eosinophil count (89 (4.2%) subjects), serum potassium (101 (4.8%) subjects), amylase, (91 (4.3%) subjects), uric acid (112 (5.4%) subjects) and triglyceride (343 (16.4%) subjects).

Safety in Special Populations

Special populations were not included in the development program.

Immunological Events

In *Study 1218.15-U09-2519-01*, no hypersensitivity or immune mediated AEs were reported in the linagliptin + pioglitazone group.

In *Study 1218.17-U09-2533-02*, bronchial hyperreactivity was reported in one subject in the linagliptin + MET group and hypersensitivity was reported in one subject in the placebo + MET group.

In *Study 1218.18-U-09-2458-02*, hypersensitivity reactions were more common in the linagliptin + MET + SU group than in the placebo + MET + SU group: eleven (1.4%) subjects compared to one (0.4%) subject.

In *Study 1218.20-U10-1465-01* hypersensitivity reactions were reported in eight (1.0%) subjects in the linagliptin + MET group and six (0.8%) subjects in the glimepiride + MET group.

In *Study 1218.35-U10-3206-01* two subjects in the linagliptin + SU group were reported with hypersensitivity events: cardio respiratory arrest (1) and urticaria (1).

Safety Related to Drug-Drug Interactions and Other Interactions

Drug-drug and food drug interactions were addressed in the section on pharmacokinetics. The safety data indicate that linagliptin does not interact adversely with drugs commonly used to treat Type 2 diabetes.

Discontinuation Due To Adverse Events

PK and PD studies

In *Study 1218.45-U08-2123-01* one subject discontinued due to an AE (influenza).

In *Study U09-1247-01*, one subject discontinued due to an AE (inability to site venous sampling cannula).

In *Study 1218.32-U09-1067-01* one subjects discontinued due to an AE (breast cancer).

In *Study 1218.3-U06-1822* one subject discontinued in the linagliptin 5 mg group (ventricular extrasystoles).

There were no discontinuations due to AE in *Studies 1218.1-U05-2072*, *1218.6-U06-1316*, *1218.10-U07-1800-01*, *1218.11-U07-3116*, *1218.25-U07-2003*, *1218.33-U10-1139-01*, *1218.58-U10-3113-02*, *1218.4-U06-3414*, *1218.9-U06-1584*, *1218.13-U07-1996*, *1218.28-U09-1674-04*, *1218.29-U09-1618-01*, *1218.31-U09-1077-01*, *1218.44-U09-1393-01*, *1218.67-U10-1328-01*, *1218.7-U08-1363-01*, *1218.2-U06-1139*, *1218.26-U10-1467-02*, *1218.27-U10-1219-01 and 1218.12-U08-3212-01.*

Phase II studies

In *Study 1218.5-U08-3761-02* discontinuation was due to AE for 14 (20.9%) subjects in the placebo group, 10 (17.2%) subjects in the 0.5 mg group, three (5.3%) subjects in the 2.5 mg group, five (9.1%) subjects in the 5 mg group and four (6.2%) subjects in the metformin group.

In *Study 1218.6-U08-1056-03,* fourteen 4.2%) subjects discontinued because of AE (one (1.4%) placebo, five (7.7%) 1 mg, three (4.5%) 5 mg, two (3.0%) 10 mg and three (4.6%) glimepiride). There was no apparent pattern to the AEs leading to discontinuation.

In *Study 1218.37-U09-2397-02* there were no discontinuations due to AEs (DAEs).

Pivotal Placebo Controlled Studies

In *Study 1218.15-U09-2519-01* DAEs were reported in four (1.5%) subjects in the linagliptin + pioglitazone group and five (3.8%) subjects in the placebo + pioglitazone group.

In *Study 1218.16-U10-1103-03* discontinuation due to AE occurred in four (1.2%) subjects in the linagliptin group and four (2.4%) subjects in the placebo group. There was no apparent pattern to the discontinuations due to AE.

In *Study 1218.17-U09-2533-02* discontinuation due to AEs occurred in eight (1.5%) subjects in the linagliptin + MET group and three (1.7%) subjects in the placebo + MET group. One subject in each group discontinued because of elevated AST and ALT.

In *Study 1218.18-U-09-2458-02*, discontinuation due to AE occurred in 23 (2.9%) subjects in the linagliptin + MET + SU group and five (1.9%) subjects in the placebo + MET + SU group. Metabolism and nutritional disorders leading to discontinuation were more common in the linagliptin + MET + SU group: eight (1.0%) subjects compared with none in the placebo + MET + SU group.

Comparator Controlled Studies

In *Study 1218.20-U10-1465-01* discontinuation resulting from AEs occurred in 45 (5.8%) subjects in the linagliptin + MET group and 76 (9.7%) subjects in the glimepiride + MET group. A greater proportion of subjects in the glimepiride + MET group was withdrawn because of hypoglycaemia.

Supportive Studies

In *Study 1218.35-U10-3206-01* discontinuation due to AE occurred in four (2.5%) subjects in the linagliptin + SU group (pyelonephritis; sinusitis; elevated liver enzymes; hypoglycaemia) and three (3.6%) subjects in the placebo + SU group (inadequate diabetes control; hypoglycaemia; hyperglycaemia).

In *Study 1218.50-U10-1277-02* discontinuation due to AEs occurred in three (2.0%) subjects in the linagliptin group (myocardial infarction; abdominal distension; worsening of diabetes), No DAEs occurred in the placebo group.

In *Study 1218.23-U10-1466-01* during the 12 week placebo controlled period, AEs leading to discontinuation of study medication were experienced by three (1.9%) subjects in the linagliptin 5 mg group, four (2.5%) subjects in the linagliptin 10 mg group and seven (8.8%) subjects in the placebo group. During the 26 week comparator controlled period AEs leading to discontinuation of study medication were reported in four (2.5%) subjects in the linagliptin 5 mg group, seven (4.4%) subjects in the linagliptin 10 mg group and twelve (7.4%) subjects in the voglibose group.

Additional Safety Studies

In *Study 1218.40 – U10-1468-01* discontinuation due to AE occurred in 45 (2.1%) subjects. The pattern of AEs leading to discontinuation was as expected for the subject group included in the study.

Evaluator's Overall Conclusions on Clinical Safety

Linagliptin did not appear to have an increased rate of adverse events in comparison with placebo. Some studies suggested an increased rate of minor infections but this finding was not consistent. The rate of hypoglycaemia was not increased significantly with linagliptin. There did not appear to be an increased rate of renal, cardiovascular or hepatic AEs. Linagliptin did not appear to have adverse effects on blood pressure, pulse or indices of cardiovascular risk such as fasting serum lipids.

Although more hypoglycaemic events were reported in the glimepiride group in 1218.20-U10-1465-01,this study involved forced titration of the glimepiride dose which may have artificially increased the rate of hypoglycaemic episodes in this group. Hence, it is

premature to conclude a better safety profile for linagliptin than glimepiride because of the artificiality of glimepiride dosing in that study.

Linagliptin did not appear to have an increased risk of SAE or death in comparison with placebo. There were relatively few such events in the development program and those events that were reported were consistent with the patient group included in the studies. However, it is also not possible to conclude that linagliptin improves the safety profile as add on therapy or that it has a superior profile, with regard to SAE or death, compared with glimepiride.

There appears to be an increased risk of elevation of serum amylase, uric acid and triglycerides with linagliptin. The significance of these findings is uncertain but would indicate that pancreatitis and pancreatic carcinoma should be included in the safety profile.

In the development program there was no consistent increase in the risk of hypersensitivity or immune mediated adverse reactions.

Linagliptin did not appear to increase the risk of discontinuation due to AE compared to placebo. AEs leading to discontinuation appeared to reflect underlying morbidity rather than drug effect. However, although there was a greater risk of discontinuation due to hypoglycaemia with glimepiride in Study 1218.20-U10-1465-01, the forced titration of the glimepiride dose may account for this increase.

List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

Pharmacokinetics

1. Have any formal assessments of the effects of linagliptin on gastric motility been performed?
2. Does the Sponsor propose performing PK studies in special populations (adolescents or pregnancy)?

Efficacy

3. Does the Sponsor have any further data to inform the optimum sequence of treatments?
4. Does the Sponsor have data for efficacy as monotherapy in comparison with metformin?
5. Can the Sponsor provide efficacy data for the Phase III study population stratified by BMI groups of >25 to 27, >27 to 30 and >30kg/m^2?

Safety

6. Does the Sponsor have safety data for subjects treated for two years or more (particularly with regard to cardiovascular safety)?

Clinical Summary and Conclusions

Linagliptin has been developed as a new chemical entity for treatment of Type 2 diabetes. There has been extensive pharmacokinetic and pharmacodynamic evaluation. In particular the pharmacodynamic characterisation has been thorough. Effects of renal impairment, hepatic impairment and food have been well characterised. The dosing regimen developed by the sponsor is supported by the PK, PD and Phase II studies.

However, apart from the drug interaction studies that indicate prolonged T_{max} and decreased C_{max} for metformin and pioglitazone there was no other data to support any effects on gastric emptying for linagliptin.

Benefit Risk Assessment

Benefits

The Phase II dose finding studies also supported the choice of the 5 mg dose form for further development. In Study 1218.5-1218.5-U08-3761-02there appeared to be a plateau in effect at the level of the linagliptin 2.5 mg dose. In Study 1218.6-U08-1056-03 the 5 mg and 10 mg dose levels had similar efficacy. Study 1218.37-U09-2397-02 –was a proof of concept study that supported the further development of linagliptin.

The data from the pivotal randomised placebo controlled studies demonstrated:

- Linagliptin in monotherapy was superior to placebo over a 24 week period: adjusted mean (95% CI) difference in change from baseline in HbA1c, linagliptin – placebo was: -0.69 (-0.85 to -0.53) %, p<0.0001 (Study 1218.16-U10-1103-03)
- The primary efficacy outcome measure demonstrated superior efficacy for linagliptin-pioglitazone in comparison with placebo-pioglitazone: adjusted mean (95% CI) difference -0.51 (-0.71 to -0.30) %, p<0.0001, (Study 1218.15-U09-2519-01).
- Linagliptin + MET was superior to placebo + MET: adjusted mean (95% CI) difference -0.64 (-0.78 to -0.50) %, p<0.0001 (Study 1218.17-U09-2533-02 –)
- Linagliptin + MET + SU was superior to placebo + MET + SU: adjusted mean (95% CI) difference from baseline in HbA1c -0.62 (-0.73 to -0.50), p<0.0001 (Study 1218.18 – U-09-2458-02)

The effect sizes were clinically significant as well as statistically significant. For all of the studies the secondary outcome measures supported the primary. Treatment effect was greater in subjects with higher HbA1c at baseline.

However, glimepiride + MET was superior to linagliptin + MET: adjusted mean (97.5% CI) difference in change from baseline for HbA1c 0.22 (0.13 to 0.31) % p<0.0001 (Study 1218.20-U10-1465-01). The secondary outcome measures supported the primary outcome measure. However, there was a mean weight loss of 2.49 kg in the linagliptin + MET group compared with the SU + MET group. In this particular study there was forced titration of glimepiride dose, which might explain the high rate of hypoglycaemia in the glimepiride + MET group and might also have influenced relative efficacy. Although in the study design the margin for non inferiority was sufficiently robust (0.35 % for the difference in HbA1c) the study results actually demonstrated inferiority for the linagliptin + MET combination.

In the supportive studies:

- Linagliptin + SU was superior to placebo + SU over 18 weeks: adjusted mean (95% CI) difference in change from baseline in HbA1c -0.47 (-0.70 to -0.24) % p<0.0001 (Study 1218.35-U10-3206-01)
- Linagliptin was superior to placebo over an 18 week period in subjects not suitable for treatment with MET: adjusted mean (95% CI) difference in change in HbA1c from baseline -0.57 (-0.86 to -0.29) %, p<0.0001 (Study 1218.5-U08-3761-02)
- In comparison with placebo both linagliptin 5 mg and 10 mg were superior with similar efficacy for HbA1c: mean (95% CI) treatment difference -0.87 (-1.04 to -0.70) % for 5 mg and -0.88 (-1.05 to -0.71) % for 10 mg (Study 1218.23-U10-1466-01).

- In comparison with voglibose both linagliptin 5 mg and 10 mg were superior with similar efficacy for HbA1c: mean (95% CI) treatment difference -0.32 (-0.49 to -0.15) % for 5 mg and -0.39 (-0.56 to -0.21) % for 10 mg (Study 1218.23-U10-1466-01)

The effect sizes were clinically significant as well as statistically significant.

The effect of linagliptin on weight was variable. There was weight gain when in combination with pioglitazone, no effect on weight for linagliptin + MET in comparison with placebo + MET but weight loss in comparison with glimepiride + MET. There did not appear to be any significant effect for linagliptin on serum lipids.

The clinical development program included sufficient data from studies with generally accepted combinations in Australia. The doses of comparator drugs were within generally accepted dosing ranges for patients in Australia, excepting the forced titration of glimepiride in Study 1218.20-U10-1465-01.

However, the clinical development program did not adequately investigate the optimal sequence of treatments. Hence, it is not clear at what stage linagliptin should be introduced and what combinations of drugs should include linagliptin.

Risks

Linagliptin did not appear to have an increased rate of adverse events in comparison with placebo. Some studies suggested an increased rate of minor infections but this finding was not consistent. The rate of hypoglycaemia was not increased significantly with linagliptin. There did not appear to be an increased rate of renal, cardiovascular or hepatic AEs.

Although more hypoglycaemic events were reported in the glimepiride group in 1218.20-U10-1465-01, this study involved forced titration of the glimepiride dose which may have artificially increased the rate of hypoglycaemic episodes in this group. Hence, it is premature to conclude a better safety profile for linagliptin than glimepiride because of the artificiality of glimepiride dosing in that study.

