Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for Linagliptin / Metformin HCL

Proprietary Product Name: Trajentamet / Jentadeuto / Trametfo / Thundrion

Sponsor: Boehringer Ingelheim Pty Ltd

First round evaluation: 25 July 2012

Second round evaluation: 22 November 2012

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The 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 <http://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Contents

List of abbreviations

Abbreviation	Meaning
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine transaminase (SGPT)
ANCOVA	Analysis of covariance
ANOVA	analysis of variance
aPTT	Activated partial thromboplastin time
ASA	Acetylsalicylic acid
AST	Aspartate transaminase (SGOT)
AUEC	Area under the glucose concentration curve
BI1356	Linagliptin
BID	Administered twice daily
BLQ	Below limit of quantification
BMI	Body mass index (weight divided by height squared)

Abbreviation	Meaning
BP	Blood pressure
CD1750	The major metabolite of linagliptin
CI	Confidence interval
CK	Creatinine kinase
Cl	Chloride
Cmax	Maximum measured concentration of the analyte in plasma
CNS	Central nervous system
CRP	C-reactive protein
CYP	Cytochrome P 450
DPP-4	Dipeptidyl-Peptidase IV
ECG	Electrocardiogram
FAS	Full analysis set
FDA	Food and Drug Administration
FDC	Fixed dose combination
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GGT	Gamma-glutamyl-transferase
GI	Gastrointestinal
GIP	Gastric inhibitory polypeptide
GLDH	Glutamate Dehydrogenase
Glim	Glimepiride
GLP-1	Glucagon-like peptide 1
gMean	geometric mean
HbA1c	Glycosylated haemoglobin A1c
HOMA	Homeostasis model assessment
HR	Heart rate

Abbreviation	Meaning
ICH	International Committee on Harmonisation
INR	International normalised ratio
IRB	Institutional Review Board
ISR	Insulin secretion rate
IVRS/IWRS	Interactive voice/web response system
LDH	Lactic dehydrogenase
Lina	Linagliptin
LLN	Lower limit of normal
LOCF	Last observation carried forward
MedDRA	Medical Dictionary for Drug Regulatory Affairs
Met	Metformin
MI	Myocardial infarction
MTT	Meal tolerance test
N	Number
NONS	Non-switched set
OAD	Oral antidiabetic agent
OC	Observed cases
OLS	Open-label arm of study
OR	Odds ratio
PD	Pharmacodynamic
PK	Pharmacokinetic
PO	per oral
PPG	Post -prandial glucose
PPS	Per protocol set
RS	Randomised set
SAE	Serious adverse event

Abbreviation	Meaning
SAF-Cx	Safety grouping from the linagliptin/metformin FDC dossier
SAF-M1	Updated safety grouping from the original linagliptin monotherapy dossier
SAF-x	Safety grouping from the original linagliptin monotherapy dossier
SC	Subcutaneous
SU	Sulphonylurea
SWS	Switched Set
T2DM	T2DM
TIA	Transient ischaemic attack
TS	Treated Set
t1/2	Terminal half-life of the analyte in plasma
tmax	Time from dosing to the maximum concentration of the analyte in plasma
tmin	Time from dosing to the minimum concentration of the analyte in plasma
ULN	Upper limit of normal
US	United States

1. Clinical rationale

More than 50% of Australians are overweight or obese and at least 4% of the population are known to have T2DM. The prevalence is much higher in the indigenous population. Three diabetics in five have cardiovascular disease, in particular coronary artery disease, and microvascular complications resulting in nephropathy, neuropathy and retinopathy. However, long-term intervention studies such as the UK PDS in T2DMs[1] and the DCCT in type 1 diabetes[2] have shown that outcomes such as retinopathy and nephropathy occur less frequently in patients with optimal glycaemic control.

Diabetes is the result of a complex metabolic dysfunction involving insulin resistance, impaired insulin secretion and increased glucose production. Linagliptin and other Dipeptidyl-Peptidase IV (DPP-4) inhibitors[3] lower blood glucose by extending the circulating half-life of glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). Both hormones increase insulin production and secretion and lower plasma glucose after a meal by enhancing glucose-stimulated insulin release, and by limiting glucagon secretion which slows gastric emptying and

[1] UK Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 1998; 352, 837-853
[2] The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993; 329(14), 977-986
[3] Elrishi MA, et al. The dipeptidyl-peptidase-4 (DPP-4) inhibitors: a new class of oral therapy for patients with T2DM. Pract Diabetes Int 2007; 24 (9), 474-482

increases satiety. However, the risk of hypoglycaemia is low because GLP-1 and GIP activity cease when plasma glucose levels approach the lower limit of normal. GLP-1 also reduces hepatic glucose output by reducing glucagon secretion from islet alpha-cells. Furthermore, in animal models islet beta-cell function is conserved although this has not been confirmed in man.

Metformin is a biguanide which has been in clinical use for 50 years.[4] It lowers basal and postprandial glucose but it does not stimulate insulin secretion. It is thought to act by inhibiting hepatic gluconeogenesis and glycogenolysis, increasing glucose uptake in muscle and delaying intestinal glucose absorption. It reduces glycosylated HbA1c but it does not cause weight gain or hypoglycaemia. It also reduces total cholesterol, low-density lipoprotein (LDL) and triglycerides independently of glucose control.

Diabetes is progressive and patients who initially respond to one OAD often require combination therapy with two or three Oral antidiabetic agent (OAD) and/or insulin. The combination of linagliptin and metformin reduces fasting plasma glucose (FPG) and HbA1c more than either component alone. A fixed dose combination (FDC) decreases the daily number of medications and may be expected to improve compliance in patients treated with oral antidiabetic agents.[5] It is proposed that the FDC be used alone or in combination with a sulphonylurea if required.

2. Contents of the clinical dossier

2.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Seven clinical pharmacology studies, including 7 that provided pharmacokinetic data and 1 that provided pharmacodynamic data. No population pharmacokinetic analyses.
- One dose ranging study (1218.6), a pivotal Phase III efficacy and safety study (1218-46) and 4 supporting studies.

2.2. Paediatric data

The submission did not include paediatric data.

2.3. Good clinical practice (GCP)

All studies were conducted in accordance with International Conference on Harmonization (ICH) GCP.

3. Pharmacokinetics

3.1. Studies providing pharmacokinetic data

Table 1 below shows the studies relating to each pharmacokinetic topic and the location of each study summary.

[4] Davidson MB, Peters AL. An overview of metformin in the treatment of T2DM. Am J Med 1997; 102(1), 99-110
[5] Melikian C, et al. Adherence to oral antidiabetic therapy in a managed care organisation: a comparison of monotherapy, combination therapy, and fixed-dose combination therapy. Clin Ther 2002; 24(3), 460-467

Table 1. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK - Single dose	ND	-
	- Multi-dose	ND	-
	Bioequivalence† - Single dose	Study 1288.1	Bioequivalence of a 2.5 mg linagliptin/1000 mg Metformin FDC tablet compared with single tablets of Linagliptin 2.5 mg and metformin 1000 mg
		Study 1288.2	Bioequivalence of a 2.5 mg linagliptin/500 mg metformin FDC tablet compared to free combination of linagliptin 2.5 mg and metformin 500 mg tablets.
		Study 1288.3	Bioequivalence of a 2.5 mg linagliptin/850 mg metformin FDC tablet compared to co-administration of free linagliptin 2.5 mg and metformin 850 mg tablets.
		Study 1288.6	Relative bioavailability of two different batches of a 2.5 mg linagliptin/1000 mg metformin FDC tablets
		Study 1218.57	Bioequivalence of BMS Glucophage® tablets and Merck Glucophage® tablets in the strengths of 1000 mg and 500 mg.
	Food effect	Study 1288.4	Investigate the effect of food on the relative bioavailability of a 2.5 mg linagliptin+1000 mg metformin FDC tablet.
PK in special populations	Target population § -Single dose	ND	-
	- Multi-dose	ND	-
	Hepatic impairment	ND	-
	Renal impairment	ND	-
	Neonates/infants/children/adole	ND	-

PK topic	Subtopic	Study ID	*
	scents		
	Elderly	ND	-
	Afro-American	Study 1218.55	Investigate the PK of 5 mg Linagliptin administered orally in patients with T2DM of African American origin.
Genetic/gender-related PK	Males vs. females	ND	-
PK interactions	ND	ND	-
Population PK analyses	Healthy subjects	ND	-
	Target population	ND	-
	Other	ND	-

* Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ND No new data was provided by the sponsor.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

3.2. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

3.2.1. Physicochemical characteristics of the active substance

The following information is derived from the Sponsor's summaries in Module 2 of the current submission.

3.2.1.1. Pharmacokinetics in healthy subjects

3.2.1.1.1. Absorption

3.2.1.1.1.1. Sites and mechanisms of absorption

After oral administration of a 5 mg dose, linagliptin (molecular weight 472.54 g/mol) is rapidly absorbed, with peak plasma concentrations occurring 1.5 to 2.5 h post dose (median T_{max}), suggesting predominant absorption in the upper parts of the intestine.

Following a single oral 5 mg dose to healthy subjects, gMean plasma area under the concentration curve from time 0 to 24 h (AUC_{0-24}) of Linagliptin was 139 nM.hr/L and peak plasma concentration (C_{max}) was 8.90 nM/L (Study 1218.25, previous submission).

Data from nonclinical studies (summarised in the sponsor's Pharmacokinetics Written Summary) and two drug-drug interaction trials (Studies 1218.31 and 1218.67, previous submission) with ritonavir and rifampicin indicate that P-glycoprotein (P-gp; ABCB1) mediated efflux governs the overall linagliptin absorption and bioavailability characteristics. In addition, the physico-chemical characteristics of linagliptin in terms of a moderate intrinsic permeability (as assessed by Caco-2 cell assays *in vitro*) and the known cytochrome P450 isozyme CYP3A4

substrate characteristics might also contribute to the incomplete systemic bioavailability of linagliptin.

3.2.1.1.2. Bioavailability

The mono-layer tablet of the intended commercial formulation of linagliptin/metformin was used in the following Phase I clinical Studies 1218.47, 1288.1, 1288.2, 1288.3, and 1288.4.

3.2.1.1.2.1. Absolute bioavailability

The absolute bioavailability of linagliptin after oral (PO) administration of 10 mg is approximately 30% (Study 1218.10; previous submission).

3.2.1.1.2.2. Bioavailability relative to an oral solution or micronised suspension

No new data.

3.2.1.1.2.3. Bioequivalence of clinical trial and market formulations

No new data.

3.2.1.1.2.4. Bioequivalence of different dosage forms and strengths

No new data.

3.2.1.1.2.5. Bioequivalence to relevant registered products

Three studies (1288.1, 1288.2 and 1288.3) examined the bioequivalence of the 2.5 mg linagliptin/1000 mg Metformin FDC tablet, 2.5 mg linagliptin/500 mg metformin FDC and 2.5 mg linagliptin/850 mg metformin FDC tablets compared to the relevant doses of the free Linagliptin and Metformin tablets. The free Linagliptin tablets used in these studies were produced by BI Pharma GmbH & Co, whereas, all three dosage strengths of the free metformin (Glucophage) tablets were obtained from Merck Pharma GmbH. These studies indicated that all three dosage strengths of the FDC formulations were bioequivalent with the relevant doses of free tablets (Tables 2, 3 and 4) in healthy Caucasian subjects.

Table 2. Study 1288.1

Adjusted geometric mean ratio, 90% confidence interval and intrasubject gCV for the pharmacokinetic parameters of linagliptin and metformin relevant for the assessment of bioequivalence

	Adjusted geometric mean ratio (%) FDC/single tablets FDC N=96 single tablets N=93	2-sided 90% confidence interval		Intrasubject gCV (%)
		Lower limit (%)	Upper limit (%)	
Linagliptin 2.5 mg				
AUC_{0-72}	106.5	102.8	110.3	14.5
C_{max}	103.4	100.3	106.7	12.7
Metformin 1000 mg				
$AUC_{0-\infty}$	103.8	100.2	107.4	14.3
AUC_{0-t}	103.9	100.3	107.7	14.6
C_{max}	104.6	100.1	109.2	17.9

For both linagliptin and metformin, the 90% CIs for both AUC and C_{max} were contained within the bioequivalence acceptance range of 80 to 125%. Therefore, bioequivalence of the FDC compared to the single tablets can be concluded.

Table 3. Study 1288.2

Adjusted gMean ratio, 90% confidence interval and intra-subject gCV for the key parameters of linagliptin and metformin

	Adjusted gMean ratio (FDC/single tablets[1]) [%]	2-sided 90% confidence interval		Intra-individual gCV [%]
		Lower limit [%]	Upper limit [%]	
Linagliptin 2.5 mg				
AUC_{0-72}	99.9	96.6	103.3	13.9
C_{max}	98.1	94.4	101.9	16.0
Metformin 500 mg				
$AUC_{0-\infty}$	99.1	96.4	102.0	11.6
AUC_{0-tz}	99.4	96.5	102.3	12.3
C_{max}	97.9	94.4	101.5	14.9

[1] FDC N=94, single tablets N=95

Table 4. Study 1288.3

Adjusted gMean ratio, 90% confidence interval and intra-subject gCV for the key parameters of linagliptin and metformin

	Adjusted gMean ratio (FDC/single tablets[1]) [%]	2-sided 90% confidence interval		Intra-individual gCV [%]
		Lower limit [%]	Upper limit [%]	
Linagliptin 2.5 mg				
AUC_{0-72}	104.0	100.2	108.0	15.4
C_{max}	105.9	102.7	109.3	12.9
Metformin 850 mg				
$AUC_{0-\infty}$	101.2	98.3	104.1	11.8
AUC_{0-tz}	100.8	98.0	103.8	11.9
C_{max}	99.8	96.2	103.6	15.4

[1] FDC: N=95; single tablets: N=94 (linagliptin), N=93 (metformin)

Study 1288.6 identified that two different batches of a 2.5 mg linagliptin/1000 mg metformin FDC tablets were bioequivalent; and Study 1218.57, which examined the bioequivalence of two different dosage strengths of Bristol-Myers Squibb and Merck Metformin tablets, identified that both the 500 mg and 1000 mg tablets of Metformin were bioequivalent. This study was conducted to confirm that the two current formulations of metformin available on the European (Merck) and US (BMS) markets were bioequivalent.