Linagliptin did not appear to increase the risk of SAE or death in comparison with placebo. There were relatively few such events in the development program and those events that were reported were consistent with the patient group included in the studies. However, it is not possible to conclude that linagliptin improves the safety profile as add on therapy or that it has a superior profile, with regard to SAE or death, compared with glimepiride.

There appears to be an increased risk of elevation of serum amylase, uric acid and triglycerides with linagliptin. The significance of these findings is uncertain but would indicate that pancreatitis and pancreatic carcinoma should be included in the safety profile.

In the development program there was no consistent increase in the risk of hypersensitivity or immune mediated adverse reactions.

Linagliptin did not appear to increase the risk of withdrawal from the study due to AE compared to placebo. AEs leading to discontinuation appeared to reflect underlying morbidity rather than drug effect. However, although there was a greater risk of withdrawal due to hypoglycaemia with glimepiride in Study 1218.20-U10-1465-01, the forced titration of the glimepiride dose may account for this increase.

Safety Specification

The sponsor currently states the identified risks in the Risk Management Plan as:

- Hypoglycaemia
- Pancreatitis

And the potential risk as:

· Exfoliative skin conditions

Pancreatic cancer and long term cardiovascular safety should be added to the Safety Specification.

Balance

Linagliptin has a favourable risk benefit profile. However, it is not clear, with regard to other antidiabetic treatments where in the treatment sequence it should be placed. In the data submitted by the sponsor it is inferior to sulphonylurea (SU). Therefore it should be used in patients that have already been trialled on these agents unless there is a specific contraindication to SU. There are no data comparing linagliptin with metformin as monotherapy. Hence, linagliptin should not be recommended as monotherapy unless MET or SU are contraindicated as first line agents.

Conclusions

The indication for which the sponsor is applying is not fully supported by the data.

The sponsor is currently applying for the indication:

> *Trajenta is indicated in adult patients with Type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, as monotherapy or as add on to metformin, sulphonylureas, thiazolidinediones or metformin plus sulphonylureas.*

However, first line treatment in patients that have not already been trialled with MET or SU is not supported by the data presented with the current application. First line treatment could only be justified when both MET and SU are contraindicated.

The following alternative indication might be suitable for approval:

> *Trajenta is indicated in adult patients with Type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, as monotherapy (where both metformin and/or sulphonylureas are either ineffective or contraindicated) or as add on to metformin, sulphonylureas, thiazolidinediones or metformin plus sulphonylureas.*

Recommended Conditions for Registration

The sponsor should be required to provide updates on long term safety as the data become available.

V. Pharmacovigilance Findings

Risk Management Plan

The sponsor's Risk Management Plan (RMP) Version 1.0, dated 01 June 2010 was evaluated by the TGA's Office of Product Review (OPR). A summary of the sponsor's RMP is provided in Table 38 below.

Table 38. Summary of RMP

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization activities (routine and additional)
Important identified risk		
Hypoglycaemia	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	Appropriate labelling (Section 4.8 of SmPC)
Pancreatitis	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	Appropriate labelling (Section 4.8 of SmPC)
Important potential risks		
Skin lesions	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data	Not applicable.
Important missing information		
Safety in subpopulations		
High risk patients with recent CV events	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data (planned CV-safety study and 1218.63 [U09-2389-01]). Ongoing CV meta-analyses of phase 3 and 4 programme at appropriate time points	Not applicable.
Old patients (> 80 years)	Routine pharmacovigilance and analysis of ongoing and planned clinical trial safety data (planned CV-safety study and 1218.63 [U09-2389-01])	Not applicable.
Severe renally impaired patients	Routine pharmacovigilance and analysis of ongoing clinical trial safety data (study 1218.43 [U08-1995-01])	Not applicable

The sponsor concluded that routine risk minimisation activities[18] (PI labelling) are sufficient to mitigate the safety concerns hypoglycaemia and pancreatitis.

OPR reviewer comment:

Routine risk minimisation activities are considered to be acceptable to mitigate these two safety concerns.

The RMP evaluation conducted by the OPR at TGA assessed RMP Version 1.0 (dated 01 June 2010) and contained several requests for information or clarification from the

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

sponsor. The questions posed by the OPR evaluator and the sponsor's responses are outlined below.

Sponsor response to the initial RMP evaluation

1. Question: It was recommended to the Delegate that the sponsor include 'Children below 18 years' and 'Safety in pregnant women/during lactation' as Important Missing Information in the Ongoing Safety Concerns as both of these were part of exclusion criteria in clinical trials.

Sponsor Response

Boehringer Ingelheim agreed with the evaluator's recommendation to include 'paediatric patients', 'pregnant and lactating patients' as Important Missing Information under Section 2.2 Summary Safety Concerns and Planned Pharmacovigilance Actions of the updated RMP (version 3.0).

2. In addition, the sponsor should also include the safety concerns, as identified in the Clinical Evaluation Report, cardiovascular disorders and neoplasia (for example, specifically consider pancreatic carcinoma) as potential risks.

Sponsor Response

Boehringer Ingelheim disagreed with the evaluator's recommendation to include 'cardiovascular disorders' and 'neoplasia' (for example, specifically pancreatic carcinoma) as important potential risks. Controlled clinical trials did not suggest an increased incidence of CV events for linagliptin compared to other oral glycaemic compounds to date. Similarly, the available nonclinical and clinical data do not indicate any increased risk for oncological adverse reactions under linagliptin treatment compared to placebo. Therefore, Boehringer Ingelheim does not consider these two safety concerns should be included as important potential risks but rather as Important Missing Information. Hence, 'oncological adverse reactions' has now been included as Important Missing Information under Section 2.2 Summary Safety Concerns and Planned Pharmacovigilance Actions in the updated RMP (version 3.0) together with the 'High risk patients with recent CV events'.

Importantly, oncological adverse events (including pancreatic carcinoma) will be actively searched and followed-up in the CV safety study CAROLINA [U10-2169] with an estimate of 6000 patients under long-term exposure. Please also refer to the RMP (version 3.0) Section 1.1.1.4.1 'Oncological adverse reactions' for discussion of the clinical trial data. Cardiovascular disorders will be investigated in the dedicated CV safety study CAROLINA [U10-2169].

3. It is recommended the sponsor specify the protocol numbers and names for the clinical trials that they intend to analyse as part of proposed pharmacovigilance activities for the safety concerns 'Skin lesions', 'Hypoglycaemia' and Pancreatitis'.

Sponsor Response

Boehringer Ingelheim disagreed with inclusion of the protocol numbers and names for the clinical trials that the company intends to analyse as part of proposed pharmacovigilance activities because the analysis for the safety concerns 'Skin lesions', 'Hypoglycaemia' and Pancreatitis' will be conducted on ALL of clinical trials listed in Section 1.2.1.1 of the RMP.

In the sponsor's opinion, listing all protocol numbers and names of the clinical trials as part of the proposed pharmacovigilance activities would not enhance readability and

would only provide duplicate information. The protocol numbers and other information relating to the clinical trials that are intended to be analysed as part of proposed pharmacovigilance activities are already included in Section 1.2.1.1 and Annex III of the RMP.

4. The sponsor should also include justification on how each of these clinical trials will further elucidate the safety concern (such as inclusion of an appropriate endpoint(s), sample size and patient inclusion criteria). In addition, the sponsor should specify starting dates for the CV Safety study and completion dates for the ongoing studies.

Sponsor Response

The CV safety study CAROLINA [U10-2169] will further elucidate the safety concerns 'Skin lesions', 'Hypoglycaemia' and Pancreatitis'. The CV safety study CAROLINA [U10-2169] is a long-term study that is randomised and placebo controlled (with active comparator). This study provides exposure in approximately 6000 patient years and therefore is considered to contribute important safety information on rare adverse events. Because adverse events such as skin lesions and pancreatitis are rare, the exposure and study duration are considered to provide reasonable sample size to evaluate these rare events.
Collection of the safety information concerning 'Skin lesions', 'Hypoglycaemia' and Pancreatitis is further detailed as follows:

hypoglycaemia: information on AE is collected in detail in the eCRF of the CAROLINA trial [U10-2169].

pancreatitis and **skin lesions**: information on these AEs will be actively collected in the CV safety study CAROLINA [U10-2169] that provides long term exposure in about 6000 patients. The investigator is requested to report the events within 24 hours and is also requested to consider working sheets so that high quality information will be available for safety analysis. In addition, the database will be actively and regularly searched of events of pancreatitis and skin lesions, which have not been reported by the investigator as required. In these cases, the investigator will be actively requested to provide information.
Overall, due to study size and duration, the CV safety study CAROLINA is considered to provide the most relevant information to safety in the ongoing and planned linagliptin development program. In addition, the starting dates for the CV Safety study has been specified in Section 2.6 Summary of outstanding actions of the Australian specific annex (ANNEX VIII – Australian Specific Information) included as Attachment III and the completion dates for the ongoing studies are included in Annex III of RMP.

5. The sponsor propose routine risk minimisation activities for the safety concerns: 'Skin lesions', 'High risk patients with recent CV events' and 'Old patients (>80 years)' (PI labelling). Currently, no risk minimisation activities are proposed for these safety concerns.

Sponsor Response

Boehringer Ingelheim agreed with the evaluator's recommendation to include risk minimisation activities for the safety concerns 'High risk patients with recent CV events' and 'Old patients (>80 years)'. Please refer to the Australian specific annex (ANNEX VIII – Australian Specific Information) included as Attachment III of RMP. There is no evidence that the identified safety concerns following administration of linagliptin in the recommended dosage is higher or the clinical course more severe than with the

administration of the standard therapies. Therefore, appropriate labelling is considered as sufficient for the identified safety concerns.
Boehringer Ingelheim disagreed with the evaluator's recommendation to include risk minimisation activities for the safety concern 'Skin lesions'. Skin lesions are presented as important potential risk based on exfoliative skin conditions reported for other gliptins, such as Januvia® and Galvus® and based on publications. However, based on the available data for linagliptin, there is no risk of skin lesions associated with the use of linagliptin. Furthermore, necrotic skin lesions observed after administration of other DPP-4 inhibitors were not seen in any of the performed preclinical studies including cynomolgus monkey studies up to one year [U08-1185] with a high dose level of 100 mg/kg/day linagliptin corresponding to 791 fold MRHD (Maximum Recommended Human Dose).

This potential risk will be monitored and reported in periodic safety updates, unless specific action is warranted based on newly emerging results. Depending on the analysis of future data, the labelling of the Australian Product Information may be adapted as appropriate.

6. The sponsor update the proposed risk minimisation activities for the safety concern 'Severe renally impaired patients' to having a routine risk minimisation activity, because the PI already contains a statement in the Pharmacokinetics section about renal impairment.

Sponsor Response

Boehringer Ingelheim agreed with the evaluator's recommendation to having a risk minimisation activity for the safety concerns 'Severe renally impaired patients'. Please refer to the Australian specific annex (ANNEX VIII – Australian Specific Information) included as Attachment III to RMP.

7. In regards to the proposed routine risk minimisation activities, the draft product information document and the draft consumer information document should be updated to include information about the safety concerns 'Skin lesions', `High risk patients with recent CV events' and `Old patients (>80 years)'.

Sponsor Response

Boehringer Ingelheim disagreed with the evaluator's recommendation to include information about the safety concerns 'Skin lesions', 'High risk patients with recent CV events' and 'Old patients (>80 years)' in the *Precautions* section of the draft product information and consumer information documents as these safety concerns have not been identified as important identified risks for linagliptin. Data to date does not support any reasonable suspicion of causal association. However, as stated in Section 2.3 *Detailed Action Plan for Specific Safety Concerns* of the RMP, these safety concerns will be monitored and depending on the analysis of data, the product information and consumer information documents will be updated accordingly.

Boehringer Ingelheim agreed with the evaluator's recommendation to update the risk management plan to include routine risk minimisation activities for safety concerns 'High risk patients with recent CV events' and 'Old patients (>80 years)'. Please refer to the Section 5. Summary of the Risk Management Plan in the Australian specific annex, (ANNEX VIII – Australian Specific Information) included as Attachment III of the RMP.

8. In regards to the RMP document, it identifies and refers to the European Medicines Agency's Summary of Product Characteristics (SmPC) and it should be updated to provide consistency in the Australian context (replace SmPC with PI), or provide an Australian specific annex which identifies this issue and any Australian relevant changes or issues.

Sponsor Response

Boehringer Ingelheim agreed with the evaluator's recommendation to provide an Australian specific annex (ANNEX VIII – Australian Specific Information) which includes the current proposed Australian Product Information for Trajenta linagliptin 5 mg blister which should be used as reference for this submission instead of the SmPC whenever SmPC is referred throughout the RMP document. Furthermore, any Australian specific changes to the RMP are also included in the Australian specific annex (i.e. ANNEX VIII – Australian Specific Information).

The sponsor's response included an updated RMP (Version 3.0, dated 02 Feb 2011) and was considered acceptable by the OPR. If this product is approved it was recommended to the Delegate that the implementation of RMP Version 3.0, dated 02 Feb 2011 and any future updates be imposed as conditions of registration.

VI. Overall Conclusion and Risk/Benefit Assessment

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

Quality

The evaluator mentions that linagliptin solubility is high. It has one chiral centre and is presented as a single (*R*) enantiomer.

All chemistry and quality control issues have been resolved and the evaluator recommends registration from a chemistry and quality point of view.

The proposed shelf life is 30 months, to be stored below 30^0C. This is acceptable based on submitted data.

The evaluator mentions that the absolute bioavailability of a 10mg linagliptin formulation (versus 5 mg IV) was 30%; there was high inter individual variability.

The submission was considered by PSC and recommended for registration from a chemistry point of view (Recommendation 2212).

Nonclinical

The evaluator mentions that the overall quality of the Australian submission was high with all pivotal toxicity studies complying with GLP; the studies also used the oral route (proposed clinical route of administration).

In vitro studies revealed inhibition of DPP-4 with nanomolar potency. *In vivo* studies showed, at subclinical exposures, a marked and sustained decrease in plasma DPP-4 activity, improved plasma glucose clearance and increased plasma insulin levels in diabetic rats and increased levels of GLP-1.

The evaluator mentions that safety pharmacology studies conducted in rodents and dogs. Pseudoallergic reactions and increased plasma histamine levels were observed in dogs at very high plasma concentrations (> 380 times the clinical C_{max}).

The pharmacokinetics was qualitatively similar to humans. The only significant metabolite, CD 1790, was pharmacologically inactive. The evaluator mentions that CD 1790 had no inhibitory activity against DPP-4 at concentrations up to 1 mM (300 times the clinical C_{max} for CD1790).

Linagliptin was shown to be an irreversible inhibitor of CYP3A4 but the evaluator was of the opinion that this was not clinically relevant "based on the kinetic parameters for the inhibition and the nanomolar circulating levels of drug in patients". There was no significant inhibition of other CYP450 isoenzymes. Linagliptin is a substrate for P-glycoprotein.

Acute oral toxicity studies did not reveal any significant effects. Chronic toxicity studies were conducted in rodents (26 weeks in rats) and monkeys (52 weeks). These were mainly oral studies and where high multiples of clinical exposures were achieved. Toxicity was observed in the liver (mice, rats, dogs and monkeys), lungs (rats), kidneys and gastrointestinal tract (mice, rats and monkeys). The exposure level at the animal: human ratio was ≥ 31. Dermal irritation studies in rabbits were unremarkable.

The US FDA Pharmacology review[19] states that linagliptin did not cause histological changes in the pancreas of animals indicative of pancreatitis or pancreatic injury despite long term exposure to very high doses of drugs. However, it should be noted that these were studied in normo glycaemic healthy animals.

Linagliptin was not genotoxic. A two year rat study (with high exposure margin) did not reveal carcinogenicity. No effect on fertility was seen in male and female rats exposed to plasma levels greater than 1000 times the clinical exposure.

Overall, the evaluator recommends approval from a nonclinical perspective.

Clinical

Pharmacokinetics

Some 25 studies are submitted. Of these, ten were pharmacokinetic studies on healthy volunteers; nine were drug interaction studies, one mass balance study, three pharmacokinetic studies in Type 2 diabetics, one pharmacokinetic study in renal impairment and one study in hepatic impairment.

The studies on healthy volunteers showed non-linear kinetics over the 1mg to 600 mg range. The pharmacokinetics could be explained by saturable protein binding, resulting in higher free fraction and increased clearance. Terminal half life was greater than 100 hours. Apparent clearance increased with dose.

The evaluator states that in a study comparing 1mg, 2.5 mg and 5 mg once daily for 7 days, steady state AUC and C_{max} decreased from 5 mg to 2.5 mg by 25.5% and 41.9% and from 5 mg to 1 mg by 43.8% and 62.5%, respectively.

Absolute bioavailability was approximately 29.5% and showed a high inter individual variability (46.7%). This was ascertained in Study 1218.10 where the 10 mg linagliptin tablet was compared to 5 mg linagliptin given IV.

Intake of high fat meal reduced C_{max} but not AUC of a 5 mg dose. This was also seen in a study of 1mg and 10 mg.

Most of the elimination was hepatic.

[19] http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/201280Orig1s000TOC.cfm

The evaluator also mentions that the pharmacokinetic parameters were similar for once daily and multiple dosing (Study 1218-58-U10-3113-02). Also, there was no pharmacokinetic advantage in dosing twice daily (2.5 mg) compared with 5 mg once daily (Study 1218.45).

Drug interaction studies:

The effect of the concomitant administration of ritonavir, rifampicin, metformin or pioglitazone on linagliptin exposure and C_{max} was evaluated. When given with ritonavir (a potent CYP3A4 and P-gp inhibitor) linagliptin AUC and C max increased by 2 and 3 fold, respectively. With rifampcin (a potent CYP3A4 and P-gp inhibitor) both AUC and C_{max} were reduced by 40%. With glyburide, metformin and pioglitazone, the change in AUC and C_{max} was less than 20%. The effect of linagliptin on other drugs, including levonorgestrel and ethinyloestradiol, was negligible.

Pharmacokinetics in subjects with Type 2 diabetes:

Two studies are discussed in the clinical evaluation report (CER). A range of doses (1mg to 10mg) was used in double blind placebo controlled studies. Pharmacokinetic parameters were not dose proportional and were similar to those of healthy adults.

Pharmacokinetics in renal impairment:

Study 1218.26-U10-1467-02 assessed the pharmacokinetics of linagliptin in patients with renal impairment. With single doses, mild renal failure increased C_{max} and AUC by approx 25% and all other severities (moderate to severe renal impairment) by approx 50%. With multiple dosing, the increases (in moderate renal impairment) were in the range of 40% to 70%. Exposure to CD 1750 (inactive metabolite) also increased to approximately 50%. The inter-individual variation was high.

Delegate's comments: No dosage adjustment is recommended in the PI. The sponsor has responded in detail to the evaluator's request for modification of dosing.

The rationale for not modifying the dosing is that linagliptin is predominantly excreted unchanged in faeces with renal excretion <1% following a 5 mg dose. Also, a higher dose of 10 mg/day linagliptin used in Study 1218.23-U10-1466-01 did not cause increased side effects. There was no increase in trough concentrations in severe renal impairment compared with moderate impairment.

The sponsor should inform the TGA if there are long term studies on renal impairment that are underway that support no dosage adjustment, in its pre Advisory Committee on Prescription Medicines (ACPM) response. This should only include summary results.

Pharmacokinetics in hepatic impairment:

Study 1218.27-U10-1219-01: After single and multiple dosing, the AUC and C_{max} were reduced in mild to moderate hepatic impairment. The AUC for CD 1750 also reduced.

Delegate's comments: The sponsor has not recommended dosing adjustment in patients with hepatic impairment. The main justification for this is that "full efficacy of linagliptin and DPP-4 inhibitors in general was shown with a DPP-4 inhibition greater or equal 80% over the whole steady state dosing interval. Considering that the DPP-4 inhibition with linagliptin in all groups of hepatically impaired subjects was consistently greater than 80%, these differences are considered to be not clinically relevant".

The Delegate accepted this justification.

Bioequivalence (Study 1218.25U07-2003).

In this study the various formulations during development were compared. They were iFF (intended formulation for marketing), TF II (trial formulation II) and TF-IIb (which was a trial formulation further optimised to improve tablet stability). Bioequivalence was demonstrated with geometric mean ratio for AUC and C_{max} being within 0.8 -1.25.

Pharmacodynamics:

There were ten studies submitted. Study 1218.1 was a single rising dose study that showed inhibition of DPP-4 in plasma. The extent of DPP-4 inhibition increased with increase in doses from 1 mg to 10 mg (Study 1218.2-U06-1139). The effect was also long lasting, DPP-4 activity had not return to baseline 96 hours after drug administration. There was no significant difference between 5 mg and 10 mg in relation to DPP-4 inhibition (Studies 1218.2-U06-1139and 1218.3-U06-1822). The 5 mg morning dosing regimen and a 2.5 mg twice a day (bd) dosing regimen showed similar DPP-4 inhibition over the entire dosing interval (Study 1218.45-U08-2123-01). The level of increase in GLP-1 (2.5 mg to 10 mg, Study 1218.3-U06-1822) plateaued with 5 mg linagliptin.

QT interval: In this four way crossover study (1218.32-U09-1067), healthy male volunteers were administered 5 mg and 100 mg linagliptin, placebo and 400 mg moxifloxacin after adequate washout. The corrected QT interval was less than 10 ms at both doses and at all time points. There was no QT prolongation with linagliptin. No study subject had a maximal QTc interval > 480 ms or experienced an increase in the QTc interval from baseline > 60ms.

There were no gastric motility studies submitted.

Efficacy studies

Dose finding studies

Three studies are discussed (Studies 1218.5-U08-3761-02, 1218.6-U08-1056-03 and 1218.37-U09-2397-02). These studies evaluated doses ranging from 0.5 mg to 10 mg linagliptin. These were all placebo controlled studies of 4 weeks to 12 weeks duration conducted in Type 2 diabetics. Selection of 5 mg was based on HbA_{1C} reduction (primary endpoint) and DPP4 inhibition and effect on GLP1 levels. There was no added benefit observed with the 10 mg dose. Study 1218.5-U08-3761-02 also included an open label part of 500 mg metformin for 4 weeks followed by 800 mg metformin for 8 weeks.

Monotherapy

Study 1218.16-U10-1103-03. In drug naive or previously treated patients. This was a multicentre randomised double blind placebo controlled parallel group study in subjects with Type 2 diabetes and insufficient glycaemic control. It evaluated efficacy and safety of 5 mg linagliptin versus placebo. There was a 6 week washout for those on anti diabetic treatment and a 2 week placebo run in followed by a 24 week treatment period. Subjects with Type 2 diabetes mellitus either treatment naive or treated with no more than one oral anti diabetic treatment (OAD) were eligible to participate.

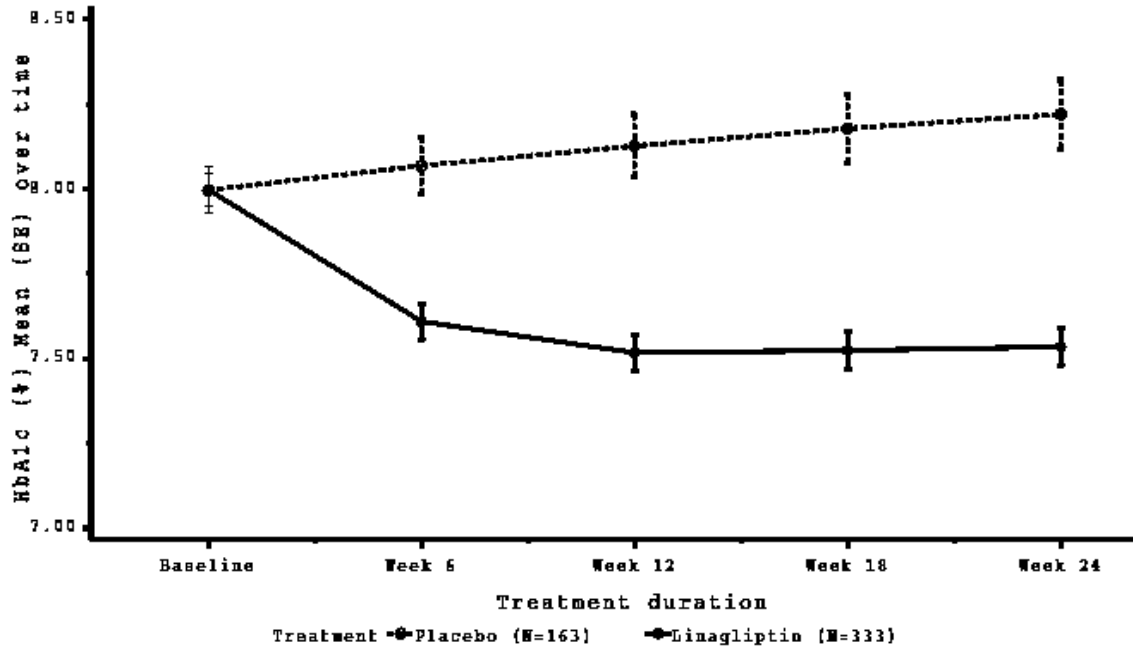
The primary efficacy endpoint was the change from baseline in HbA_{1c} after 24 weeks treatment. There were multiple secondary endpoints and included other measures relating to the reduction in HbA1c, FPG, use of rescue therapy , body weight, plasma DPP inhibition and others.

This was designed as a superiority study. Some 167 subjects were randomised to placebo treatment and 336 subjects to active treatment. The treatment groups were similar in baseline demographic characteristics.

Linagliptin was superior to placebo by the primary efficacy outcome measure. The adjusted mean (95% CI) difference in change from baseline in HbA1c, linagliptin – placebo was: -0.69 (-0.85 to -0.53) %, p<0.0001. Randomisation was stratified by HbA1c at the beginning of the placebo run in period (<8.5% or ≥8.5%). The results in these subgroups in relation to the primary efficacy endpoint should be submitted in the sponsor's pre ACPM response.

The treatment difference is seen in the Figure 5 below.

Figure 5. HbA1c (%) mean (SD) over time – FAS (LOCF).



There was a statistically significant difference seen in relation to FPG. Other secondary endpoint results are noted in the CER. No significant changes were observed in relation to mean weight or waist circumference.

Study 1218.5-U08-3761-020 was a multicentre, randomised, double blind, placebo controlled study (Part I) followed by an active controlled (sulfonylurea) treatment phase (Part 2). Part 1 was submitted and this was 18 weeks in duration.

Patients with Type 2 diabetes with insufficient glycaemic control and for whom metformin therapy was inappropriate were eligible to participate. Inclusion and exclusion criteria were similar to those of the previous study.

A total of 137 subjects were randomised to linagliptin and 64 to placebo therapy.

Linagliptin was superior to placebo in relation to the primary endpoint. Adjusted mean (95% CI) difference in change in HbA1c from baseline was -0.57 (-0.86 to -0.29) %, p<0.0001. The secondary efficacy endpoints were similar to those of the previous study.