3.2.1.1.2.6. Influence of food

Study 1288.4 investigated the effect of a high fat, high caloric meal on the relative bioavailability of a 2.5 mg linagliptin+1000 mg metformin FDC tablet in healthy Caucasian subjects. Administration of the FDC tablet with a high-fat meal had little effect on linagliptin AUC_{0-72} and C_{max};, gMean AUC_{0-72} of linagliptin was 162 nM.h/L and 164 nM.h/L under fed and fasted conditions, respectively (Tables 5 and 6) and C_{max} was 4.56 and 4.99 nM/L, respectively.

Table 5. Study 1288.4

Key pharmacokinetic parameters of linagliptin after administration of 2.5 mg linagliptin and 1000 mg metformin as FDC tablet with and without food

	Noncompartmental parameters of linagliptin			
	Fed condition (Test) (N=32)		Fasted condition (Reference) (N=32)	
	gMean	gCV [%]	gMean	gCV [%]
AUC_{0-72} [nmol·h/L]	162	20.7	164	21.3
C_{max} [nmol/L]	4.56	19.3	4.99	19.7
t_{max}* [h]	3.00	(1.00-12.00)	3.50	(1.00-8.00)

* for t_{max} the median and range (min-max) are given.

Table 6. Study 1288.4. Comparison of 90% CI of $AUC_{0-¥}$ (metformin), AUC_{0-72h} (linagliptin) and C_{max} (both analytes).

Parameter	Test (fed condition) N	Reference (fasted condition) N	Adjusted gMean ratio test/reference [%]	90% Confidence interval Lower limit [%]	90% Confidence interval Upper limit [%]	Intra-ind. gCV [%]
Linagliptin 2.5 mg						
AUC_{0-72}	32	32	98.7	94.5	103.0	10.1
C_{max}	32	32	91.4	86.2	96.9	13.9
Metformin hydrochloride 1000 mg						
$AUC_{0-\infty}$	32	32	96.0	89.2	103.2	17.3
C_{max}	32	32	81.9	76.8	87.3	15.2

Concomitant administration of a high fat, high caloric meal also had little effect on metformin AUC_{0-inf} (fasted: 12000 ng.h/mL, fed: 11500 ng.h/mL), whereas, it prolonged the time to reach maximum plasma concentrations by about 2 h (median T_{max} increased from 2.00 h to 4.00 h) and lowered the C_{max} by about 18.1% (fasted: 1820 ng/mL; fed: 1490 ng/mL).

3.2.1.1.2.7. Dose proportionality

No new data.

3.2.1.1.2.8. Bioavailability during multiple-dosing

No new data.

3.2.1.1.2.9. Effect of administration timing

No new data.

3.2.1.1.3. Distribution

3.2.1.1.3.1. Volume of distribution

No new data.

3.2.1.1.3.2. Plasma protein binding

No new data.

3.2.1.1.3.3. Erythrocyte distribution

No new data.

3.2.1.1.3.4. Tissue distribution

No new data.

3.2.1.1.4. Metabolism

3.2.1.1.4.1. Interconversion between enantiomers

No new data.

3.2.1.1.4.2. Sites of metabolism and mechanisms/enzyme systems involved

No new data.

3.2.1.1.4.3. Non-renal clearance

No new data.

3.2.1.1.4.4. Metabolites identified in humans

Active metabolites

No new data.

Other metabolites

No new data.

Pharmacokinetics of metabolites

No new data.

Consequences of genetic polymorphism

No new data.

3.2.1.1.5. Excretion

3.2.1.1.5.1. Routes and mechanisms of excretion

No new data.

3.2.1.1.5.2. Mass balance studies

No new data.

3.2.1.1.5.3. Renal clearance

No new data.

3.2.1.2. Pharmacokinetics in the target population

No new data.

3.2.1.3. Pharmacokinetics in other special populations

3.2.1.3.1. Pharmacokinetics in subjects with impaired hepatic function

No new data.

3.2.1.3.2. Pharmacokinetics in subjects with impaired renal function

No new data.

3.2.1.3.3. Pharmacokinetics according to age

No new data.

3.2.1.3.4. Pharmacokinetics related to genetic factors

No new data.

3.2.1.3.5. Pharmacokinetics in Afro-American subjects

Study 1218.55 investigated the PK of 5 mg Linagliptin in patients with T2DM of African American origin. In these subjects, Linagliptin was rapidly absorbed with median T_{max} values of 1.5 h following a single dose and at steady state. Steady state for linagliptin was achieved following the third to fifth dose. At steady state the $AUC_{\tau,ss}$ was 194 nmol.h/L and $C_{max,ss}$ (at steady-state) was 16.4 nmol/L were observed. Geometric mean single dose exposure as measured by C_{max} and AUC_{0-24} was 10.9 nmol/L and 137 nmol.h/L, respectively. The accumulation half-life was low, with accumulation factors of 1.40 and 1.49 for AUC and C_{max}, respectively.

3.2.1.4. Pharmacokinetic interactions

3.2.1.4.1. Pharmacokinetic interactions demonstrated in human studies

No new data.

3.2.1.4.2. Clinical implications of in vitro findings

No new data.

3.3. Evaluator's overall conclusions on pharmacokinetics

All three dosage strengths of the FDC formulation (2.5 mg linagliptin/1000 mg Metformin FDC tablet, 2.5 mg linagliptin/500 mg metformin FDC and 2.5 mg linagliptin/850 mg metformin FDC tablets) were bioequivalent with the relevant doses of free tablets of linagliptin and metformin, which were produced by BI Pharma and Merck, respectively. Across all three studies, the 90% CIs for linagliptin AUC and C_{max} ranged from 97 to 110 and 94 to 102, respectively, whereas, for metformin AUC and C_{max} the 90% CIs ranged from 96 to 107 and 94 to 109, respectively. In addition, the US (BMS) and European (Merck) formulations of the free metformin tablets were bioequivalent.

A high fat, high caloric meal had little effect on Linagliptin AUC and C_{max} and the AUC of Metformin, whereas, it prolonged metformin T_{max} by about 2 h and lowered the Metformin C_{max} by about 18.1%.

In Afro-American subjects with T2DM the T_{max} following 5 mg oral linagliptin was 1.5 h and at steady state the $AUC_{\tau,ss}$ was 194 nmol.h/L and $C_{max,ss}$ was 16.4 nmol/L.

In 8 Caucasian men, aged 42 to 64 years, with Type 2 diabetes (Study 1218.2) the corresponding values were 1.5 hours, 74.7 ng.h/ml (158 nmol.h/L) and 5.24 ng/mL (11.1 nmol/L), respectively, possibly indicating that the AUC_{ss} and $C_{max,ss}$ were approximately 23% and 48% higher, respectively, in Afro-American subjects compared to Caucasians.

The accumulation factors at steady state in these subjects were 1.40 and 1.49 for linagliptin AUC and C_{max}, respectively; however, no studies have examined the BE of the free and FDC tablet combinations at steady-state.

No studies have examined the drug-drug interactions between the proposed FDC tablets with other drugs.

4. Pharmacodynamics

4.1. Studies providing pharmacodynamic data

Table 7 shows the studies relating to each pharmacodynamic topic and the location of each study summary.

Table 7. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	ND	ND	-
Secondary Pharmacology	ND	ND	-
Gender other genetic and Age-Related Differences in PD Response	Effect of race	Study 1218.55	To investigate the PD linagliptin in patients with T2DM of African American origin.
PD Interactions	ND	ND	-
Population PD and PK-PD analyses	Healthy subjects	ND	-
	Target population	ND	-

* Indicates the primary aim of the study.§ Subjects who would be eligible to receive the drug if approved for the proposed indication.‡ And adolescents if applicable. ND No new data provided was provided by the sponsor.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

4.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

4.2.1. Mechanism of action

Linagliptin is a selective, orally administered, xanthine-based inhibitor of dipeptidylpeptidase-4 (DPP-4), which lowers blood glucose by extending the short half life of glucagon like peptide 1 (GLP-1), which is secreted by intestinal L-cells in response to a meal and glucose-dependent insulinotropic peptide (GIP), both of which exert glucose-dependent insulinotropic effects and thereby contribute to the maintenance of post-meal glycaemic control. GLP-1 lowers blood glucose by augmenting the glucose stimulated insulin release and limiting glucagon secretion to slow gastric emptying and to induce satiety. DPP-4 inhibitors maintain long-term β-cell function, which has been demonstrated in animal models.

Although the mechanism of metformin's action is not yet fully understood, metformin lowers blood glucose levels primarily by suppressing hepatic gluconeogenesis; it is believed that this is achieved through metformin-induced activation of adenosine monophosphate-activated protein kinase, an energy-regulating enzyme in the liver. Furthermore, metformin improves the insulin sensitivity of peripheral tissues, decreases gastrointestinal tract glucose absorption, and acts as an insulin sensitiser without exerting any direct effect on pancreatic β-cell insulin secretion.

4.2.2. Pharmacodynamic effects

4.2.2.1. Primary pharmacodynamic effects

No new data was provided by the sponsor.

4.2.2.2. Secondary pharmacodynamic effects

No new data was provided by the sponsor.

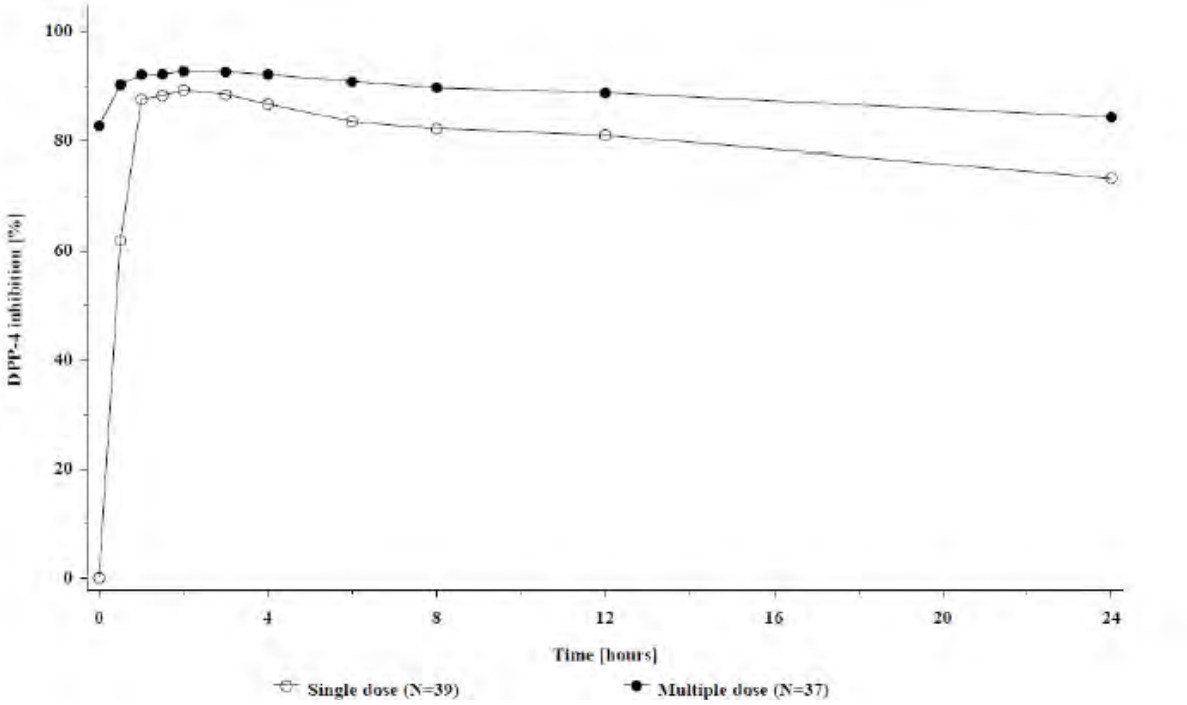
4.2.2.3. Time course of pharmacodynamic effects

No new data was provided by the sponsor.

4.2.2.4. Relationship between drug concentration and pharmacodynamic effects

In Afro-American subjects with Type II diabetes mellitus inhibition of plasma DPP-4 activity correlated well with linagliptin plasma concentrations (Figure 1).

Figure 1. Arithmetic mean DPP-IV inhibition versus time profiles after single and multiple oral administration of 5 mg linagliptin



4.2.2.5. Genetic, gender and age related differences in pharmacodynamic response

4.2.2.5.1. Race

At steady-state in Afro-American subjects with Type II diabetes mellitus following 7 days of treatment with daily doses of 5 mg linagliptin (Study 1218.55), plasma DPP-4 activity was inhibited over 24 h by >80% with a median 24 h trough inhibition of 84.7%.