Delegate's comments; A significant deficiency in relation to the data submitted to support initial monotherapy is that there is no active comparator trial, especially with metformin which is the drug of first choice in Australia. In addition, the maximum duration to support monotherapy is 24 weeks (based on Study 1218.16-U10-1103-03) and the durability of effect of linagliptin cannot be ascertained based on this study. Study 1218.5-U08-3761-020 is also placebo controlled (with small number of subjects, with a small effect size, in relation to efficacy. More data are needed; a longer term study versus metformin in drug naive subjects

is needed. The present data only shows short term efficacy versus placebo and is considered preliminary.

Dual therapy. Add on therapy with metformin.

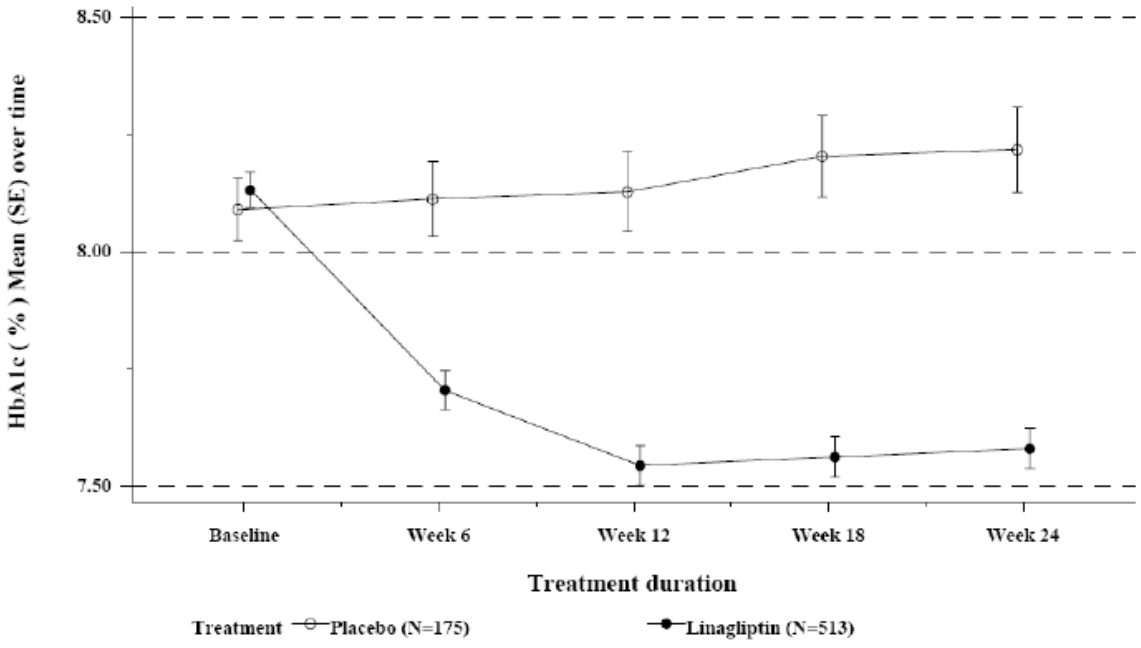
Placebo controlled study (Study 1218.17-U09-2533-02). This was similar in design to the previous study. Subjects on a dose ≥ 1500 mg/ day metformin or on maximum tolerated dose of metformin and stable for at least 12 weeks before randomisation were eligible for inclusion. Other inclusion and exclusion criteria are listed in the CER. The primary and secondary efficacy endpoints were similar to those of the previous study.

The margin used to determine clinical superiority is not stated. The sponsor should clarify this in its pre-ACPM response.

A total of 524 subjects were randomised to linagliptin and 177 subjects to placebo. The treatment groups were similar in relation to demographic characteristics, baseline variables and time since diagnosis of diabetes. Those on metformin dose less than 1500 mg/day comprised 7.2% of subjects in the linagliptin group and 6.9% of subjects in the placebo group.

Results: For the primary efficacy outcome measure, linagliptin + metformin was superior to placebo + metformin: adjusted mean (95% CI) difference -0.64 (-0.78 to -0.50) %, p<0.0001. This is illustrated in Figure 6 below.

Figure 6. Mean HbA1c (%) and SE over time – FAS (LOCF)



There was a statistically significant decrease in FPG with dual therapy. Similarly, endpoints relating to HbA1c, rescue medications showed statistically significant difference between treatment groups. No significant difference was reported in relation to body weight or waist circumference.

*Active controlled study (1218.20-U10-1465-01).*An interim report at 52 weeks in a 104 week study is submitted. This was a multi centre randomised double blind active control study. Subjects were those with diabetes mellitus Type 2 with insufficient glycaemic

control despite metformin therapy were recruited. These subjects received 5 mg linagliptin in comparison with glimepiride (1-4 mg/day) as add on therapy to metformin. Glimepiride was to be initiated at 1 mg/day. In the first 12 weeks it could be titrated to 4 mg/day.

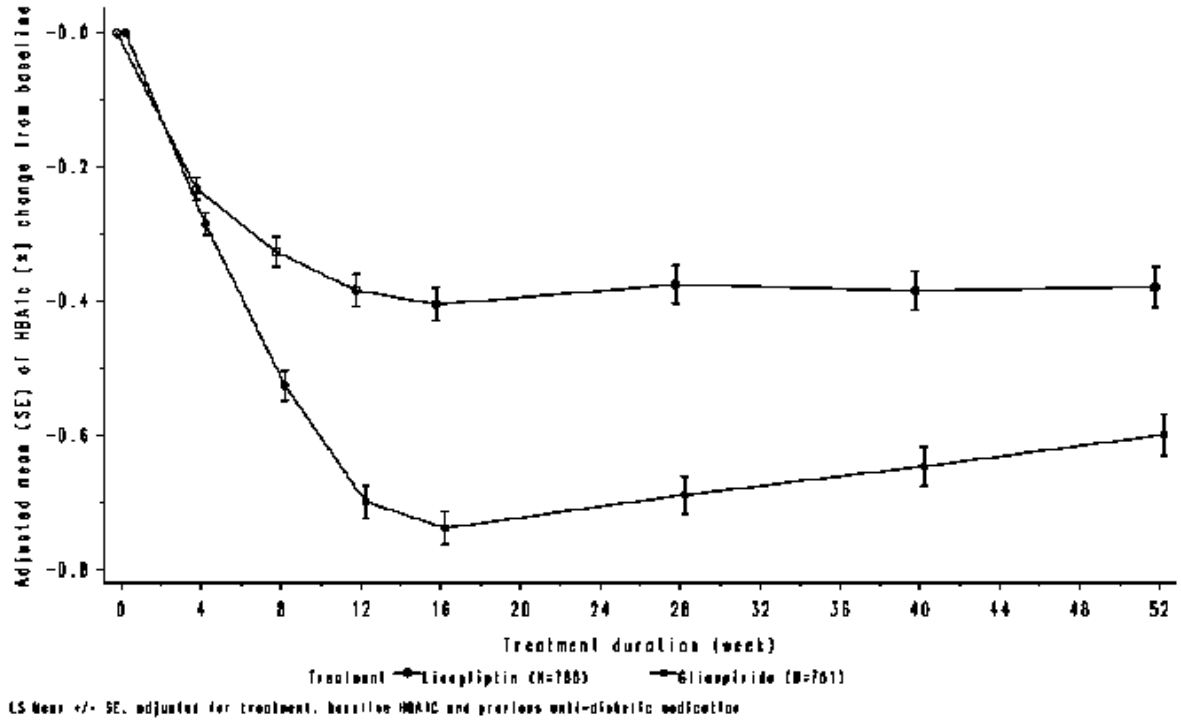
This was designed as a non inferiority study versus glimepiride in relation to HbA1c change from baseline. Superiority of linagliptin versus glimepiride in relation to body weight change and hypoglycaemic events were also included in the statistical considerations.

This study had more males (60.2%) and the majority were White (84.6%). Other baseline characteristics were similar between the groups. Baseline HbA1c was 7.8%. This was lower than in the other Phase III studies where it was ≥ 8%.

Of the 1560 subjects randomised, 779 were included in the linagliptin + metformin group and 636 were included in the glimepiride +metformin group.

In relation to the primary efficacy endpoint, glimepiride + metformin was superior to linagliptin + metformin: adjusted mean (97.5% CI) difference in change from baseline for HbA1c 0.22 (0.13 to 0.31) % p<0.0001. The evaluator states that, "although the sponsor's predefined criteria for non-inferiority were met, the non-inferiority analysis was superseded by the test of superiority".

Figure 7. Adjusted mean HbA1c (SE) over time – FAS (LOCF)



Of note with respect to the secondary efficacy endpoints:

Weight loss: linagliptin + metformin group showed statistically significant difference - adjusted mean (97.5% CI) difference -2.49 (-2.92 to -2.06) kg p<0.0001

FPG: decrease was greater in the glimepiride + metformin group: adjusted mean (95% CI) difference 7.61 (4.33 to 10.90) mg/dL p<0.0001

Rescue therapy: A higher proportion of subjects in the linagliptin + metformin group required rescue therapy with pioglitazone: 125 (16.3%) subjects compared with 92 (12.1%) p=0.0113.

Waist circumference: -1.0 (5.3) cm in the linagliptin + metformin group compared with 0.6 (5.3) cm in the glimepiride + metformin

Endpoints relating to HbA1C showed a statistically significant difference favouring the linagliptin+ metformin combination.

Delegate's comments: This study showed a clear superiority of metformin+glimepiride in relation to HbA1c; glimepiride group had better glycaemic control and lower FPG. It is stated that the mean dose of glimepiride during treatment was 3 mg. The percentage on 4 mg/day was not stated. The sponsor should provide the breakdown of glimepiride dose; percentage of subjects on 1 mg, 2 mg, 3 mg and 4 mg.

Dual therapy with pioglitazone

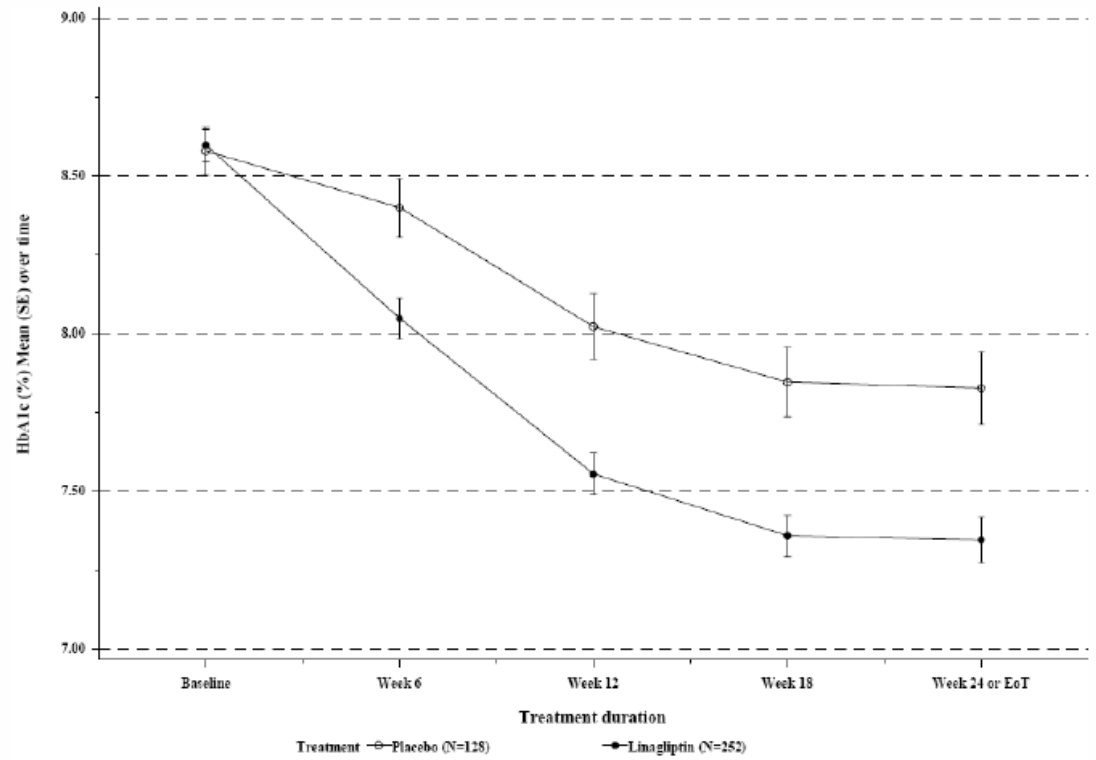
Study 1218.15-U09-2519-01. This study was also similar in design to the previous studies. A 5 mg linagliptin dose was combined with 30 mg pioglitazone and compared to placebo combined with 30 mg pioglitazone. This, however, was an initial combination therapy study. Inclusion and exclusion criteria are listed in the CER; (the exclusion criteria encompassed the contraindications in the pioglitazone PI. Those who were treatment naive or previously treated with any oral hypoglycaemic agent were eligible to participate).

The efficacy endpoints were similar to those of the previous studies.

Some 259 subjects were randomised in each group. The evaluator mentions that the baseline demographics were similar in the two groups. It is noted that 49.7% of the subjects were treatment naive.

The primary efficacy outcome measure demonstrated superior efficacy for linagliptin-pioglitazone in comparison with placebo-pioglitazone: adjusted mean (95% CI) difference -0.51 (-0.71 to -0.30) %, p<0.0001 (Figure 8).