4.2.3. Pharmacodynamic interactions

No new data was provided by the sponsor.

4.3. Evaluator's overall conclusions on pharmacodynamics

Only one new study (as summarised below) examined the PD of the proposed FDC formulation.

In Afro-American subjects with Type II diabetes mellitus inhibition of plasma DPP-4 activity correlated with linagliptin plasma concentrations.

In these subjects at steady-state, the E_{24} and E_{ss} of plasma DPP-4 inhibition was 75% and 85%, respectively. By comparison in Caucasian subjects (Study 1218.2), these values were 71% and 85%, respectively, possibly indicating that the increased exposure in Afro-American subjects, seen in the PK study, does not translate to a change in inhibition of plasma DPP-4 activity.

No information is provided comparing the PD of the free tablets and FDC combination following single-doses or at steady-state in healthy subjects or in subjects with Type 2 diabetes.

5. Dosage selection for the pivotal studies

5.1. Dose ranging study

5.1.1. Study 1218.6

5.1.1.1. Study design, objectives, locations and dates

This Phase IIb study was a randomised, double-blind, placebo-controlled, five parallel group comparison of the safety and efficacy of linagliptin (1 mg, 5 mg and 10 mg given PO once daily) over 12 weeks as add-on therapy in patients with type 2 diabetes and insufficient glycaemic control. It included an open-label glimepiride treatment arm. It was a dose ranging study to investigate the efficacy, safety and tolerability of linagliptin versus placebo. It also aimed to explore the efficacy of glimepiride versus placebo for sensitivity analysis and to investigate population PK. It was a multi-centre, multinational study conducted at 47 centres in France, Germany, Slovakia, Sweden, Ukraine and the United Kingdom (UK). The study was conducted between April 2006 and August 2007.

Patients treated with metformin and an additional OAD stopped their current therapy with the exception of metformin and entered a 6 week wash-out phase. In the last two weeks of the wash-out phase, they entered an open-label, placebo run-in phase. Patients pre-treated with metformin alone entered directly into the run-in phase. They then entered a 12 week treatment phase during which they received one of the three doses of linagliptin, or placebo, or glimepiride in addition to metformin.

5.1.1.1.1. Inclusion and exclusion criteria

Key inclusion criteria included: male and female patients with type 2 diabetes diagnosed for at least 3 months; previously treated with metformin alone or one other OAD with the exception of rosiglitazone or pioglitazone; HbA1c 7-9% at screening for patients treated with metformin and one OAD; HbA1c 7.5-10.0% at screening for patients treated with metformin alone; glycated haemoglobin (HbA1c) 7.5-10.0% at the beginning of the placebo run-in phase; age ≥21 and ≤75 years; body mass index (BMI) ≥25 and ≤40 kg/m^2.

Key exclusion criteria included: clinically relevant cardiovascular disease or myocardial infarction, stroke or transient ischaemic attack (TIA) within previous 6 months; liver function tests (LFTs) x3 upper limit of normal (ULN); serum creatinine above ULN; clinically relevant neurological disease; rosiglitazone or pioglitazone within 6 months; treatment with insulin within 3 months of screening; FPG >240 mg/dL.

5.1.1.1.2. Study treatments

The randomised treatments were dispensed double-blind, double-dummy with the exception of the glimepiride open-label arm as shown in Table 8 below.

Table 8. BI1356, placebo and glimepiride treatments, oral administration per dose group and day

Treatment	5 mm round tablet	9 mm round tablet	Oval tablet
1 mg	1 mg tablet	Placebo tablet	Placebo tablet
5 mg	Placebo tablet	5 mg tablet	Placebo tablet
10 mg	Placebo tablet	Placebo tablet	10 mg tablet
Placebo	Placebo tablet	Placebo tablet	Placebo tablet
Active comparator	N/A	N/A	N/A

5.1.1.1.3. Efficacy variables and outcomes

The primary efficacy endpoint in this study was the change in HbA1c from baseline to Week 12.

Other efficacy outcomes included:

- Change in FPG after 12 weeks treatment compared with baseline
- Absolute efficacy response defined as HbA1c ≤7%

5.1.1.1.4. Randomisation and blinding methods

Patients were randomised 1:1:1:1:1 to the treatment groups using envelope ID numbers distributed by the sponsor to each site. The linagliptin study medication and its placebo were matched and double-blind but the active comparator glimepiride was open-label. Patients assigned to double-blind treatment took three tablets daily, either three placebo tablets or one active treatment and two placebo tablets. Access to the randomisation list by the investigator for emergency un-blinding was controlled but the method was not explained in the CSR.

5.1.1.1.5. Analysis populations

The randomised set (RS) included all patients who had been randomised to study medication. The treated set (TS) included all patients who had taken at least one dose of study drug. The primary analysis was performed on the FAS which consisted of all randomised patients with baseline and at least one HbA1c measurement following at least dose of randomised treatment. The PPS included all patients who had followed the essential protocol criteria and was used for sensitivity analyses.

5.1.1.1.6. Sample size

The original sample size was based on a planned effect size in HbA1c of 0.5%. The original sample size was 375 patients (75 patients per treatment arm) but, based on data from other ongoing studies, the sample size was later revised in a protocol amendment to 225 patients (45 patients in each arm). The revised sample size calculation was based on a treatment effect of 0.7% and on a standard deviation of the HbA1c change of 1%.

5.1.1.1.7. Statistical methods

Based on a hierarchical testing analysis, the objective was to demonstrate superiority of at least the highest dose of linagliptin compared with placebo. The open-label glimepiride arm was used for sensitivity analysis within this patient population. The primary efficacy endpoint was the change in HbA1c from baseline to Week 12: this was analysed by analysis of covariance (ANCOVA) using baseline HbA1c as a covariate. The superiority of treatment with linagliptin (tested sequentially from highest to lowest dose) to placebo was tested by the comparison of HbA1c change from baseline. Each hypothesis test was performed at the one-sided α=0.025 level.

5.1.1.1.8. Participant flow

A total of 669 patients were enrolled and 333 patients (49.8%) were randomised and treated. The main reason for excluding the remaining 336 patients was the violation of inclusion/exclusion criteria. A total of 286 patients (85.9%) completed the study while 47 patients discontinued early. The main reasons for premature discontinuations included lack of efficacy in 20 patients (6.0%, mostly in the placebo group) and the occurrence of AEs in 14 patients (4.2%).

Major protocol violations/deviations

Of the 333 randomised patients, 21% had pre-defined important protocol violations. These are summarised in Table 9.

Table 9. Important protocol violations. Treated set.

	Placebo	BI1356 1mg	BI1356 5mg	BI1356 10mg
Number of patients	71(100.0)	65(100.0)	66(100.0)	66(100.0)
Patients with important violation				
no	58(81.7)	53(81.5)	51(77.3)	55(83.3)
yes	13(18.3)	12(18.5)	15(22.7)	11(16.7)
Violation Description				
No important violation	58(81.7)	53(81.5)	51(77.3)	55(83.3)
BMI not as specified in the protocol	2(2.8)	1(1.5)	0(0.0)	1(1.5)
Dose change of combination therapy	0(0.0)	0(0.0)	2(3.0)	1(1.5)
Follow up visit too short after end of treatment	9(12.7)	8(12.3)	9(13.6)	5(7.6)
Glucose status not as specified in the protocol	1(1.4)	2(3.1)	1(1.5)	0(0.0)
HbA1c for primary endpoint not taken according to schedule	1(1.4)	1(1.5)	6(9.1)	2(3.0)
HbA1c outside of inclusion interval	0(0.0)	0(0.0)	1(1.5)	0(0.0)
Incorrect trial medication taken	0(0.0)	0(0.0)	0(0.0)	1(1.5)
Medication taken before blood draw at the same day	1(1.4)	1(1.5)	1(1.5)	1(1.5)
Non-compliance	0(0.0)	0(0.0)	1(1.5)	0(0.0)
Prohibited medication use/ interfering concomitant medication	1(1.4)	1(1.5)	0(0.0)	0(0.0)

5.1.1.1.9. Baseline data

The demographic data across the treatment groups were comparable. Nearly all patients were White (98.5%) and 58.0% of patients were male with a mean age of approximately 60 years. Mean weight was 91.4 kg and mean BMI was 31.9 kg/m^2. Most patients (96.1%) had at least one concomitant diagnosis, most commonly vascular disease including hypertension (67.6%). Concomitant therapies were used by 94% of patients, most commonly ASA, antihypertensive drugs and lipid lowering agents. Mean duration of diabetes was 7.0 years. A total of 68.5% of patients had metabolic syndrome and coronary artery disease was reported in 19.8% of patients. Diabetic neuropathy and retinopathy were present in 16.2% and 12.3% of patients respectively.

Baseline efficacy parameters were comparable across treatment groups. Mean baseline HbA1c ranged from 8.2% to 8.5% and mean FPG ranged from 179.9 mg/dL to 189.3 mg/dL. The frequency of patients receiving antidiabetic treatment other than metformin ranged from 28.1% in the glimepiride group to 42.4% in the linagliptin 10 mg group.

5.1.1.2. Results for the primary efficacy outcome

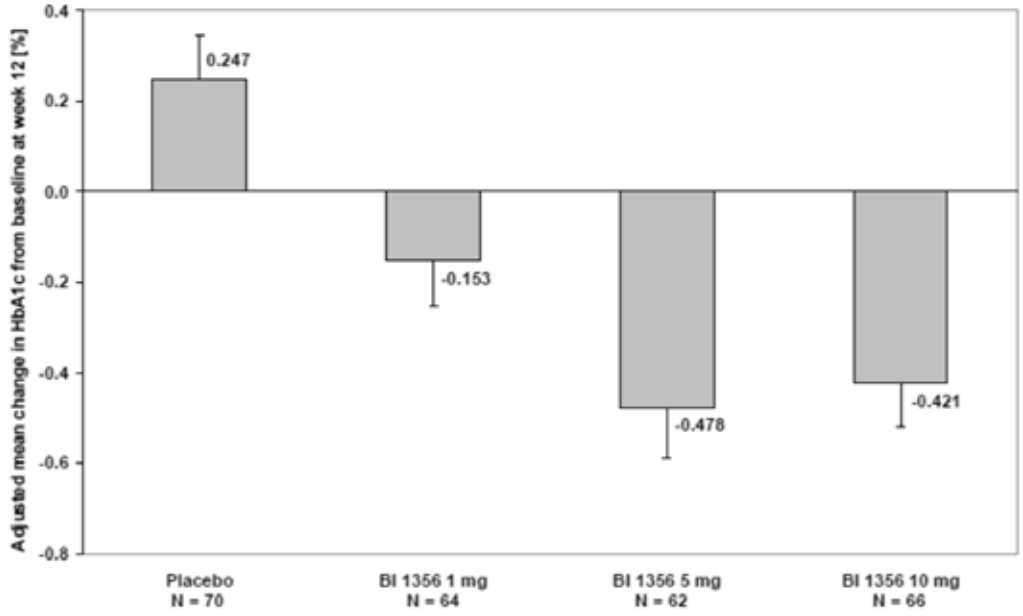
The results of the primary analysis are shown in Table 10 and **Figure 6.9 (p**Error! Bookmark not defined.**)**. For each of the linagliptin treatments, the change in HbA1c from baseline to Week 12 was superior to placebo. The mean difference to placebo was -0.40% (95% CI -0.68, -0.12, p=0.0055) for linagliptin 1 mg, -0.73% (95% CI -1.01, -0.44, p<0.0001) for linagliptin 5 mg and -0.67% 95% CI -0.95, -0.39, p<0.0001) for linagliptin 10 mg. There were comparable decreases in HbA1c for the 5 mg and 10 mg linagliptin doses from baseline to Week 12, -0.48% and -0.42% respectively. There was a small HbA1c decrease (-0.15%) in the linagliptin 1 mg group and a small rise in the placebo group (0.25%).

Table 10.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)		–0.40 (0.14)	–0.73 (0.14)	–0.67 (0.14)
95% CI		(–0.68, –0.12)	(–1.01, –0.44)	(–0.95, –0.39)
p-value		0.0055	<.0001	<.0001

Means are adjusted based on a model with baseline HbA1c, treatment

Figure 2. Study 1218.6



Error bars indicate the standard error for the adjusted mean
Means are adjusted based on a model with baseline HbA1c, treatment

5.1.1.3. Results for other efficacy outcomes

Secondary analyses were performed to investigate the effect of different subgroups (including age, gender, BMI, baseline HbA1c, metformin dose and antidiabetic therapy status) on the change in HbA1c from baseline; and to investigate changes in HbA1c with the active comparator glimepiride. None of the exploratory subgroup analyses affected interpretation of the primary analysis; however, the effects of race were not explored as most patients were White. There was a change in HbA1c of -0.68% over 12 weeks in patients who received the active comparator glimepiride and the mean difference to placebo was -0.93%. After adjustment for other antidiabetic therapy, the difference to placebo was -0.90% (95% CI -1.16, -0.64, p<0.0001). In the placebo group, one patient (1.4%) reached the absolute HbA1c response criterion of 7.0% compared with 15-21% in the linagliptin groups after 12 weeks treatment.

In all linagliptin groups, there was a significant mean change in FPG from baseline to Week 12 compared with placebo. The mean differences were -19.2 mg/dL (95% CI -31.3, -7.1, p=0.002) in the 1 mg group; -34.7 mg/dL (95% CI -46.8, -22.5, p<0.0001) in the 5 mg group; and -29.0 mg/dL (95% CI -41.0, -17.1, p<0.0001). In the glimepiride group, the mean change in FPG from baseline to Week 12 was -25.0 mg/dL compared with an increase of 13.0 mg/dL in the placebo group.

Mean trough plasma concentrations of linagliptin were approximately constant from Weeks 4-12 in all dose groups. The concentrations were non-linear in keeping with the known PK characteristics of the drug. The frequencies of patients with DPP-4 inhibition ≥80% were 8%, 87% and 93% in the linagliptin 1 mg, 5 mg and 10 mg groups respectively.

Comment: The endpoints of HbA1c, FPG, PK and DPP-4 inhibition together showed that the linagliptin 5 mg and 10 mg doses were approximately equivalent and both were superior to the 1 mg dose, all doses given once daily (QD).

6. Clinical efficacy

6.1. Type 2 diabetes mellitus

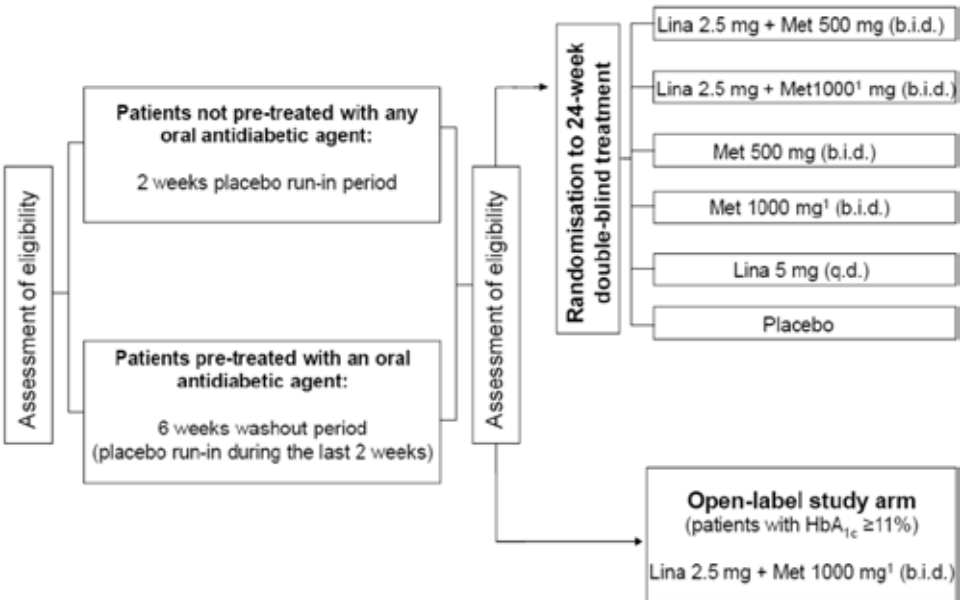
6.1.1. Pivotal efficacy study

6.1.1.1. Study 1218.46

6.1.1.1.1. Study design, objectives, locations and dates

This was a randomised, double-blind, placebo-controlled parallel group study comparing the efficacy and safety of twice daily administration of the free combination of linagliptin (Lina) 2.5 mg + metformin (Met) 500 mg or of Lina 2.5 mg + Met 1000 mg, with the individual components of metformin (500 mg or 1000 mg twice daily) and linagliptin (5 mg once daily) over 24 weeks in drug naive or previously treated T2DM patients with inadequate glycaemic control. This was followed by an optional open-label extension study for a further 24 weeks. It was a multicentre trial conducted at 133 sites in 14 countries (Canada, Croatia, Estonia, France, Germany, India, Lithuania, Mexico, Romania, Russia, Sweden, The Netherlands, Tunisia and Ukraine). The trial was conducted between December 2008 and May 2010. An overview of the study is shown in Figure 3 below.

Figure 3. Study design



b.i.d=twice a day

Patients pre-treated with one oral antidiabetic agent (OAD) underwent a 6 week washout period including 2 weeks placebo run-in. Patients not pre-treated with an oral anti-diabetic treatment had a 2 week placebo run-in period. Patients with baseline HbA1c ≥11% were enrolled into an open-label arm. All patients randomised to metformin 1000 mg underwent a forced titration phase. Patients who completed the randomised period of the study were then invited to participate in the 24 week extension Study 1218.52 which is discussed further below.

Rescue medications (sulphonylureas, thiazolidinediones or insulin) were permitted only during the randomised treatment period and only if the following FPG criteria were met: FPG >240 mg/dL (between Visits 3 to 5); or random FPG >400 mg/dL; or FPG >200 mg/dL (after Visits 5-7). The use of any other antidiabetic agents (including insulin) was otherwise prohibited until the end of the study.

Comment: FPG is reported in imperial units in the submitted data. This convention is retained in this evaluation to ensure compatibility with the study reports, text, tables and figures.

6.1.1.1.2. Inclusion and exclusion criteria:

Key inclusion criteria included: males and females with T2DM, treatment naive or previously treated with not more than one oral antidiabetic drug; age range ≥18 to ≤80 years; BMI ≤40 kg/m^2; HbA1c ≥7.5 to <11.0% (for treatment naive patients) and ≥7.0 to ≤10.5% (for treatment washout patients); patients with poor glycaemic control (HbA1c ≥11.0%) enrolled into an open-label study arm.

Key exclusion criteria included: myocardial infarction (MI), stroke or TIA within six months; alanine transaminase (ALT), aspartate transaminase (AST) or alkaline phosphatase (ALP) above x3 ULN; treatment with rosiglitazone, pioglitazone, GLP-1 analogues, insulin, or anti-obesity drugs within 3 months; alcohol abuse; current steroid use; renal impairment with eGFR <60 ml/min; unstable or acute congestive cardiac failure; history of metabolic acidosis.

6.1.1.1.3. Study treatments

The study treatments are shown in Table 11 below.

Table 11. Study treatments

	Identity of investigational products					
	Linagliptin 2.5 mg	Linagliptin 5 mg	Metformin	Placebo matching linagliptin 2.5 mg	Placebo matching linagliptin 5 mg	Placebo matching metformin 500 mg or 1000 mg
Pharmaceutical form	Tablet	Tablet	Tablet	Tablet	Tablet	Tablet
Unit strength	2.5 mg	5 mg	500 mg or 1000 mg[1]	Not applicable	Not applicable	Not applicable
Route of administration	Oral	Oral	Oral	Oral	Oral	Oral
Dosage regimen	Twice daily	Once daily	Twice daily	Twice daily	Once daily	Twice daily
Source	BI Pharma GmbH & Co. KG	BI Roxanne Inc.	Merck Pharma GmbH	BI Pharma GmbH & Co. KG	BI Roxanne Inc.	BI Pharma GmbH & Co. KG

6.1.1.1.4. Efficacy variables and outcomes

The primary efficacy outcome was the change of HbA1c from baseline to Week 24.

Key secondary efficacy outcomes included:

- HbA1c reduction from baseline by visit over time
- Treat-to-target efficacy response at 24 weeks (HbA1c <7.0% or <6.5%)
- Relative efficacy response at 24 weeks (HbA1c lowering by at least 0.5%)
- Change from baseline of FPG at 24 weeks and by visit over time
- The use of rescue medication

Other secondary endpoints included waist circumference, HOMA indices, GLP-1, DPP-4 inhibition, Insulin secretion rate (ISR), health utilisation questionnaires and Meal tolerance test (MTT) parameters. These exploratory endpoints are not reviewed as they are not relevant to the overall study conclusions.

6.1.1.1.5. Randomisation and blinding methods

Patients were randomly assigned to one of the six treatment groups described above by Interactive voice/web response system (IVRS/IWRS). Randomisation was performed at Visit 3 and stratified by baseline HbA1c and the number of prior OADs (none or one). Patients with very poor glycaemic control (HbA1c ≥11.0%) were eligible for the open-label arm (OLS) of the study. The placebo run-in period was open-label while the randomised period was double-blind. Investigators had access to the randomisation code by IVRS but it was not broken for any patient during the trial. The study was unblinded after database lock.

6.1.1.1.6. Analysis populations

The primary analysis was performed of the full analysis set (FAS), consisting of all randomised patients who received at least one dose of study drug, had a baseline HbA1c, and had at least one HbA1c on treatment. A per protocol set (PPS) consisted of patients who followed all essential elements of the protocol. Patients with important protocol violations were excluded from the PPS analysis.

6.1.1.1.7. Sample size

The sample size was derived from confidence intervals in a published study of sitagliptin versus glipizide in which the standard deviation for change in HbA1c from baseline was approximately 1.1% at 52 weeks. An additional 10% more patients were planned to allow for early withdrawals in the present study. In the randomised group, it was planned to enter 144 patients into the five active treatment arms and 72 patients into the placebo arm. The number of patients in the OLS was determined by the number of patients not eligible for the randomised part of the study (excluded for HbA1c ≥11.0%). Based on recruitment data from previous studies, it was assumed that approximately 50 of the 908 screening failures would meet this criterion.

6.1.1.1.8. Statistical methods

The primary endpoint was analysed by ANCOVA comparing the change of HbA1c from baseline after 24 weeks treatment. For patients who received rescue therapy, the last available HbA1c value before intervention was used for the analysis. The FAS was used for the primary analysis with the last observation carried forward to replace missing data. Baseline values were not carried forward. Sensitivity analyses for the primary endpoint used the Per protocol set (PPS) and Full analysis set (FAS) completers to assess the effects of protocol violations and premature discontinuations. Centre effects and the prior use of OADs were explored using two models of ANCOVA. Changes in FPG were explored on the FAS using the same methodology employed for HbA1c. Subgroup analyses were performed for baseline HbA1c, number of prior OAD, geographical region, country, race, ethnicity, gender, age, BMI, time since diagnosis and the presence of metabolic syndrome at baseline.

The superiority of the two free combination treatments (twice daily linagliptin 2.5 mg and metformin 500 mg or 1000 mg) over the individual metformin components of the free combination treatments (500 mg and 1000 mg, both twice a day (BID)) and to linagliptin 5 mg QD was tested for HbA1c change from baseline to Week 24 at the 2-sided α=0.05 level. The null-hypothesis of superiority of linagliptin alone or metformin alone over the combination was to be rejected if $p<0.05$ for the associated contrast was below 0.0%, as indicated by the upper bound of the confidence interval for the effect of the combination minus the individual component.

6.1.1.1.9. Participant flow

Overall, 1770 patients were screened and 791 patients were randomised to study medication. The FAS consisted of 756 treated patients who had a baseline and at least one on-treatment HbA1c measurement. The FAS-completers were a FAS subset of 666 patients who completed 24 weeks of treatment without receiving rescue medication. The PPS consisted of a 730 patient

subset of the FAS which excluded patients with significant protocol violations. An overview of the analysis sets is provided in Table 12.

Table 12. Number of patients by analysis set.

	Placebo N (%)	Lina 5 N (%)	Met 500 N (%)	Met 1000 N (%)	Lina 2.5 + Met 500 N (%)	Lina 2.5 + Met 1000 N (%)	Total N (%)
Randomised set	72 (100.0)	142 (100.0)	144 (100.0)	147 (100.0)	143 (100.0)	143 (100.0)	791 (100.0)
Treated set	72 (100.0)	142 (100.0)	144 (100.0)	147 (100.0)	143 (100.0)	143 (100.0)	791 (100.0)
FAS	65 (90.3)	135 (95.1)	141 (97.9)	138 (93.9)	137 (95.8)	140 (97.9)	756 (95.6)
FAS-completers	52 (80.0)	118 (87.4)	120 (85.1)	122 (88.4)	125 (91.2)	129 (92.1)	666 (88.1)
PPS	63 (96.9)	130 (96.3)	140 (99.3)	129 (93.5)	133 (97.1)	135 (96.4)	730 (96.6)
MTT set	9 (13.8)	16 (11.9)	17 (12.1)	15 (10.9)	12 (8.8)	15 (10.7)	84 (11.1)
OLS	--	--	--	--	--	--	66

FAS = full analysis set, MTT = meal tolerance test, OLS = open-label set, PPS = per-protocol set
Note: if combined with metformin 500 mg or 1000 mg, linagliptin was administered as 2.5 mg b.i.d.

6.1.1.1.10. Major protocol violations/deviations

In the randomised treatment period, pre-defined significant protocol deviations related to efficacy occurred in 54 patients (6.8%) and they were excluded from the PPS. The number of excluded patients ranged from two patients (1.4%) in the Met 500 group to 17 patients (11.6%) in the Met 1000 group. In the open-label arm, 19 patients (28.8%) had significant deviations related to efficacy but they were not excluded from the analysis. Most deviations in this arm related to concomitant medication.

Non-compliance was pre-defined as outside the range of 80% to 120%. Compliance during the run-in was 95.7% and 95.3% during the randomised treatment period. The groups with the lowest non-compliance rates were the Met 1000 and Lina 2.5 + Met 1000 groups (2.9%) during run-in, and the maximum non-compliance rate was 4.7% in the placebo group during the randomised period.

6.1.1.1.11. Baseline data

In the total patient group, more than half were male (53.9%), approximately two thirds (66.8%) were White and nearly one third was Asian (32.5%). The mean age was 55.3 years, 79% were ≤65 years and 2.5% were aged over 75 years. Mean weight was 79.1 kg and mean BMI was 29.1kg/m^2. Approximately half the patients (51.7%) had normal renal function while 42.2% had mild renal impairment (estimated glomerular filtration rate (eGFR) 60 to <90 ml/min). There were no patients with severe renal impairment (eGFR <30 ml/min). In the open label arm (OLS), there were more females (60.6%) than males but the other baseline characteristics were similar to those in the randomised arm.