Figure 8. Mean HbA1c (%) and SE over time – FAS (LOCF)



Secondary efficacy endpoints: In relation to HbA1c endpoints, there was statistically significant difference favouring the active combination. This combination (linagliptin and pioglitazone), however showed statistically significant weight increase and waist circumference.

Delegate's comments: It is noted that 49.7% of the recruited population did not receive any prior therapy with OAD. This study design is different to the other add on therapy studies in that this was an initial combination therapy study. Thus, this study does not support the claim for add on therapy where the setting would be the use of add on linagliptin to pioglitazone due to inadequate glycaemic control.

Add on therapy with suphonylurea (SU)

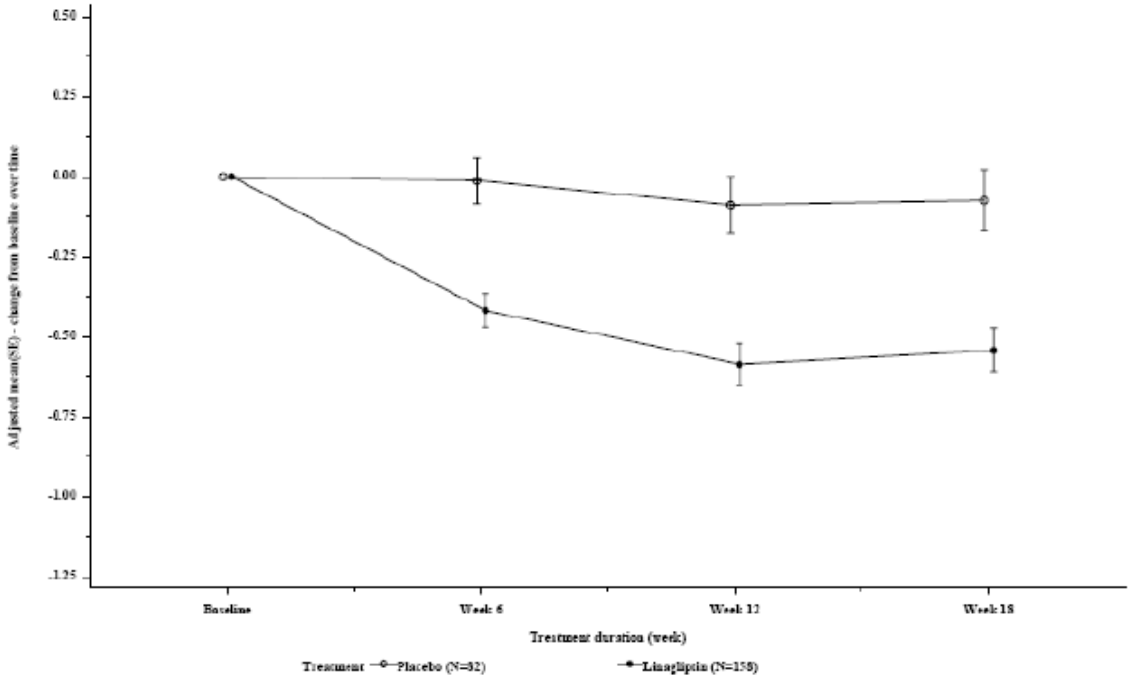
Study 1218.35-U10-3206-01 was considered as a supportive study (smaller and shorter duration) by the evaluator.

Those on sulfonylurea with insufficient glycaemic control (HbA1c 7.0 -10%) were eligible to participate. SU dose of at least one half the maximum dose (or less if documented as the maximum tolerated does for at least 12 weeks) were eligible to participate. This study was of 18 weeks duration. The efficacy endpoints were similar to those of previous studies.

Some 161 patients were randomised to linagliptin + sulfonylurea and 84 patients to placebo + sulfonylurea. The baseline demographics were similar between groups. It is noted that 28.5% of the subjects had both sulfonylurea + metformin at study entry. The dose of sulfonylurea at entry is not included in the report. The sponsor should include this (that is, mean dose and percentage of subjects taking maximum recommended dose, half the dose in each group) in their pre-ACPM response.

The primary efficacy endpoint: adjusted mean (95% CI) difference in change from baseline in HbA1c -0.47 (-0.70 to -0.24) % p<0.0001 (Figure 9).

Figure 9. Adjusted mean HbA1c (%) and SE over time – FAS (LOCF)



There were no significant difference between treatment groups in FPG, body weight or waist circumference.

Triple therapy

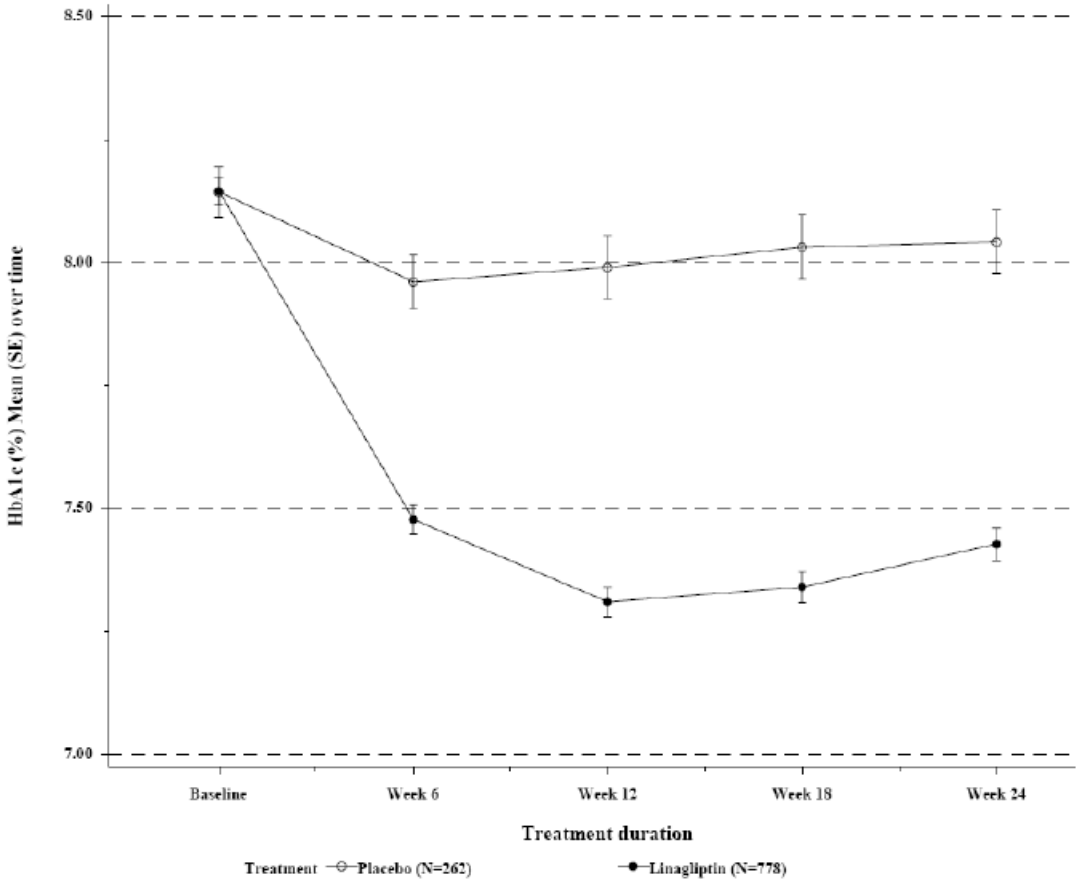
One study examining triple therapy was submitted with the current Australian submission.

Study 1218.18-U09-2458-02 was also a multicentre, randomised, db, placebo controlled parallel group study in patients with diabetes mellitus Type 2 and insufficient glycaemic control despite treatment with metformin and sulfonylurea. Those on stable, total daily dose of ≥1500 mg metformin + a dose of sulfonylurea that had been documented (by the study investigators) to be the individual maximal tolerated dose were included. The dose of both drugs and dosing should be unchanged for 10 weeks. The study was of 24 weeks duration. The efficacy endpoints were similar to the other studies.

Some 793 subjects were randomised to linagliptin and 265 subjects were randomised to placebo. It was stated that the baseline demographics were similar in both treatment groups. The mean dose of metformin and sulfonylurea at baseline were not included in the CER. The sponsor should provide this in their pre-ACPM response.

For the primary efficacy outcome variable, linagliptin + MET + SU was superior to placebo + MET + SU: adjusted mean (95% CI) difference from baseline in HbA1c -0.62 (-0.73 to -0.50), p<0.0001. Other HbA_{1C} endpoints also showed superiority with linagliptin treatment. There was no significant difference in waist circumference and weight.

Figure 10. Mean HbA1c (%) and SE over time. FAS (LOCF).



Delegate's comment: Slight upward trend in HbA1C is observed around 15 weeks of treatment suggesting that the durability of effect is short.

Safety

The evaluator listed the patient exposure, adverse events in pharmacology studies, Phase II studies, pivotal placebo controlled and active controlled studies.

A total of 454 healthy subjects were randomised to linagliptin. In the studies in patients with diabetes mellitus, 4687 were randomised to receive linagliptin (any dose) and 4040 randomised to linagliptin 5 mg.

Of those treated with 5 mg linagliptin, 3430 subjects were exposed for ≥ 6months, 2390 subjects for ≥ 12 months, 536 subjects for ≥ 18months.

Deaths are discussed under individual studies. The cause of death varied and the incidence was less in the linagliptin treated group than placebo (linagliptin 5 mg=8; placebo=4; active comparator=10).

SAEs

In the placebo controlled studies the total incidence was 3.8% versus 3.1% in linagliptin. The rates were low and there were no trends observed. The rates were also low in the active comparator trials.

Hypoglycaemia

In the pivotal Phase III studies hypoglycaemia was reported in 8.7% of subjects in the linagliptin group versus 5.3% of subjects given placebo. In the studies with SU the incidence was higher with linagliptin (20.7% versus 13.3%).

Other events

In the placebo controlled studies there were no increases seen in relation to hypersensitivity, renal events and hepatic events.

Pancreatitis

The FDA medical review, based on its own search concluded that there were 8 cases of pancreatitis in those treated with linagliptin as compared to 0 in the placebo treated groups. The sponsor should update this information (in completed studies) in its pre-ACPM response.

Long term data

Study 1218.40 – U10-1468-01 was an open extension of the pivotal studies. Approximately 2122 patients on LNG are followed up for 78 weeks. Interim results are provided at 42 weeks. Since this is open label in design, this contributes to safety only.

The safety results were in line with those reported in the comparative Study 1218.20-U10-1465-01.

Other information

The sponsor states that it is currently conducting a cardiovascular outcome study (1218.74) of linagliptin versus glimepiride in patients with Type 2 diabetes at high cardiovascular risk. This study is to be of 400 weeks duration and enrolment commenced in November 2010.

The final 2 year result of Study 1218.20-U10-1465-01 which contains the prospectively adjudicated CV events safety results (U11-1485) should now be available. The sponsor should submit this, to update the PI as a condition of registration.

Overall conclusion and recommendation of the evaluator:

Overall, the evaluator accepts the superiority of linagliptin as monotherapy and combination therapy versus placebo. The effect sizes were clinically significant as well as statistically significant. This related to primary and secondary efficacy endpoints.

However, in a study where there was an active comparator (glimepiride + metformin versus linagliptin+metformin), glimepiride + metformin was superior in relation to efficacy.

The evaluator states that the clinical development program did not “adequately investigate the optimal sequence of treatments. Hence, it is not clear at what stage linagliptin should be introduced and what combinations of drugs should include linagliptin”.

Safety results did not reveal any significant risks. However, the class effects are mentioned as inclusions in the safety specification.

The evaluator concludes that linagliptin has a favourable risk benefit profile. However, the issues identified by the evaluator are:

1. Sulphonylureas appear to be superior to linagliptin; this was demonstrated in a dual therapy (add on) study. Linagliptin use, in this setting, is only supported if SUs are contraindicated.
2. No comparison with metformin as monotherapy has been conducted. Thus, use with linagliptin as monotherapy is recommended only when SU, metformin are contraindicated.

In light of these concerns, the evaluator recommended the following indication:

Trajenta is indicated in adult patients with Type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, as monotherapy (where both metformin and/or sulphonylureas are either ineffective or contraindicated) or as add on to metformin, sulphonylureas, thiazolidinediones or metformin plus sulphonylureas.

Risk Management Plan

The evaluator has requested further details on the additional studies that are proposed to assess skin lesions, hypoglycaemia and pancreatitis. The evaluator also mentions the cardiovascular outcomes study that is to be conducted. Routine risk minimisation activities relating to skin lesions, high risk patients with CV effects and older patients (80 years and over) are also proposed.

Risk-Benefit Analysis

Delegate Considerations

The Delegate agreed with the clinical evaluator that the risk benefit profile is favourable. However, the data provided support the indication as follows:

Trajenta is indicated in adult patients with Type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, as add on to metformin, sulphonylurea, or metformin plus sulphonylurea.

The Delegate proposed to reject the proposed indication of monotherapy as there are no good quality comparator studies versus metformin. The 12 week Phase II b study which compared linagliptin with metformin is insufficient, as its primary aim was as a dose finding study. The placebo controlled study (comparing linagliptin versus placebo as monotherapy) submitted is a preliminary study that needs to be confirmed with a metformin controlled study. There are inadequate data provided to recommend this product for a qualified monotherapy indication, that is, where both metformin and/or sulphonylureas are either ineffective or contraindicated.

The Delegate proposed to reject dual combination therapy with thiazolidinediones, as the only study submitted (with pioglitazone), Study 1218.15-U09-2519-01 is an initial combination study where approximately 50% of the patients did not have prior therapy with ODA. Thus, this study does not adequately inform regarding the efficacy of linagliptin when added to pioglitazone, when therapy with pioglitazone is inadequate that is, is linagliptin effective in combination therapy, further following disease progression? This

study does not address this. Also the submitted study, due to the nature of its design, does not provide information whether this combination is likely to provide an adequate durability of effect (3-4 years) when this combination is used in a clinical setting.