A total of 78.9% of patients had concomitant illnesses at screening, ranging from 72.2% in the placebo group to 83.3% in the Met 500 group. The most frequent diagnoses were metabolism and nutrition disorders (38.7%), vascular disorders (mainly hypertension, 37.3%), muscular and connective tissue disorders (22.4%), cardiac disorders (13.1%), eye disorders (12.1%), gastrointestinal disorders (12.1%) and neurological disorders (10.9%). The frequency of concomitant illnesses was similar in the OLS arm. Overall, 60.8% of patients were taking at least one concomitant medication at screening, ranging from 57.3% in the Lina 2.5 + Met 1000 group to 64.1% in the Lina 5 group. In the placebo group 72.2% of patients were taking concomitant medications. The most commonly used medications were antihypertensives and lipid lowering agents.

The main efficacy parameters and the number of prior OADs at baseline are shown in Table 13. The overall mean baseline HbA1c was 8.65% and the mean values were comparable between

the groups. In total, 26.6% of patients had baseline HbA1c in the range 7.0% to <8.0%, 37.6% between 8.0% and <9.0% and 35.2% >9.0%. The overall mean baseline FPG was 195.6 mg/dL, ranging from 191.2 mg/dL in the Met 500 group to 198.6 mg/dL in the Lina 2.5 + Met 500 group.

Approximately half the patients (47.0%) were pre-treated with one OAD (mainly metformin or SU) with comparable percentages in all treatment groups. As expected, mean baseline HbA1c was higher (11.8%) in the OLS group and mean FPG was 261.8 mg/dL.

The time since diagnosis of diabetes in the FAS was tabulated in the submission. A total of 37.4% of the patients had a history of diabetes of less than one year, 36.9% between one and five years and 25.7% more than five years. In total, 14.3% of patients had microvascular disease, 55.1% had macrovascular disease and 54.1% had metabolic syndrome (Table 14). Diabetes related disease was more common at baseline in the placebo group. The time since diagnosis of diabetes was similar in the OLS group compared with the FAS. Microvascular disease was present in 7.6% of patients, macrovascular disease in 40.0% and metabolic syndrome in 50%.

Table 13. Study 1218.46 Baseline efficacy variables and number of prior diabetic drugs-FAS.

	Placebo	Lina 5	Met 500	Met 1000	Lina 2.5 + Met 500	Lina 2.5 + Met 1000	Total
Baseline HbA_{1c} [%]							
Number of patients, N (%)	65 (100.0)	135 (100.0)	141 (100.0)	138 (100.0)	137 (100.0)	140 (100.0)	756 (100.0)
Mean (SD)	8.67 (0.95)	8.70 (0.97)	8.66 (0.90)	8.52 (0.87)	8.71 (0.95)	8.68 (1.03)	8.65 (0.94)
Baseline HbA_{1c} [%], categorical, N (%)							
Number of patients, N (%)	65 (100.0)	135 (100.0)	141 (100.0)	138 (100.0)	137 (100.0)	140 (100.0)	756 (100.0)
<7.0	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	1 (0.7)	2 (1.4)	5 (0.7)
7.0 to <8.0	18 (27.7)	36 (26.7)	32 (22.7)	45 (32.6)	36 (26.3)	34 (24.3)	201 (26.6)
8.0 to <9.0	21 (32.3)	55 (40.7)	57 (40.4)	47 (34.1)	49 (35.8)	55 (39.3)	284 (37.6)
≥9.0	26 (40.0)	44 (32.6)	51 (36.2)	45 (32.6)	51 (37.2)	49 (35.0)	266 (35.2)
Baseline FPG [mg/dL]							
Number of patients, N (%)	62 (100.0)	134 (100.0)	139 (100.0)	135 (100.0)	135 (100.0)	138 (100.0)	743 (100.0)
Mean (SD)	203.7 (51.2)	195.3 (50.2)	191.2 (46.9)	192.3 (52.8)	198.6 (60.2)	196.9 (51.2)	195.6 (52.3)
Number of prior OADs, N (%)							
Number of patients, N (%)	65 (100.0)	135 (100.0)	141 (100.0)	138 (100.0)	137 (100.0)	140 (100.0)	756 (100.0)
0	32 (49.2)	61 (45.2)	69 (48.9)	67 (48.6)	65 (47.7)	65 (46.4)	359 (47.5)
1	33 (50.8)	74 (54.8)	71 (50.4)	71 (51.4)	72 (52.6)	75 (53.6)	396 (52.4)

Note: if combined with metformin 500 mg or 1000 mg, linagliptin was administered as 2.5 mg b.i.d.
Note that there was one patient (patient 47091) in the met 500 group who received 2 prior OADs (a combination therapy of metformin and SU), although only one prior OAD was permitted, this patient is counted separately; see also Section 10.1 and

Table 14. Study 1218.46 Concomitant diagnoses to diabetes at baseline. Treated set.

	Placebo	Lina 5	Met 500	Met 1000	Lina 2.5 + Met 500	Lina 2.5 + Met 1000	Total
Number of patients, N (%)	72 (100.0)	142 (100.0)	144 (100.0)	147 (100.0)	143 (100.0)	143 (100.0)	791 (100.0)
Patients with, N (%)							
Microvascular disease[1]	17 (23.6)	23 (16.2)	19 (13.2)	23 (15.6)	17 (11.9)	14 (9.8)	113 (14.3)
Macrovascular disease[2]	48 (66.7)	85 (59.9)	72 (50.0)	79 (53.7)	81 (56.6)	71 (49.7)	436 (55.1)
Diabetic foot	0 (0.0)	1 (0.7)	4 (2.8)	0 (0.0)	0 (0.0)	1 (0.7)	6 (0.8)
Metabolic syndrome[3]	45 (62.5)	69 (48.6)	76 (52.8)	81 (55.1)	83 (58.0)	74 (51.7)	428 (54.1)

6.1.1.2. Results for the primary efficacy outcome

In the FAS, mean baseline HbA1c was similar in each treatment group, ranging from 8.52% in the Met 1000 group to 8.71% in the Lina 2.5 + Met 500 group. Both free combinations consisting of twice daily linagliptin 2.5 mg and metformin 500 mg and 1000 mg were superior to the individual metformin components (500 mg and 1000 mg BID) and to linagliptin 5 mg QD for the change in HbA1c from baseline to Week 24 (Table 15).

Table 15. Study 1218.46 Adjusted means for the change in HbA1c (%) from baseline at Week 24. FAS (LOCF).

	Met 0	Met 500 b.i.d.	Met 1000 b.i.d.
Lina 0			
N	65	141	138
Baseline, unadjusted mean (SD)	8.67 (0.95)	8.66 (0.90)	8.52 (0.87)
End of study, adjusted mean (SE)	8.78 (0.11)	8.01 (0.08)	7.58 (0.08)
Change from baseline, adjusted mean (SE)	0.13 (0.11)	-0.64 (0.08)	-1.07 (0.08)
Lina 5 q.d. / Lina 2.5 b.i.d.[1]			
N	135	137	140
Baseline, unadjusted mean (SD)	8.70 (0.97)	8.71 (0.95)	8.68 (1.03)
End of study, adjusted mean (SE)	8.21 (0.08)	7.43 (0.08)	7.07 (0.08)
Change from baseline, adjusted mean (SE)	-0.45 (0.08)	-1.22 (0.08)	-1.59 (0.08)
Difference to metformin component			
Adjusted mean (SE)		-0.58 (0.11)	-0.51 (0.11)
95% confidence interval		-0.79, -0.36	-0.73, -0.30
p-value		<0.0001	<0.0001
Difference to lina 5			
Adjusted mean (SE)		-0.77 (0.11)	-1.14 (0.11)
95% confidence interval		-0.99, -0.55	-1.36, -0.92
p-value		<0.0001	<0.0001

Model includes treatment, continuous baseline HbA_{1c}, and number of prior OADs
N = number of patients with baseline and on-treatment results
[1] If combined with metformin 500 mg or 1000 mg, linagliptin was administered as 2.5 mg b.i.d.

The free combination of Lina 2.5 + Met 1000 was superior to Met 1000 alone: the mean treatment difference in HbA1c from baseline to Week 24 was -0.51% (95% CI -0.73, -0.30, p<0.0001). The combination of Lina 2.5 + Met 1000 was superior to Lina 5 alone: the mean difference in HbA1c from baseline to Week 24 was -1.14% (95% CI -1.36, -0.92, p<0.0001). The combination of Lina 2.5 + Met 500 was superior to Met 500 alone: the mean difference in HbA1c was -0.58% (95% CI -0.79, -0.36, p<0.0001). The combination of Lina 2.5 + Met 500 was superior to Lina 5 alone: the mean difference in HbA1c from baseline to Week 24 was -0.77% (95% CI -0.99, -0.55, p<0.0001). Placebo adjusted values showed a mean difference in HbA1c from baseline to Week 24 with linagliptin monotherapy compared to placebo of -0.57% (95% CI -0.85, -0.30). In the OLS, mean baseline HbA1c was 11.84% in patients treated with open-label Lina + Met 1000, and the mean change at Week 24 was -3.74% (Table 16).

Table 16. Study 1218.46 Mean for the change in HbA1c (%) from baseline at Week 24. OLS (OC).

	Lina 2.5 +Met 1000
Number of patients	66
Baseline	
Mean (SD)	11.84 (1.42)
End of study	
Mean (SD)	7.90 (1.21)
Change from baseline	
Mean (SD)	-3.74 (1.69)

Note: linagliptin 2.5 + metformin 1000 were administered twice daily (b.i.d.)

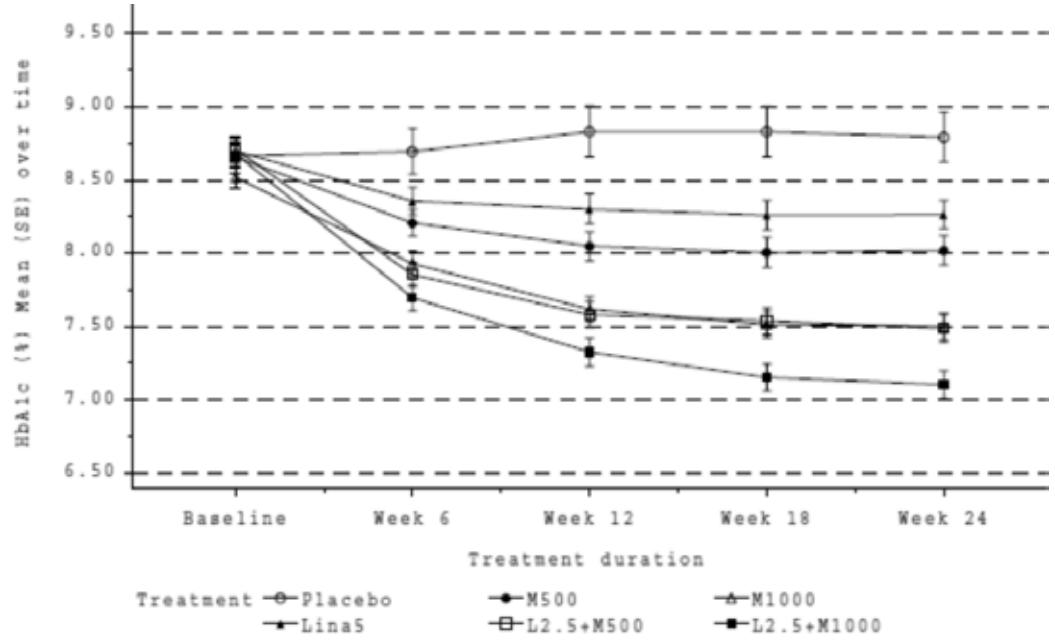
The influence of protocol violations and premature discontinuations was assessed by calculating the adjusted mean HbA1c from baseline for the PPS and FAS-completers. The PPS analysis showed similar differences between the treatment groups with all p-values <0.0001.

6.1.1.3. Results for other efficacy outcomes

The main secondary endpoints for the randomised and open-label arms were HbA1c and FPG changes from baseline by visit over time. Secondary endpoints for the randomised group only were: occurrence of treat-to-target (categorical) HbA1c and FPG response; the occurrence of relative efficacy response after 24 weeks, the change in FPG from baseline after 24 weeks; and use of rescue therapy.

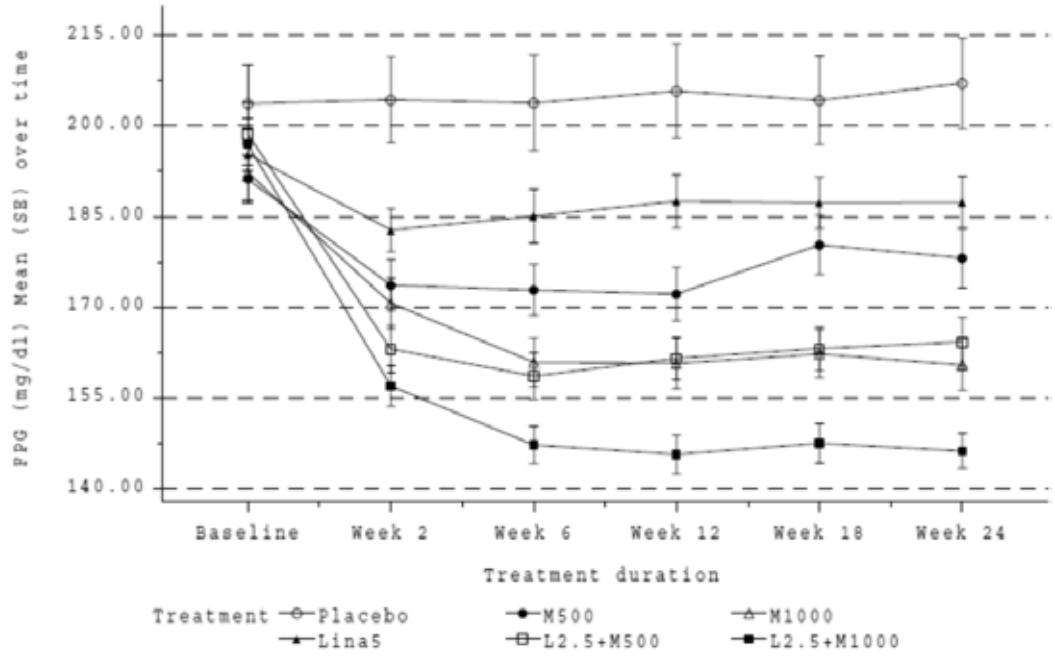
The mean change in HbA1c over time in the FAS is shown in Figure 4. There was a continuous fall in HbA1c in all treatment groups up to Week 24. Similar changes were observed in the OLS group with the maximal fall in HbA1c occurring at Week 18**.** The mean changes in HbA1c after 24 weeks in sub-groups indicated that the effect in the sub-groups was consistent with the overall data. No meaningful interactions were observed and there were no clinically significant differences related to age or gender.

Figure 4. Study 1218.46. Unadjusted HbA1c (%) and SE over time. FAS (LOCF).



Mean baseline FPG values were similar in the active treatment groups, ranging from 190.6 mg/dL in the Met 500 and Met 1000 groups to 198.6 mg/dL in the Lina 2.5 + Met 500 group. Mean baseline FPG was 203.3 mg/dL in the placebo group. Te treatment difference in FPG from baseline to Week 24 was -17.2 mg/dL (95% CI -27.1, -7.3, p=0.0006) for the free combination of Lina 2.5 + Met 1000 compared to Met 1000. The difference was -40.8 mg/dL (95% CI -50.6, -31.0, p<0.0001) for the free combination of Lina 2.5 + Met 1000 compared to Lina 5; -17.4 mg/dL (95% CI -27.2, -7.6, p=0.0005) for the free combination of Lina 2.5 + Met 500 compared to Met 500; and -24.6 mg/dL (95% CI -34.4, -14.8, p<0.0001) for the free combination of Lina 2.5 + Met 500 compared to Lina 5. The mean treatment difference in FPG for linagliptin compared to placebo was -18.74 mg/dL (p=0.0033). The mean change in FPG over time is shown in Figure 5, with all p-values <0.05. With respect to changes in FPG over 24 weeks in the OLS, the maximum change from baseline was -85.1 mg/dL at Week 6.

Figure 5. Study 1218.46. Unadjusted mean FPG (mg/dL) and SE over time. FAS (LOCF).



Categorical efficacy analyses were performed only in the randomised group to determine how many patients reached target HbA1c (<7.0% or <6.5%) after 24 weeks treatment. In patients with baseline HbA1c >7.0%, 10.8% of patients in the placebo group, 10.4% in the Lina 5 group, 18.6% in the Met 500 group, 30.7% in the Met 1000 group, 30.1% in the Lina 2.5 + Met 500 group, and 53.6% of the Lina 2.5 + Met 1000 group achieved a response of HbA1c <7.0% at Week 24. Patients treated with Lina 2.5 + Met 1000 were four times more likely to achieve HbA1c <7.0% compared to Met 1000 alone (OR 4.163; 95% CI 2.343-7.397, p<0.0001). The same patient group was 17 times more likely to achieve HbA1c compared to Lina 5 alone (OR 17.094; 95% CI 8.238-35.471, p<0.0001). Among patients with baseline HbA1c >6.5%, the number of responders, odds ratios and p-values was approximately similar.

Overall, the percentages of patients with an HbA1c reduction of at least 0.5% were higher in the active treatment groups (range 42.2% to 81.4%) compared to placebo (29.2%). The odds of achieving a HbA1c reduction of at least 0.5% at week 24 was two-fold higher in the Lina 25 + Met 1000 group compared to Met 1000 alone (OR 2.382; 95% CI 1.352-4.196, p=0.0027), and 6.5 times higher compared to Lina 5 alone (OR 6.529; 95% CI 3.724-11.445, p<0.0001).

The proportion of patients requiring rescue therapy was higher in the placebo group (29.2%) than in the active treatment groups (ranging from 4.3% in the Lina 2.5 + Met 1000 group to 13.5% in the Met 500 group). The odds of requiring rescue medication was approximately 3 fold lower in the Lina 2.5 + Met 1000 group compared to Met1000 (OR 0.326; 95% CI 0.109-0.973, p=0.0445). No meaningful changes in body weight in any treatment group were observed over the 24 week treatment period. The mean change in body weight in the Lina 2.5 + Met 1000 group was -0.23 kg (95% CI -0.93, 0.47, p=0.52) compared with -0.96 kg (95% CI -1.67, -0.24, p<0.01) in the Met 1000 group alone.

6.1.2. Other efficacy studies

6.1.2.1. Study 1218.43

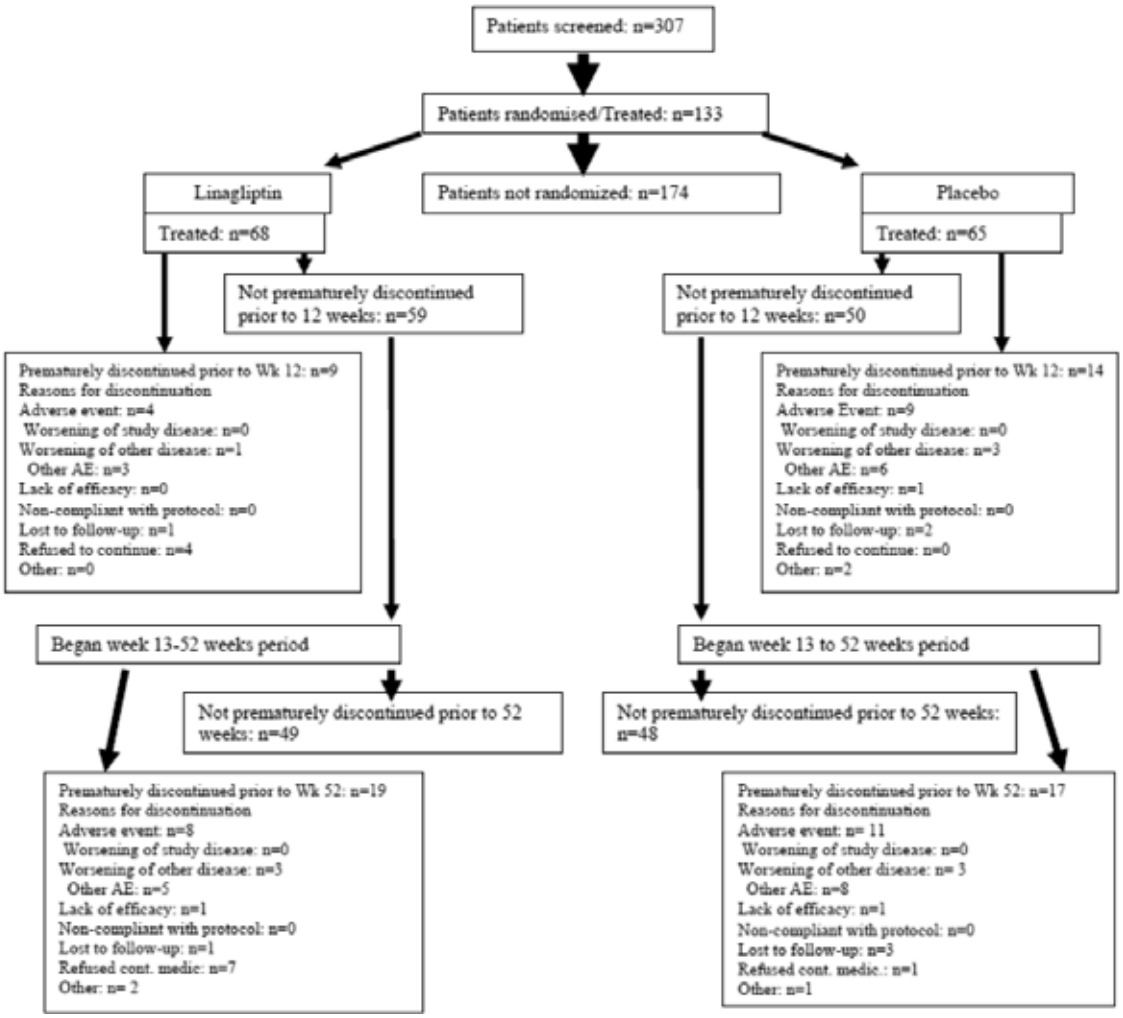
6.1.2.1.1. Study design and objectives

This was a Phase III, randomised, double-blind, placebo-controlled, parallel group, safety and efficacy study of linagliptin 5 mg compared to placebo as add on to pre-existing antidiabetic therapy (insulin or any combination with insulin; sulphonylurea or glinides as monotherapy;

pioglitazone or any other anti diabetics, excluding only DPP-4 inhibitors other than linagliptin) over 52 weeks in T2DMs with severe chronic renal failure. Study treatments were linagliptin tablets 5 mg or matching placebo given once daily. Key inclusion criteria were male and female patients with type 2 diabetes treated with insulin and/or OADs; eGFR <30 ml/min; insulin and/or OAD dose stable for at least 8 weeks; HbA1c >7.0 to ≤10.0%; BMI ≤45 kg/m^2. The main endpoints were the change in HbA1c from baseline to Week 12 and Week 52, analysed by ANCOVA.

A total of 307 patients were enrolled and 133 patients were randomised and received linagliptin 5 mg (68 patients) or placebo (65 patients) as shown in Figure 6. Baseline demographic data showed that overall, 60.2% of patients were male and 73.7% were White. Mean age was 64.4 years and 13.5% were over 75 years of age. Mean weight was 87.8 kg and mean BMI was 32 kg/m^2. Baseline HbA1c was 8.2% in both treatment groups. Fewer than 10% of patients had baseline HbA1c <7.0% and approximately 20% had HbA1c ≥9.0%. Overall, 62.5% of patients were treated with insulin alone at baseline.

Figure 6. Study 1218.43. Patient flow

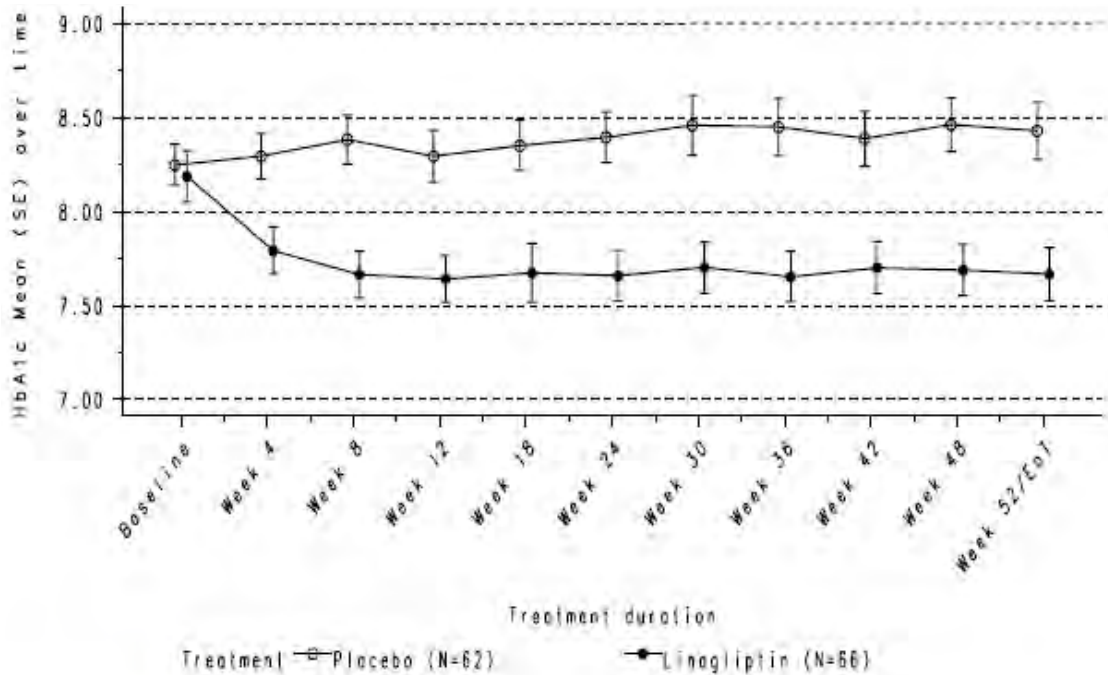


6.1.2.1.2. Efficacy outcomes

After adjustment for stratification factors and baseline variates in the FAS, there was a mean treatment difference in HbA1c of -0.72% (95% CI -1.03, -0.41) at the end of 52 weeks treatment, indicating superiority of linagliptin compared with placebo (p<0.0001). The difference in the PPS was similar to that in the FAS (-0.64%, p=0.0003). Changes in HbA1c over time are shown in Figure 7. The maximum difference in HbA1c was achieved by 12 weeks and sustained

thereafter. A categorical analysis showed that in the linagliptin group 18.2% of patients achieved HbA1c <7.0% compared with 9.7% in the placebo group.