The Delegate agreed with the evaluator that the PI should include a factual representation of Study 1218.20-U10-1465-01 with statistical results.

It is also noted that in the combination of linagliptin and SU increased the incidence of hypoglycaemia. This finding should also be included in the PI.

All the submitted studies show that most of the effect in relation to HbA1c is gained by Week 12. If there is inadequate response after three months, an alternative drug therapy should be instituted. This should be included in the PI.

The Advisory Committee on Prescription Medicines' advice was sought.

Response from Sponsor

1. TGA Delegate's comments and proposed action

Boehringer Ingelheim (BI) welcomed the TGA Delegate's recommendation to approve Trajenta linagliptin 5 mg film-coated tablet for the treatment of patients with Type 2 diabetes mellitus. However, BI considers the monotherapy indication remains a viable option for those patients intolerant to metformin or patients contraindicated for metformin due to renal impairment. Therefore, based on the submitted data provided in this submission, Trajenta should be approved for the following indication:

> *"Trajenta is indicated in adult patients with Type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, as monotherapy (where metformin is inappropriate due to intolerance, or contraindicated due to renal impairment) or as add on to metformin, sulphonylureas or metformin plus sulphonylureas."*

2. Pharmacokinetics in renal impairment

As mentioned above, BI conducted Study 1218.43, a placebo controlled 52 week study in patients with Type 2 diabetes and severe renal impairment. The final results of this study are available and support the use of linagliptin in this patient population and will be submitted soon after approval is received for the current application. A statistically significant and clinically relevant reduction in HbA1c after 52 weeks of treatment was observed for linagliptin compared to placebo and the safety and laboratory results were comparable between linagliptin and placebo with no distinct safety concerns observed for this population. As requested by the Delegate the summary results of the efficacy and safety analyses after 52 weeks are presented below:

Disposition of randomised patients

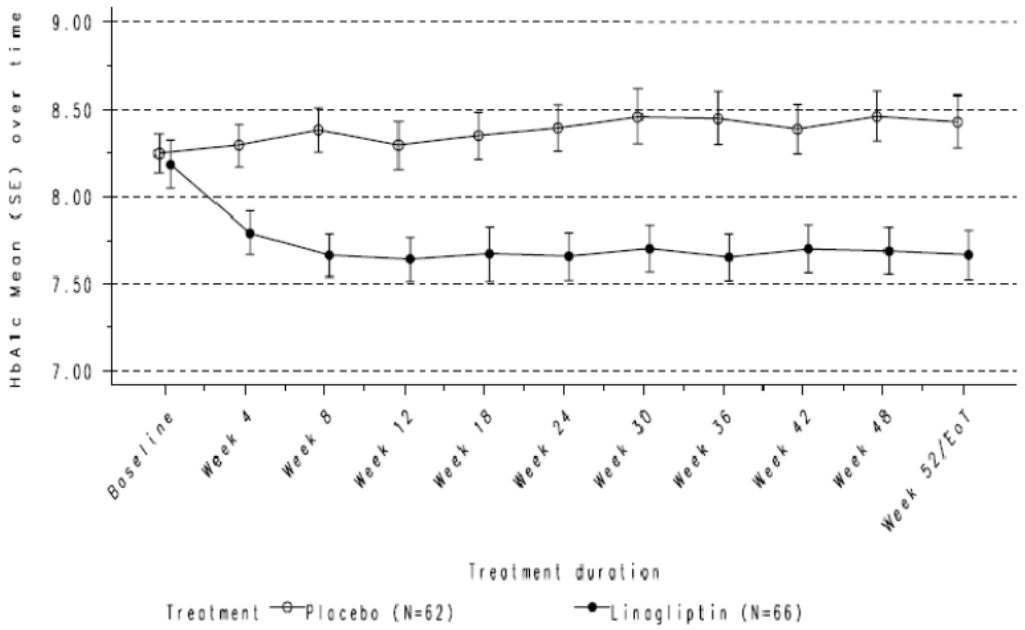
A total of 307 patients were enrolled and 139 entered a 2 week placebo run in period; 133 were randomised in a 1:1 ratio to receive treatment with either placebo (65 patients) or linagliptin 5 mg (68 patients). Randomisation was stratified by baseline HbA1c and background antidiabetic therapy. All randomised patients were treated. Of the 133 treated patients, 48 patients (73.8%) in the placebo group and 49 patients (72.1%) in the linagliptin group completed the study; 36 patients (27.1%) prematurely discontinued trial medication (17 [26.2%] placebo; 19 [27.9%] linagliptin) most frequently due to adverse events. One patient in each treatment group discontinued due to lack of efficacy.

Summary of Efficacy Results

The primary endpoint for the final analysis was the change from baseline in HbA1c to Week 52 of treatment. The treatment difference between linagliptin (n=66) and placebo

(n=62), calculated as the adjusted mean change in HbA1c from baseline at Week 52, was -0.72% (95% CI -1.03, -0.41), demonstrating superiority of linagliptin over placebo ($p<0.0001$) in the reduction of HbA1c. The analysis of the mean HbA1C change from baseline over time shows sustained improvements in glycaemic control with linagliptin up to 52 weeks.

Figure 11. HbA1c (%) mean and SE over time in Study 1218.43. FAS (LOCF).



Summary of Safety Results

Mean exposure to study medication was 299.18 days for patients randomised to placebo and 313.37 days for patients randomised to linagliptin. The median exposure was 364 days for both treatment groups. Overall, the frequency of AEs was comparable between both treatment groups; 60 patients (92.3%) were reported with AEs in the placebo group and 64 patients (94.1%) were reported with AEs in the linagliptin group. The most frequently reported AEs were in the system organ classes (SOCs) metabolism and nutrition disorders (70.8% placebo; 77.9% linagliptin); the most commonly reported preferred term (PT) in this SOC was hypoglycaemia (49.2% placebo; 63.2% linagliptin). A summary of the different AE categories is provided in Table 39.

The reported safety and laboratory results were comparable between linagliptin and placebo, with no distinct safety concerns observed except for the observed difference in hypoglycaemic events (49.2% placebo; 63.2% linagliptin). However, the rates of documented symptomatic hypoglycaemia were comparable between placebo and linagliptin, with the majority of hypoglycaemic events being of mild intensity. There was no difference between groups for severe hypoglycaemic events. The reporting of hypoglycaemic events can be attributed to the use of background therapy of insulin or a non glucose dependent secretagogue (SU or glinide). Of note, there were 81.5% of patients in the placebo group and 79.4% of patients in the linagliptin group who had been previously treated with insulin or any combination with insulin as background therapy. No change in body weight or waist circumference was observed. Linagliptin trough levels were similar across visits and renal staging groups, underlying the non renal excretion of linagliptin.

Table 39. Adverse event overall summary for BI trial 1218.43. Treated set.

	Placebo N (%)	Linagliptin 5 mg N (%)
Patient years of exposure	42.3	47.3
Number of patients	65 (100.0)	68 (100.0)
Patients with any AE	60 (92.3)	64 (94.1)
Patients with severe AEs	15 (23.1)	20 (29.4)
Patients with investigator-defined drug-related AEs	29 (44.6)	31 (45.6)
Patients with AEs of special interest[a]	3 (4.6)	4 (5.9)
Patients with other significant AEs (based upon ICH E3)	4 (6.2)	1 (1.5)
Patients with AEs leading to discontinuation of trial medication	11 (16.9)	9 (13.2)
Patients with serious AEs	27 (41.5)	25 (36.8)
Immediately life threatening	3 (4.6)	3 (4.4)
Disabling	1 (1.5)	2(2.9)
Requiring hospitalisation	23 (35.4)	23 (33.8)
Prolonging hospitalisation	4 (6.2)	6 (8.8)
Other	2 (3.1)	0 (0.0)

[a] i.e. hypersensitiviy reactions, renal events, hepatic events (based on investigator-reporting; excluding severe cutaneous adverse reactions and pancreatitis). Source data: Final CTR 1218.43 [U11-3170, Table 15.3.2: 1]

3. Monotherapy: in drug naïve or previously treated patients (Study 1218.16-U10-1103-03)

The analysis of the primary endpoint (change in HbA1c from baseline after 24 weeks of treatment) by baseline HbA1c (<8.5% versus ≥8.5%) was done as part of the analyses for the clinical trial report. This analysis showed that linagliptin was superior to placebo in both baseline HbA1c categories (p <0.0001 for both categories). The placebo corrected HbA1c change from baseline was somewhat smaller in patients with a baseline HbA1c value below 8.5% than in patients with a baseline value of 8.5% or above (-0.62% versus -0.84%). This is in line with the findings for other anti diabetic medications and consistent with the results of the pooled analysis of the 4 placebo-controlled linagliptin Phase III studies where the placebo-corrected HbA1c change from baseline was found to increase with increasing baseline HbA1c. Nevertheless, for Study 1218.16-U10-1103-03, the p value for the baseline HbA1c by treatment interaction term (0.2117) did not indicate a relevant influence of baseline HbA1c on the treatment effect of linagliptin.

4. Dual therapy. Add on to metformin.

Placebo controlled *Study 1218.17-U09-2533-02*. No predefined margin was defined in the study protocol with regards to determining clinical superiority; the study protocol describes the statistical assumptions for defining statistical superiority. Nevertheless, the observed treatment difference in HbA1c from baseline of −0.64% in Study 1218.17-U09-2533-02 would be widely accepted as being clinically significant. This is consistent with the project standard non inferiority margin of -0.35%, hence a greater difference than this would be considered clinically relevant.

5. Dual therapy: Add on to metformin.

Active controlled *Study 1218.20-U10-1465-01*. At Week 12, that is, after the up titration period for glimepiride, about half of the patients (363 of 716; 50.7%) in the glimepiride group received 4 mg glimepiride, 18.9% of patients received 3 mg, 15.2% of patients received 2 mg, and 15.2% of patients received 1 mg. Between Week 12 and Week 52, there was no increase in the glimepiride dose in any of the patients, whereas the glimepiride

dose was decreased to 3 mg in 19 patients, to 2 mg in 17 patients and to 1 mg in 21 patients.

6. Dual therapy with sulfonylurea (SU).

SU background doses in *Study 1218.35-U10-3206-01.* Patients in this study were taking various sulphonylureas (SUs) as background medication, hence calculating a mean daily SU dose at start of placebo run in would not be meaningful. Furthermore, for Trial 1218.35-U10-3206-01 information on the breakdown of the type of SU used, the mean SU background doses and dose categories is not available, since only changes in the background SU dose were captured. Relevant changes in the background dose of SU in study 1218.35-U10-3206-01 were rare. A change of the background dose by more than 20% was only recorded for 1 patient in the study; this patient was in the linagliptin group and was recorded with a decrease in the SU dose by more than 20%.

Therefore, there is no evidence to support a relevant influence of the background medication dose or dose changes on the study results.

7. Triple therapy (Study 1218.18-U09-2458-02)

Metformin background doses

At start of the placebo run-in period of *Study 1218.18-U09-2458-02*, the mean daily dose of metformin was 1781.1 mg in the placebo group, and 1776.7 mg in the linagliptin group.

SU background doses

The study protocol of the triple combination *Study 1218.18-U09-2458-02* did not specify the kind of SU to be used together with metformin as background therapy. As a consequence, the patients in Study 1218.18-U09-2458-02 used different kinds of SUs as background therapy. A categorisation into SU background dose categories would therefore not be meaningful. However, the trade names and international non proprietary names (INNs) of the SUs and the dose taken at baseline are available. The most frequently used SUs (INN /daily dose taken by more than 5% of patients) were glimepiride 4 mg (9.2%), glibenclamide 15 mg (8.1%), glibenclamide 10 mg (7.5%), gliclazide 60 mg (6.4%), glimepiride 6 mg (6.4%), glimepiride 8 mg (5.4%) and gliclazide 120 mg (5.2%).

BI disagrees with the Delegate's comment that the durability effect of linagliptin is short. The majority of patients in Study 1218.18-U09-2458-02, continued into the open label extension Study 1218.40, hence the Australian submission contains efficacy data for linagliptin patients from Study 1218.18-U09-2458-02 for over 1 year. The efficacy response observed in linagliptin patients was sustained, and at Week 54 was observed to be -0.69% change from baseline HbA1c.

8. Safety

The numbers of cases described in the US PI were the total number of cases that were identified in the linagliptin clinical program. This data was submitted by BI to the FDA.

Cases of pancreatitis were identified using the narrow Standardized MedDRA[20] Query (SMQs): MedDRA 12.1 'acute pancreatitis' and the MedDRA PT 'chronic pancreatitis'. In placebo-controlled trials, no cases of pancreatitis were identified in the placebo groups. In

[20] The Medical Dictionary for Regulatory Activities (MedDRA).

total, 8 cases of pancreatitis (4 cases of chronic pancreatitis, 3 cases of acute pancreatitis and one case of pancreatitis), were identified in the linagliptin group from all studies (placebo controlled, active controlled and open label studies).

9. The sponsor also commented on the PI changes proposed by TGA.

Advisory Committee Considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, agreed with the Delegate's proposal.

The ACPM advised the following:

Efficacy

The data submitted demonstrate linagliptin is superior to placebo as monotherapy; that linagliptin when added to metformin, sulphonylurea or pioglitazone is superior to treatment where placebo is added to these products; and that linagliptin + metformin + sulphonylurea is superior to placebo + metformin + sulphonylurea. It was noted, however, that glimepiride + metformin is superior to linagliptin + metformin. No data were provided on the sequence of these therapies therefore these studies do not necessarily relate to clinical treatment protocols.