Figure 7. Study 218.43. HbA1c (%) mean and SE over time. FAS (LOCF).



Comment: Although defined as a Phase III study by the sponsor, this was an exploratory Phase II study in an important sub-group of the T2DM population. The study supports the use of linagliptin monotherapy or add-on therapy in patients with any level of renal impairment. However, it has little supportive value for the FDC application as metformin is contra-indicated in patients with severe renal failure.

6.1.3. Study 1218.62

6.1.3.1. Study design and objectives

This was a Phase IIb randomised, double-blind, placebo-controlled, parallel-group efficacy and safety study of linagliptin 2.5 mg twice daily versus 5 mg once daily over 12 weeks as add-on therapy to a twice daily dosing regimen of metformin in patients with type 2 diabetes and insufficient glycaemic control. A total of 451 randomised patients were planned and 771 patients were enrolled at 81 sites. Patients treated with one previous OAD stopped treatment while background metformin therapy continued. During this period they received one of the two dose frequencies of linagliptin (QD or BID) or placebo in addition to twice daily metformin background therapy. Key inclusion criteria were male and female patients with type 2 diabetes aged ≥18 and ≤80 years; patients treated with metformin and no more than one other OAD; metformin dose stable in the 12 weeks before enrolment; HbA1c ≥7.0 to ≤9.5% for patients undergoing OAD washout; HbA1c ≥7.0 to ≤10.0% for patients not undergoing OAD washout; HbA1c ≥7.0 to ≤10.0% at start of run-in; BMI ≤45 kg/m^2.

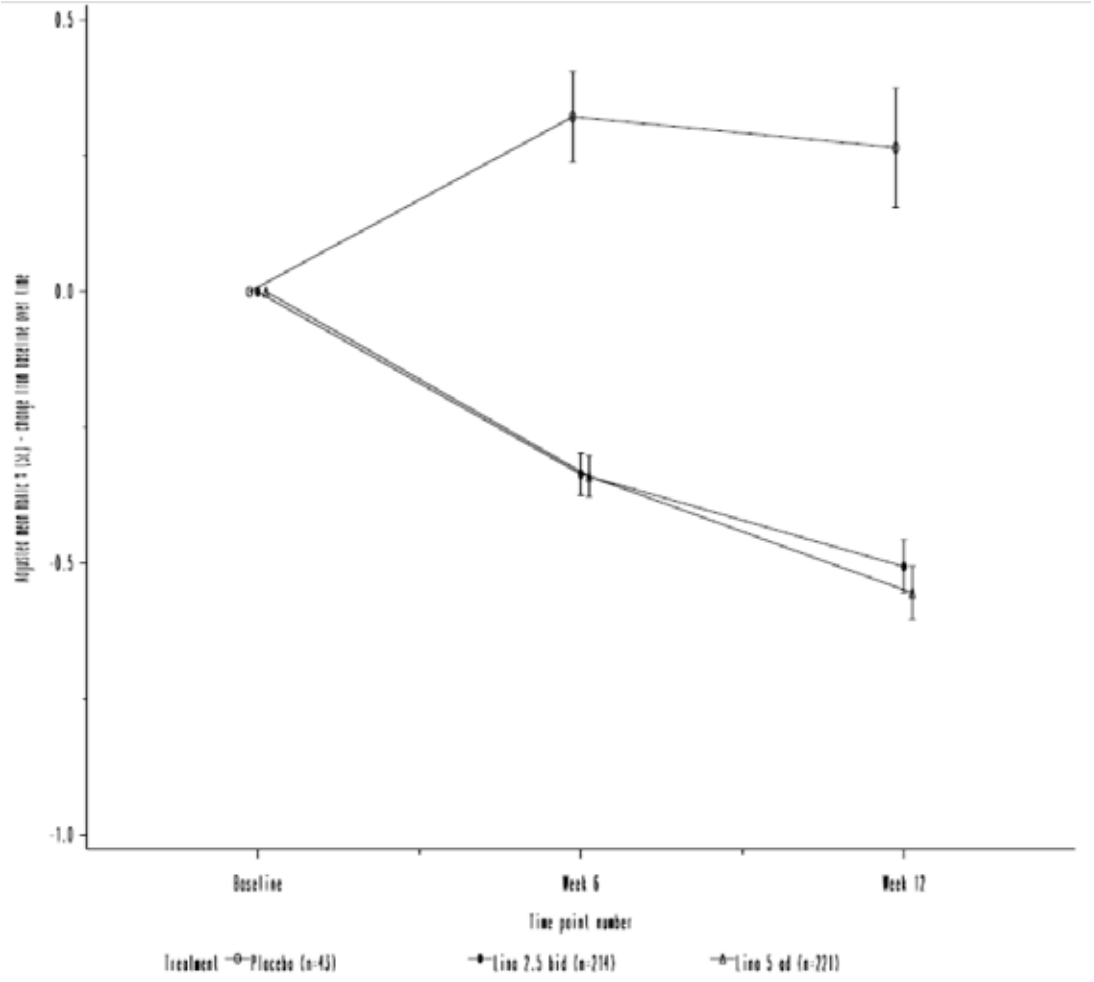
Patients were randomly assigned to linagliptin 5 mg QD, linagliptin 2.5 mg BID or placebo in a 5:5:1 ratio. Randomisation was stratified by HbA1c at the beginning of the placebo run-in period (<8.0% or ≥8.0%) and the previous use of OAD (metformin monotherapy or combination therapy). The primary analysis was performed using ANCOVA. The objective was to demonstrate non-inferiority of linagliptin 2.5 mg BID to linagliptin 5 mg QD using a pre-defined non-inferiority margin and to demonstrate the superiority of each treatment over placebo. The primary endpoint was the change in Hba1c from baseline to Week 12. The demographic data of the treatment groups were comparable. Most of the population was male, 65.4% were White and 33.8% were Asian. The mean age was 58.6 years and only 6.7% were 75 years or older.

Mean weight was 81.0 kg and mean BMI was 29.6kg/m^2. At baseline, 46.6% of patients had normal renal function (eGFR ≥90 ml/min) and 48.3% had mild renal impairment (eGFR 60 to <90 ml/min). There were no patients with severe renal impairment (eGFR <30 ml/min). The mean baseline HbA1c values were comparable in the treatment groups with an overall mean of 7.97%.

6.1.3.2. Efficacy outcomes

Both linagliptin treatment groups (2.5 mg BID and 5 mg QD) were superior to placebo in HbA1c reduction from baseline to 12 weeks. The adjusted mean difference in HbA1c change from baseline to Week 12 for Lina 2.5 BID minus placebo was -0.74% (95% CI -0.97, -0.52, p<0.0001). The adjusted mean difference in HbA1c change from baseline to Week 12 for Lina 5 QD minus placebo was -0.80% (95% CI -1.02, -0.58, p<0.0001). The adjusted mean difference in HbA1c change from baseline to Week 12 for Lina 2.5 BID minus Lina 5 QD was 0.06% (95% CI -0.07, 0.19). Non-inferiority was confirmed as the pre-specified margin in the protocol was 0.35. A total of 16.3% of placebo treated patients achieved an HbA1c response of at least 0.5% compared with 55.1% in the Lina 2.5 BID group and 59.7% in the Lina 5 QD group. Changes over time were similar in each linagliptin group and significantly different from placebo (Figure 8).

Figure 8. Study 1218.62. Changes over time in HbA1c



Comment: The studies submitted in this application include linagliptin treatment arms dosed as 2.5 mg BID (proposed for the FDC) and/or linagliptin 5 mg QD (the approved linagliptin dose for monotherapy). Surprisingly, no PK analyses were performed in this head-to-head comparator study of linagliptin in patients treated with

metformin background therapy. However, it clearly showed that the two dosage regimens were both therapeutically equivalent and significantly superior to placebo.

6.1.4. Study 1218.40

6.1.4.1. Study design and objectives

This was a Phase III, multi-national, multi-centre trial conducted at 231 sites in 32 countries. It was a 78 week open-label extension to trials assessing the safety and efficacy of linagliptin 5 mg as monotherapy, or in combination with other antidiabetic medications in T2DM patients. The objective of the study was to investigate the long-term safety and tolerability of linagliptin 5 mg QD during open-label treatment. An additional objective was to assess the efficacy of linagliptin alone or in combination with other commonly prescribed medications in diabetic patients. Enrolled patients continued their previous treatment from Study 1218.15 (linagliptin 5 mg plus pioglitazone 30 mg), Study 1218.16 (linagliptin 5 mg alone), Study 1218.17 (linagliptin 5 mg plus metformin) or Study 1218.18 (linagliptin 5 mg plus metformin and SU). Patients treated with placebo in previous trials were treated with linagliptin 5 mg in this study. Up to 2000 patients who met the entry criteria were to continue their treatment, starting ideally one the same day but with a window of up to 10 days from the last treatment day of the previous study. The key inclusion criterion was completion of the entire treatment period of the preceding double-blind trial, whether or not they had required rescue medication. The statistical analyses were descriptive and the main efficacy endpoint was change from baseline in HbA1c over time.

A total of 2121 patients were treated with study medication. The demographic data were comparable between the 'new' Lina group (589 patients previously treated with placebo) and the 'old' Lina group (1532 patients previously treated with linagliptin). Overall, 51.8% were male and the majority were White (56.7%) or Asian (42.0%). Mean age was 57.5 years and the majority (75.1%) were below 65 years. Mean BMI was 29.0 kg/m^2. The mean HbA1c in the total population was 7.51% (7.38% in the old Lina group and 7.87% in the new Lina group). There were more patients with good diabetic control (HbA1c <7.0%) in the old Lina group, and more patients with poor diabetic control (HbA1c >8.0%) in the new Lina group.

6.1.4.2. Efficacy outcomes

In the former linagliptin group (old Lina), HbA1c levels already achieved during the 24 week treatment period were maintained with a maximum reduction of -0.03% at Week 30. In the former placebo group (new Lina), the mean baseline HbA1c was higher than in the old Lina group (7.87% versus 7.38%). The maximum effect of linagliptin on HbA1c in the new Lina group was recorded at Week 18 (mean 7.17% with change from baseline -0.68%). Overall, the changes in the old and new Lina groups were sustained over the 78 week duration of the study. Among patients with HbA1c ≥7.0% at baseline, the frequency of patients with HbA1c <7.0% increased progressively in both linagliptin groups up until Week 30 (Table 17). At Week 78, HbA1c levels <7.0% were observed in 20% of the old Lina group and 30.1% of the new Lina group in patients with baseline HbA1c ≥7.0%. A tabulation of the number of patients who achieved a reduction of HbA1c of at least 0.5% showed that at Week 78, 24.9% of the old Lina patients and 49.9% of the new Lina patients had achieved a response. Rescue therapy was required by 31.4% and 28.0% of the old and new Lina patients respectively.

Table 17. Study 1218.40. Number of patients with HbA1c <7% over time by exposure to linagliptin/TS.

	Old lina		New lina	
Response criterion	n^1 / N^2	%	n^1 / N^2	%
Week 6				
HbA_{1c} <7.0%	500 / 1443	34.7	174 / 550	31.6
Among patients with baseline HbA_{1c} ≥7.0%	103 / 940	11.0	81 / 451	18.0
Week 18				
HbA_{1c} <7.0%	513 / 1454	35.3	232 / 567	40.9
Among patients with baseline HbA_{1c} ≥7.0%	152 / 943	16.1	135 / 461	29.3
Week 30				
HbA_{1c} <7.0%	521 / 1426	36.5	237 / 554	42.8
Among patients with baseline HbA_{1c} ≥7.0%	174 / 921	18.9	154 / 451	34.1
Week 42				
HbA_{1c} <7.0%	463 / 1399	33.1	213 / 544	39.2
Among patients with baseline HbA_{1c} ≥7.0%	160 / 903	17.7	131 / 441	29.7
Week 54				
HbA_{1c} <7.0%	431 /1368	31.5	204 / 535	38.1
Among patients with baseline HbA_{1c} ≥7.0%	145 / 878	16.5	130 / 434	30.0
Week 66				
HbA_{1c} <7.0%	463 / 1354	34.2	217 / 533	40.7
Among patients with baseline HbA_{1c} ≥7.0%	182 / 868	21.0	141 / 431	32.7
Week 78				
HbA_{1c} <7.0%	384 / 1131	34.0	168 / 443	37.9
Among patients with baseline HbA_{1c} ≥7.0%	145 / 724	20.0	109 / 362	30.1

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

Comment: This study confirms the long-term efficacy of linagliptin for up to 78 weeks in both linagliptin experienced and naive patients. Patients who had achieved good HbA1c control with linagliptin and other OADs maintained control. Patients who received linagliptin in addition to their previous OADs achieved an additional clinically meaningful benefit which was also sustained long-term.

6.1.5. Study 1218.52

6.1.5.1. Study design and objectives

This was a Phase III, randomised, double-blind, parallel group extension study to investigate the safety and efficacy of twice daily administration of the free combination of linagliptin 2.5 mg + metformin 500 mg or of linagliptin 2.5 mg + metformin 1000 mg versus monotherapy with metformin 1000 mg twice daily over 54 weeks in T2DM patients previously completing the double-blind part of Study 1218.46. It was a multi-national, multi-centre comprising a two week titration period followed by 52 weeks of treatment. Patients randomised to Lina 2.5 + Met 500, Lina 2.5 + Met 1000, or Met 1000 in the preceding trial continued the same medication into this extension study. Patients randomised in the previous trial to metformin 500 mg BID, linagliptin 5 mg QD or placebo, were randomised to one of the same treatments in the extension trial (Table 18). The key inclusion criterion was completion of the entire double-blind treatment period of Study 1218.46 without rescue medication. There was no primary endpoint but there was a descriptive analysis of several secondary endpoints which included the change from baseline in Hba1c and the occurrence of a relative efficacy response (HbA1c lowering of at least 0.5%).