The Committee noted that the sponsor is no longer requesting use with thiazolidinediones in light of the poor trial design issues in the only study submitted with this product group.

The Committee was not supportive of the request for monotherapy where patients are metformin intolerant. The ACPM was concerned that the safety and efficacy data submitted refer only to short term use, whereas patients may well use the product for a considerable period. The maximum monotherapy trial was only for 24 weeks. The long term study on those with renal impairment, which was submitted in the pre ACPM response, requires evaluation by the TGA in order that the monotherapy indication can be considered.

There are no data that linagliptin is an appropriate therapy compared to sulphonylurea monotherapy in the metformin intolerant. The comparator study against glimepiride suggests that it is likely to be less efficacious; however, it is reasonable to consider monotherapy with linagliptin if there is renal impairment which contraindicates use of metformin.

Safety

There does not appear to be an increase in adverse events, including renal, cardiovascular or hepatic adverse events, compared to placebo but minor infections are increased in some studies. Some increases in triglyceride and in amylase and uric acid levels were reported.

The Committee noted the identified risks of hypoglycaemia and pancreatitis in the RMP and the potential risk of exfoliative skin reactions. The sponsor's agreement to submit cardiovascular event updates to the TGA was considered appropriate.

The dose finding studies suggest the 5 mg dose proposed is appropriate.

The presented data supports the following indication:

Trajenta is indicated in adult patients with Type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, as add on to metformin, sulphonylurea, or metformin plus sulphonylurea.

The Committee was in agreement with the sponsor's pre ACPM response that any change in treatment due to an inadequate response after 3 months should be left to the treating doctor.

The ACPM advised that, in addition to the evidence provided for the safety and efficacy of linagliptin (Trajenta), the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA would support the safe and effective use of this product.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Trajenta (linagliptin) 5 mg film coated tablet blister pack for oral administration indicated for:

> *Trajenta is indicated in adult patients with Type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, as add on to metformin, sulphonylueras or metformin plus sulphonylueras.*

Attachment 1. Product Information

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

TRAJENTA®
(Linagliptin)

NAME OF THE MEDICINE

Active ingredient: Linagliptin

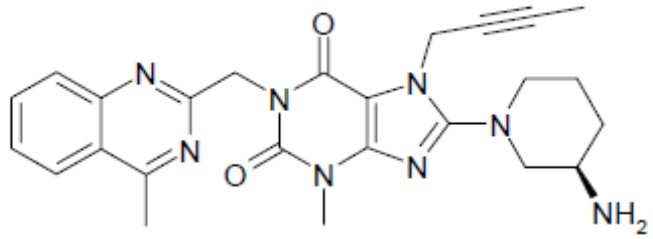
Chemical name: 1H-Purine-2,6-dione, 8-[(3R)-3-amino-1-piperidinyl]-7-(2-butyn-1-yl)-3,7-dihydro-3-methyl-1-[(4-methyl-2-quinazolinyl)methyl]-

Molecular formula: $C_{25}H_{28}N_8O_2$

CAS number: 668270-12-0

Molecular weight: 472.54

Structural formula:



DESCRIPTION

Linagliptin is a white to yellowish, not or only slightly hygroscopic solid substance. It is very slightly soluble in water. Linagliptin is soluble in methanol, sparingly soluble in ethanol, very slightly soluble in isopropanol and very slightly soluble in acetone. Dissociation Constants: pKa_1 = 8.6; pKa_2 = 1.9. Partition Co-efficient: Log P = 1.7 (free base); Log D (pH 7.4) = 0.4.

TRAJENTA are film-coated tablets for oral administration containing 5 mg linagliptin.

Excipients: Each TRAJENTA tablet also contains starch - pregelatinised maize, starch - maize, mannitol, copovidone, magnesium stearate and the colouring agent Opadry Pink 02F34337.

PHARMACOLOGY

Pharmacotherapeutic group: DPP-4 inhibitor, ATC code: A10BH05

Pharmacodynamics

Linagliptin is an inhibitor of the enzyme DPP-4 (Dipeptidyl peptidase 4), an enzyme which is involved in the inactivation of the incretin hormones GLP-1 and GIP (glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide). These hormones are rapidly degraded by the enzyme DPP-4. Both incretin hormones are involved in the physiological regulation of glucose homeostasis. Incretins are secreted at a low basal level throughout the day and levels rise immediately after meal intake. GLP-1 and GIP increase insulin biosynthesis and secretion from pancreatic beta cells in the presence of normal and elevated blood glucose levels. Furthermore GLP-1 also reduces glucagon secretion from pancreatic alpha cells, resulting in a reduction in hepatic glucose output. Linagliptin binding to DPP-4 is reversible but long lasting and thus leads to a sustained increase and a prolongation of active incretin levels. *In vitro*, linagliptin inhibits

DPP-4 with nanomolar potency and exhibits a >10000 fold selectivity versus DPP-8 or DPP-9 activity.

Pharmacokinetics

The pharmacokinetics of linagliptin has been extensively characterised in healthy subjects and patients with type 2 diabetes. After oral administration of a 5 mg dose to healthy volunteer patients, linagliptin was rapidly absorbed, with peak plasma concentrations (median T_{max}) occurring 1.5 hours post-dose.

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 the drug. The effective half-life for accumulation of linagliptin, as determined from oral administration of multiple doses of 5 mg linagliptin, is approximately 12 hours. After once-daily dosing, steady-state plasma concentrations of 5 mg linagliptin are reached by the third dose. Plasma area under the curve (AUC) of linagliptin increased approximately 33% following 5 mg doses at steady-state compared to the first dose. The intra-subject and inter-subject coefficients of variation for linagliptin AUC were small (12.6% and 28.5%, respectively). Plasma AUC of linagliptin increased in a less than dose-proportional manner. The pharmacokinetics of linagliptin was generally similar in healthy subjects and in patients with type 2 diabetes.

Absorption

The absolute bioavailability of linagliptin is approximately 30%. Because co-administration of a high-fat meal with linagliptin had no clinically relevant effect on the pharmacokinetics, linagliptin may be administered with or without food.

In vitro studies indicated that linagliptin is a substrate of P-glycoprotein and of CYP3A4. Ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, led to a two-fold increase in exposure (AUC) and multiple co-administration of linagliptin with rifampicin, a potent inducer of P-glycoprotein and CYP3A, resulted in an approximate 40% decreased linagliptin steady-state AUC, presumably by increasing/decreasing the bioavailability of linagliptin by inhibition/induction of P-glycoprotein.

Distribution

As a result of tissue binding, the mean apparent volume of distribution at steady state following a single 5 mg intravenous dose of linagliptin to healthy subjects is approximately 1110 litres, indicating that linagliptin extensively distributes to the tissues. Plasma protein binding of linagliptin is concentration-dependent, decreasing from about 99% at 1 nmol/L to 75-89% at ≥ 30 nmol/L, reflecting saturation of binding to DPP-4 with increasing concentration of linagliptin. . At the peak plasma concentration in humans at 5 mg/day, approximately 10% of linagliptin is unbound.

Metabolism

Following a [^{14}C]-linagliptin oral 10 mg dose, approximately 5% of the radioactivity was excreted in urine. Metabolism plays a subordinate role in the elimination of linagliptin. One main metabolite with a relative exposure of 13.3% of linagliptin at steady state was detectedand was found to be pharmacologically inactive and thus does not contribute to the plasma DPP-4 inhibitory activity of linagliptin.

Elimination

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.

Pharmacokinetics in special patient groups:

Pharmacokinetics in children: Studies characterising the pharmacokinetics of linagliptin in paediatric patients have not been performed.

Pharmacokinetics in the elderly: 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 78 years) had comparable plasma concentrations of linagliptin compared to younger subjects.

Body Mass Index (BMI): No dosage adjustment is necessary based on BMI. Body mass index had no clinically relevant effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data.

Gender: No dosage adjustment is necessary based on gender. Gender had no clinically relevant effect on the pharmacokinetics of linagliptin based on a population pharmacokinetic analysis of Phase I and Phase II data.

Race: No dosage adjustment is necessary based on race. 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-American, 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.

Pharmacokinetics in patients with renal impairment: A multiple-dose, open-label study was conducted to evaluate the pharmacokinetics of linagliptin (5 mg dose) in patients with varying degrees of chronic renal insufficiency compared to normal healthy control subjects. The study included patients with renal insufficiency classified on the basis of creatinine clearance as mild (50 to < 80 mL/min), moderate (30 to < 50 mL/min), and severe (< 30 mL/min), as well as patients with end stage renal disease (ESRD) on haemodialysis. In addition, patients with type 2 diabetes mellitus and severe renal impairment (< 30 mL/min) were compared to patients with type 2 diabetes mellitus and normal renal function. Creatinine clearance was measured by 24-hour urinary creatinine clearance measurements or estimated from serum creatinine based on the Cockcroft-Gault formula: CrCl = [140 - age (years)] x weight (kg) {x 0.85 for female patients} [72 x serum creatinine (mg/dL)]. Under steady-state conditions, linagliptin exposure in patients with mild renal impairment was comparable to healthy subjects. In moderate renal impairment, a moderate increase in exposure of about 1.7 fold was observed compared with control. Exposure in patients with type 2 diabetes mellitus and severe renal insufficiency was increased by about 1.4 fold compared to patients with type 2 diabetes mellitus and normal renal function. Steady-state predictions for AUC of linagliptin in patients with ESRD indicated comparable exposure to that of patients with moderate or severe renal impairment. In addition, linagliptin is not expected to be eliminated to a therapeutically significant degree by haemodialysis or peritoneal dialysis. Therefore, no dosage adjustment of linagliptin is necessary in patients with any degree of renal insufficiency. In addition, mild renal insufficiency had no effect on linagliptin pharmacokinetics in patients with type 2 diabetes mellitus as assessed by population pharmacokinetic analyses.

Pharmacokinetics in patients with hepatic impairment: In patients with mild moderate and severe hepatic insufficiency (according to the Child-Pugh classification), mean AUC and C_{max} of linagliptin were similar to healthy matched controls following administration of multiple 5 mg doses of linagliptin. No dosage adjustment for linagliptin is necessary for patients with mild, moderate or severe hepatic insufficiency.

CLINICAL TRIALS

Eight phase III randomised controlled trials involving 5,239 patients with type 2 diabetes, of which 3,319 were treated with linagliptin were conducted to evaluate efficacy and safety. These studies had 929 patients of 65 years and over who were on linagliptin. There were also 1,238 patients with mild renal impairment, and 143 patients with moderate renal impairment on linagliptin. Linagliptin once daily produced clinically significant improvements in glycaemic control, with no clinically relevant change in body weight. Reductions in HbA1c were seen across different subgroups including gender, age, race, renal impairment and body mass index (BMI), with a higher baseline HbA1c being associated with a greater reduction in HbA1c.

Linagliptin as add on to metformin therapy

The efficacy and safety of linagliptin in combination with metformin was evaluated in a double blind placebo-controlled study of 24 weeks duration. Linagliptin provided significant improvements in HbA1c (-0.64% change compared to placebo) from a mean baseline HbA1c of 8%. Linagliptin also showed significant improvements in fasting plasma glucose (FPG), 2-hour post-prandial glucose (PPG) and a greater portion of patients achieved a target HbA1c of < 7.0%, compared to placebo. The observed incidence of hypoglycaemia in patients treated with linagliptin was similar to placebo. Body weight did not differ significantly between the groups.

Linagliptin as add on to sulphonylurea therapy

The efficacy and safety of linagliptin in combination with sulphonylurea was evaluated in a double blind placebo-controlled study of 18 weeks duration. Linagliptin provided significant improvements in HbA1c (-0.47% change compared to placebo) from a mean baseline HbA1c of 8.6%. Linagliptin also showed significant improvements in patients achieving a target HbA1c of < 7.0%. Body weight did not differ significantly between the groups.

Linagliptin as add on to a combination of metformin and sulphonylurea therapy

A placebo controlled study of 24 weeks in duration was conducted to evaluate the efficacy and safety of linagliptin 5 mg to placebo in patients not sufficiently treated with a combination with metformin and a sulphonylurea. Linagliptin provided significant improvements in HbA1c (-0.62% change compared to placebo) from a mean baseline HbA1c of 8.14%. Linagliptin also showed significant improvements in patients achieving a target HbA1c of < 7.0%, and also for fasting plasma glucose (FPG), and 2-hour post-prandial glucose (PPG), compared to placebo. Body weight did not differ significantly between the groups.

Linagliptin 12 month data, as add onto metformin in comparison with glimepiride

In a study comparing the efficacy and safety of the addition of linagliptin 5 mg or glimepiride (a sulphonylurea agent) in patients with inadequate glycaemic control on metformin monotherapy, both linagliptin and glimepiride reduced HbA1c from baseline (-0.4% for linagliptin, -0.6% for glimepiride) from a baseline mean of 7.7% after 52 weeks of treatment. In this study, the proinsulin to insulin ratio, a marker of efficiency of insulin synthesis and release, showed a statistically significant improvement with linagliptin compared with glimepiride treatment. The incidence of hypoglycaemia in the linagliptin group (5.3%) was significantly lower than that in the glimepiride group (30.3%). Patients treated with linagliptin exhibited a significant mean decrease from baseline in body weight compared to a significant weight gain in patients administered glimepiride (-1.02 versus +1.46 kg).

Cardiovascular risk

In a prospective, pre-specified meta-analysis of independently adjudicated cardiovascular events from 8 phase III clinical studies involving 5,239 patients with type 2 diabetes, linagliptin treatment was not associated with an increase in cardiovascular risk. The primary endpoint, the composite of: the occurrence or time to first occurrence of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalisation for unstable angina, was significantly lower for linagliptin versus combined active and placebo comparators [Hazard ratio 0.34 (95% confidence interval 0.17;0.70)].

INDICATIONS

TRAJENTA is indicated in adult patients with type 2 diabetes mellitus to improve glycaemic control in conjunction with diet and exercise, as add on to metformin, sulphonylureas or metformin plus sulphonylureas.

CONTRAINDICATIONS

Hypersensitivity to the active ingredient or to any of the excipients.

PRECAUTIONS

General

TRAJENTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypoglycaemia

Linagliptin alone showed a comparable incidence of hypoglycaemia to placebo.

In clinical trials of linagliptin as part of combination therapy with agents not known to cause hypoglycaemia (metformin), rates of hypoglycaemia reported with linagliptin were similar to rates in patients taking placebo.

Sulphonylureas are known to cause hypoglycaemia. Therefore, caution is advised when linagliptin is used in combination with a sulphonylurea. A dose reduction of the sulphonylurea may be considered.

The use of linagliptin in combination with insulin has not been adequately studied.

Effects on ability to drive and use machines

No studies on the effect on the ability to drive and use machines have been performed. If patients experience dizziness, they should avoid potentially hazardous tasks such as driving or operating machinery.

Effects on Fertility

No studies on the effect on human fertility have been conducted for TRAJENTA. No adverse effects on fertility were observed in male and female rats given linagliptin orally up to the highest dose of 240 mg/kg/day (yielding approximately 1000 times the plasma AUC obtained in patients at the maximum recommended human dose [MRHD] of 5 mg/dayprior to and throughout mating.

Use in Pregnancy (Category B3)

There are limited data from the use of linagliptin in pregnant women. Linagliptin was shown to cross the placenta in rats and rabbits.

In animal embryofetal development studies, linagliptin was shown to be not teratogenic in rats at oral doses up to 240 mg/kg/day (approximately 1000 times the exposure in patients at the MRHD, based on plasma AUC) and up to 150 mg/kg/day in the rabbit (approximately 2000 times human exposure). However, postimplantation loss was increased in both species at these upper dose levels (together with maternotoxicity), and there was an increase in runts and a slight increase in the incidence of fetal visceral variations in the rabbit. No adverse effects on embryofetal development were observed at up to 30 mg/kg/day in the rat (50 times human exposure) and up to 25 mg/kg/day in the rabbit (78 times human exposure). However, as animal studies are not always predictive of human response, as a precautionary measure, it is preferable to avoid the use of TRAJENTA during pregnancy.

Use in Lactation

Linagliptin and its metabolites were shown to be readily excreted in the milk of lactating rats. A risk to the newborns / infants cannot be excluded. TRAJENTA should not be used during breast-feeding.

Paediatric use

TRAJENTA is not recommended for use in children below 18 years due to lack of data on its safety and efficacy.

Carcinogenicity

No evidence of carcinogenicity was observed with linagliptin in 2-year studies in mice and rats given oral doses up to 80 mg/kg/day and 60 mg/kg/day, respectively.

These doses correspond to approximately 300- and 400-times the human exposure (plasma AUC) at the MRHD of 5 mg/day.

Genotoxicity

Linagliptin was not mutagenic or clastogenic with or without metabolic activation in the Ames bacterial mutagenicity assay, a chromosomal aberration test in human lymphocytes, and an *in vivo* micronucleus assay in the rat.

INTERACTIONS WITH OTHER MEDICINES

In vitro assessment of drug interactions

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 inhibits P-glycoprotein mediated transport of digoxin with low potency. Based on this result and *in vivo* drug interaction studies, linagliptin is considered unlikely to cause interactions with other P-glycoprotein substrates. However, as linagliptin is a P-glycoprotein substrate, inhibitors/inducers of this transporter may affect linagliptin plasma kinetics.

In vivo assessment of drug interactions

Clinical data described below suggest that the risk for clinically meaningful interactions by co-administered medicinal products is low. No clinically significant interactions requiring dose adjustment were observed. Linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glibenclamide, simvastatin, pioglitazone, warfarin, digoxin or oral contraceptives providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C9, CYP2C8, P-glycoprotein, and organic cationic transporter (OCT).

Metformin: Co-administration of multiple three-times-daily doses of 850 mg metformin with a supratherapeutic dose of 10 mg linagliptin once daily did not clinical meaningfully alter the pharmacokinetics of linagliptin or metformin in healthy volunteers. Therefore, linagliptin is not an inhibitor of OCT-mediated transport.

Sulphonylureas: The steady-state pharmacokinetics of 5 mg linagliptin were not changed by co-administration administration of a single 1.75 mg dose glibenclamide (glyburide) and multiple oral doses of 5 mg linagliptin. However, there was a clinically not relevant reduction of 14% of both AUC and Cmax of glibenclamide. Because glibenclamide is primarily metabolised by CYP2C9, these data also support the conclusion that linagliptin is not a CYP2C9 inhibitor. Clinically meaningful interactions would not be expected with other sulphonylureas (e.g. glipizide, tolbutamide and glimepiride) which, like glibenclamide, are primarily eliminated by CYP2C9.

Ritonavir: A study was conducted to assess the effect of ritonavir, a potent inhibitor of P-glycoprotein and CYP3A4, on the pharmacokinetics of linagliptin. Co-administration of a single 5 mg oral dose of linagliptin and multiple 200 mg oral doses of ritonavir increased the AUC and Cmax of linagliptin approximately two-fold and three-fold, respectively. Simulations of steady-state plasma concentrations of linagliptin with and without ritonavir indicated that the increase in exposure will not be associated with an increased accumulation. These changes in linagliptin pharmacokinetics were not considered to be clinically relevant. Therefore, clinically relevant interactions would not be expected with other P-glycoprotein or CYP3A4 inhibitors and dose adjustment is not required.

Rifampicin: A study was conducted to assess the effect of rifampicin, a potent inductor of P-glycoprotein and CYP3A4, on the pharmacokinetics of 5 mg linagliptin. Multiple co-administration of linagliptin with rifampicin, resulted in a 39.6% and 43.8% decreased linagliptin steady-state AUC and Cmax and about 30% decreased DPP-4 inhibition at trough. Thus linagliptin in combination with strong P-glycoprotein inducers is expected to be clinically efficacious, although full efficacy might not be achieved.

Digoxin: Co-administration of multiple of 5 mg linagliptin with multiple doses of 0.25 mg digoxin had no effect on the pharmacokinetics of digoxin in healthy volunteers. Therefore, linagliptin is not an inhibitor of P-glycoprotein-mediated transport *in vivo*.

Warfarin: Multiple daily doses of 5 mg linagliptin did not alter the pharmacokinetics of S(-) or R(+) warfarin, a CYP2C9 substrate, showing that linagliptin is not an inhibitor of CYP2C9.

Simvastatin: Multiple daily doses of 10 mg linagliptin (supratherapeutic) had a minimal effect on the steady state pharmacokinetics of simvastatin, a sensitive CYP3A4 substrate, in healthy volunteers. Following administration of 10 mg linagliptin concomitantly with 40 mg of simvastatin daily for 6 days, the plasma AUC of simvastatin was increased by 34%, and the plasma Cmax by 10%. Therefore, linagliptin is considered to be a weak inhibitor of CYP3A4-mediated metabolism, and dosage adjustment of concomitantly administered substances metabolised by CYP3A4 is considered unnecessary.

Oral Contraceptives: Co-administration with 5 mg linagliptin did not alter the steady-state pharmacokinetics of levonorgestrel or ethinylestradiol.

The absolute bioavailability of linagliptin is approximately 30%. Because co-administration of a high-fat meal with linagliptin had no clinically relevant effect on the pharmacokinetics, linagliptin may be administered with or without food.

ADVERSE EFFECTS

Adverse Events in Clinical Trials

The safety of TRAJENTA has been evaluated overall in 4,687 patients with type 2 diabetes mellitus of which 4,040 patients received the target dose of 5 mg.

In placebo-controlled studies, 3,749 patients were included and 2,566 patients were treated with the therapeutic dose of 5 mg linagliptin. 2,360 patients were exposed to linagliptin 5 mg once daily for $\geq$ 12 weeks.

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

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

TRAJENTA 5 mg once daily was studied as monotherapy in two placebo-controlled trials of 18- and 24 weeks duration. Five placebo-controlled studies investigated linagliptin in combination with other oral anti-glycaemic agents: two with metformin (12- and 24-weeks treatment duration); one with a sulfonylurea (18-weeks treatment duration); one with metformin and sulfonylurea (24-week treatment duration); and one with pioglitazone (24-week treatment duration). In placebo-controlled clinical studies, adverse reactions that occurred in ³ 5% of patients receiving TRAJENTA (n = 2566) and more commonly than in patients given placebo (n = 1183) included nasopharyngitis (5.8% vs 5.5%).

Adverse reactions reported in ≥ 2% of patients treated with TRAJENTA 5 mg daily as monotherapy or in combination with sulfonylurea or metformin and at least 2-fold more commonly than in patients treated with placebo are shown in Table 1.

Table 1 Adverse Reactions Reported in ≥ 2% of Patients Treated with TRAJENTA and at Least 2-Fold Greater than with Placebo in Placebo-Controlled Clinical Studies of TRAJENTA Monotherapy or Combination Therapy

	Linagliptin + Metformin # n (%)		Linagliptin + Sulfonylurea n (%)		Linagliptin + Metformin + Sulfonylurea n (%)	
SOC Adverse reaction	TRAJENTA n = 590	Placebo n = 248	TRAJENTA n = 161	Placebo n = 84	TRAJENTA n = 791	Placebo n = 263
Infections & infestations						
Nasopharyngitis	--	--	7 (4.3)	1 (1.2)	--	--
Metabolism & nutrition disorders						
Hyperlipidaemia	--	--	--	--	--	--
Hypertriglyceridaemia†	--	--	4 (2.4)	0 (0.0)	--	--
Respiratory, thoracic & mediastinal disorders						
Cough	--	--	--	--	19 (2.4)	3 (1.1)
Investigations						
Weight increased	--	--	--	--	--	--

Pooled data from 2 studies
† Includes reports of hypertriglyceridemia (n = 2; 1.2%) and blood triglycerides increased (n = 2; 1.2%)

Following 52 weeks treatment in a controlled study comparing linagliptin with glimepiride in which all patients were also receiving metformin, adverse reactions reported in ≥ 5% patients treated with linagliptin (n = 776) and more frequently than in patients treated with a sulfonylurea (n = 775) were arthralgia (5.7% vs 3.5%), back pain (6.4% vs 5.2%), and headache (5.7% vs 4.2%).

Other adverse reactions reported in clinical studies with treatment of TRAJENTA were hypersensitivity (e.g., urticaria, angioedema, localised skin exfoliation, or bronchial hyperreactivity) and myalgia. In the clinical trial program, pancreatitis was reported in 8 of 4687 patients (4311 patient years of exposure) while being treated with TRAJENTA compared with 0 of 1183 patients (433 patient years of exposure) treated with placebo. Three additional cases of pancreatitis were reported following the last administered dose of linagliptin.

Hypoglycaemia

In the placebo-controlled studies, 195 (7.6%) of the total 2566 patients treated with TRAJENTA 5 mg reported hypoglycaemia compared to 49 patients (4.1%) of 1183 placebo treated patients. The incidence of hypoglycaemia was similar to placebo when linagliptin was administered as monotherapy or in combination with metformin or with pioglitazone. When linagliptin was administered in combination with metformin and a sulfonylurea, 181 of 791 (22.9%) of patients reported hypoglycaemia compared with 39 of 263 (14.8%) of patients administered placebo in combination with metformin and a sulfonylurea.

Laboratory Tests

Changes in laboratory findings were similar in patients treated with TRAJENTA 5 mg compared to patients treated with placebo. Changes in laboratory values that occurred more frequently in the TRAJENTA group and ³ 1% more than in the placebo group were increases in uric acid (1.3% in the placebo group, 2.7 % in the TRAJENTA group).

DOSAGE AND ADMINISTRATION

Adults: The recommended dose is 5 mg once daily.

TRAJENTA can be taken with or without a meal at any time of the day.

If a dose is missed, it should be taken as soon as the patient remembers. A double dose should not be taken on the same day.

The elderly: No dose adjustment is necessary.

Children: TRAJENTA is not recommended for use in children below 18 years due to lack of data on safety and efficacy.

Patients with renal impairment: No dosage adjustment is required for patients with renal impairment.

Patients with hepatic impairment: No dosage adjustment is required for patients with hepatic impairment.

OVERDOSAGE

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia)

Symptoms

During controlled clinical trials in healthy subjects, single doses of up to 600 mg linagliptin (equivalent to 120 times the recommended dose) were well tolerated. There is no experience with doses above 600 mg in humans.

Treatment

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g. remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring and institute clinical measures as required.

PRESENTATION AND STORAGE CONDITIONS

TRAJENTA tablets are round, light red, biconvex, bevel-edged film-coated tablets, one side debossed with the Boehringer Ingelheim company logo and on the other side debossed with ‘D5’. Each tablet contains 5 mg linagliptin.

TRAJENTA is available in blister packs containing 10 (sample) and 30 tablets.

Store below 30°C

NAME AND ADDRESS OF THE SPONSOR

Boehringer Ingelheim Pty Limited

ABN 52 000 452 308

78 Waterloo Road

North Ryde NSW 2113

POISON SCHEDULE OF THE MEDICINE

S4 – Prescription Only Medicine

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG):

1 November 2011

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
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