Table 18. Study 1218.52. Study design

Randomised treatment in trial 1218.46 *†					
Linagliptin 2.5 mg plus metformin 500 mg b.i.d. (lina 2.5 + met 500)	Linagliptin 2.5 mg plus metformin 1000 mg b.i.d. (lina 2.5 + met 1000)	Metformin 1000 mg b.i.d. (met 1000)	Placebo*	Linagliptin 5 mg q.d.*	Metformin 500 mg b.i.d. (met 500)
↓	↓	↓	↓	↓	↓
Double-blind treatment in trial 1218.52					
Patients continue previous treatment			*Patients randomised to 1 of 3 treatments as follows:*		
lina 2.5 + met 500	lina 2.5 + met 1000	met 1000	lina 2.5 + met 500 or lina 2.5 + met 1000* or met 1000* (1:1:1 ratio)	lina 2.5 + met 500 or lina 2.5 + met 1000* (1:1 ratio)	lina 2.5 + met 500 or met 1000 (1:1 ratio)

* Patients not treated with metformin in trial 1218.46 who were randomised to treatment with metformin 1000 mg b.i.d. were to be treated with a lower dose of metformin (500 mg b.i.d.) for the first 2 weeks of this extension trial.

† Patients treated with open-label therapy in trial 1218.46 were not eligible to continue into this extension trial.

Note: The study was still ongoing when the CSR was written and the full Week 54 data were not available. The results presented are those of a second interim analysis.

A total of 566 patients were treated and 333 (58.7%) patients continued the treatment to which they had been randomised in Study 1218.46. A total of 233 patients (41.1%) switched treatments in the extension trial and were randomised to Met 1000 (n=61), Lina 2.5 + Met 500 (n=112) and Lina 2.5 + Met 1000 (n=60) as shown in Table 19. The demographic characteristics were similar in each treatment group. Overall, the majority of patients were White (65.2%) and male (54.8%) with mean age 55.8 years. Mean BMI was 29.0 kg/m^2 and mean body weight was 79.6 kg. There were no meaningful demographic differences between the switched (SWS) and non-switched (NONS) patient groups at baseline. The baseline efficacy variables were comparable with mean HbA1c 7.5%. The mean HbA1c in the switched set (7.95%) was higher than for the TS (7.5%) and fewer patients had a baseline HbA1c <7.0% (18.0% versus 33.0%).

Table 19. Study 1218.52. Disposition of patients entering the extension trial. Screened set.

	met 1000 N (%)	lina 2.5 + met 500 N (%)	lina 2.5 + met 1000 N (%)	Total N (%)
Entered				567
Randomised	171	225	171	567
Not treated	1	0	0	1
Treated [1]	170 (100.0)	225 (100.0)	171 (100.0)	566 (100.0)
Not prematurely discontinued trial medication [2]	156 (91.8)	199 (88.4)	153 (89.5)	508 (89.8)
Prematurely discontinued trial medication	14 (8.2)	26 (11.6)	18 (10.5)	58 (10.2)
Reason for discontinuation				
Adverse event	6 (3.5)	7 (3.1)	7 (4.1)	20 (3.5)
Study disease worsening	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Other disease worsening	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other AE	6 (3.5)	6 (2.7)	7 (4.1)	19 (3.4)
Lack of efficacy [3]	2 (1.2)	6 (2.7)	0 (0.0)	8 (1.4)
Non-compliance to protocol	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)
Lost to follow-up	1 (0.6)	1 (0.4)	2 (1.2)	4 (0.7)
Refused to continue trial medication	3 (1.8)	4 (1.8)	3 (1.8)	10 (1.8)
Other reason	2 (1.2)	7 (3.1)	6 (3.5)	15 (2.7)

1 'Treated' refers to treatment with randomised study drug

2 Includes all randomised patients for whom no end of trial eCRF page was completed up to the cut-off date for the second interim analysis

3 Includes patients who discontinued due to hyperglycaemia

6.1.5.2. Efficacy outcomes

In the first 30 weeks of treatment (when meaningful patient numbers were available), there was a modest benefit in HbA1c change from baseline in the linagliptin groups compared with the Met 1000 group (Table 20). In the SWS, the mean change in HbA1c from baseline to Week 30 was more marked in the Lina 2.5 + Met 1000 group (-1.25%) than in the Lina 2.5 + Met 500 group (-0.89%) and the Met 1000 group (-0.58%). The NONS group continued to receive the randomised treatment from the previous Study 1218.46 and there were no meaningful changes in HbA1c during the extension study. Categorical HbA1c responses (HbA1c <7.0% and <6.5%) showed that overall, more patients in the Lina 2.5 + Met 1000 group achieved target responses than patients in the Lina 2.5 + Met 500 and Met 1000 treatment groups.

Comment: This was a second interim analysis of an ongoing study with meaningful data available up to Week 30. Patients who did not switch treatment from the previous study maintained the treatment benefit in the extension study. Patients who did switch treatment from monotherapy or placebo to the combination of linagliptin and metformin had additional benefit. Overall, there was a treatment benefit in favour of Lina 2.5 + Met 1000 compared with Lina 2.5 + Met 500 and Met 1000. The frequency of relative responders (HbA1c reduction ≥0.5%) was higher in both linagliptin combination groups than in the metformin monotherapy group.

Table 20. Study 1218.52. Mean values at each visit and mean change in HbA1c from baseline to each visit. TS.

	met 1000 (N=170)		lina 2.5 + met 500 (N=225)		lina 2.5 + met 1000 (N=171)	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
HbA_{1c} [%]						
Baseline	165	7.48 (0.99)	224	7.64 (1.04)	170	7.35 (1.12)
Week 6	161	7.36 (0.96)	205	7.32 (0.91)	161	7.04 (0.88)
Week 18	140	7.18 (0.84)	186	7.18 (0.88)	149	6.96 (0.89)
Week 30	75	7.04 (0.75)	98	7.10 (0.88)	89	6.85 (0.78)
Week 42	21	6.80 (0.78)	23	6.92 (0.73)	28	6.57 (0.71)
Week 54	6	6.95 (0.73)	4	6.95 (0.87)	7	6.59 (0.43)
Change in HbA_{1c} [%] from baseline						
To Week 6	156	-0.06 (0.41)	204	-0.25 (0.52)	160	-0.27 (0.60)
To Week 18	136	-0.08 (0.56)	185	-0.30 (0.80)	148	-0.34 (0.93)
To Week 30	71	-0.19 (0.78)	98	-0.46 (0.87)	88	-0.40 (0.90)
To Week 42	20	-0.56 (0.90)	22	-0.34 (0.83)	27	-0.49 (1.07)
To Week 54	6	0.10 (0.75)	3	-0.20 (0.72)	6	-0.15 (0.63)

6.2. Analyses performed across trials (pooled analyses and meta-analyses)

None reported.

6.3. Evaluator's conclusions on the clinical efficacy of the combination of linagliptin and metformin for the treatment of type 2 diabetes

The three proposed linagliptin/metformin FDC formulations are 2.5 mg/500 mg, 2.5 mg/850 mg and 2.5 mg/1000 mg given twice daily. The 2.5 mg/850 mg combination is intended to permit optimal titration of the metformin dose when the highest dose is not indicated or not tolerated. The intermediate dose was not tested in the pivotal efficacy study but it is justifiable to interpolate from the lowest and highest dose data.

The pivotal study was placebo-controlled and compared the highest and lowest dose free combinations, linagliptin 2.5 mg BID and metformin 500 mg or 1000 mg BID, and the respective monotherapies, linagliptin 5 mg QD (which is therapeutically equivalent to 2.5 mg BID as shown in Study 1218.62) or metformin 500 mg or 1000 mg BID. The pivotal study was extended into an uncontrolled[6] long-term extension Study 1218.52 in which the treatments were the same (with the exception of placebo). Another uncontrolled long-term Study 1218.40 compared the efficacy of the linagliptin and metformin combination (with and without SU) in patients extending treatment from supporting studies. The main efficacy variable in all studies was changes in HbA1c from baseline over time and the key secondary variables included FPG and target HbA1c <7.0%. To allow meaningful comparisons, randomisation in the key studies was stratified by the quality of diabetic control at baseline (HbA1c above or below 8.5%) and the number of OADs being used at the time of enrolment. Studies that investigated the efficacy of the linagliptin and metformin combination lasted from 12 to 104 weeks but exposure was similar in the respective treatment groups in each study. With the exception of the open-label extension studies[7], the pivotal and supportive studies were randomised, double-dummy, double-blind and placebo and/or active-controlled. The studies were well balanced for baseline characteristics including age, gender, race, disease characteristics and baseline HbA1c, and they were representative of the target diabetic patient population. [information redacted].

[6] Sponsor comment: "1218.52 was a metformin monotherapy controlled double-blind randomised extension study."
[7] Sponsor comment: "There was only one open-label uncontrolled extension study (study 1218.40)".

In the pivotal study, both free combinations of twice daily linagliptin 2.5 mg and metformin 500 mg and 1000 mg were superior to the individual metformin components (500 mg and 1000 mg BID) and to linagliptin 5 mg QD. The mean treatment differences in HbA1c from baseline to Week 24 were -0.51% (95% CI -0.73, -0.30, p<0.0001) for Lina 2.5 + Met 1000 compared with Met 1000 alone, and -1.14% (95% CI -1.36, -0.92, p<0.0001) for Lina 2.5 + Met 1000 compared to Lina 5 mg alone. The Lina 2.5 + Met 500 combination was also superior to the individual components (p<0.0001 for both comparisons), and overall there was a benefit in favour of Lina 2.5 + Met 1000 compared with Lina 2.5 + Met 500, and Met 1000 monotherapy. In the extension studies, the benefit in favour of the linagliptin/metformin combination treatments was either sustained or marginally increased for up to 102 weeks of continuous therapy. Patients who had received linagliptin + metformin + SU had a decrease in mean HbA1c of -0.72% from baseline to Week 24 and this was also sustained for up to 102 weeks.

There were statistically significant and clinically meaningful reductions in FPG with the linagliptin/metformin treatment groups in all trials from baseline until the end of the observation periods. This was associated with reduced use of rescue medication and more patients achieved HbA1c levels <7.0%. These and other efficacy endpoints were notably consistent with mean changes in HbA1c ranging from -0.51% to -0.64% in the various studies. Changes in HbA1c ≥0.5% are clinically meaningful and lead to improved disease outcomes in patients with any baseline level of HbA1c. Overall, there is a clear efficacy benefit in favour of the linagliptin/metformin combination compared with either component alone.

7. Clinical safety

7.1. Studies providing evaluable safety data

The studies tabulated below provided evaluable safety data with groupings based on the study treatments, comparators, background treatment and study duration (note the SAF-C nomenclature) (Table 21).

Table 21. Studies providing safety data in this submission. Groupings of studies for the evaluation of safety.

Safety grouping	Study characteristics and objectives	Studies	Phase	Planned treatment duration	Treatments	Number of patients, N Randomised (total)	Treated
SAF-C1	Double-blind, placebo-controlled study with metformin background; comparing safety of linagliptin plus metformin versus metformin alone	1218.17	III	24 weeks	Lina: 5 mg qd Met: background	701	Lina+Met: 523 Met:177 total 700
SAF-C2	Double-blind, active-controlled study with metformin background; comparing safety of linagliptin plus metformin versus glimepiride plus metformin	1218.20	III	104 weeks	Lina: 5 mg qd Glim: 1 to 4 mg qd Met: background	1552	Lina+Met: 776 Glim+Met: 775 total 1551
SAF-C3	Double-blind, placebo-controlled study with metformin background (different metformin doses); comparing safety of linagliptin plus metformin versus metformin alone	1218.62	II	12 weeks	Lina: 2.5 mg bid[9] Lina: 5 mg qd[9] Met: background	491	Lina2.5+Met:223 Lina5+Met: 224 Met: 44 total 491
SAF-C4	Double-blind, placebo-controlled study; comparing different doses of linagliptin and metformin combination therapies with respective monotherapies	1218.46[1]	III	24 weeks	Pbo Lina: 5 mg qd Met: 500 mg bid Met: 1000 mg bid Lina 2.5 mg + Met 500 mg, bid Lina 2.5 mg + Met 1000 mg, bid	791	Pbo: 72 Lina5: 142 Met500: 144 Met1000: 147 Lina2.5+Met500: 143 Lina2.5+Met1000:143 total 791
SAF-C5[10]	Double-blind, placebo-controlled studies with metformin background; comparing safety of linagliptin plus metformin (free or fixed combination) with metformin alone	1218.6[2] 1218.17 1218.46[1] 1218.62	II III III II	≤24 weeks	Lina: 5, 10 mg qd; Met:background see SAF-C1 see SAF-C4 see SAF-C3	333 701 791 491 total 1971	Lina5:66,Lina10:66,Met:71 see SAF-C1 see SAF-C4 see SAF-C3
SAF-C6	Studies to assess long-term safety of linagliptin and metformin combination therapy	1218.46[1] 1218.52[5]	III III	≤78 weeks[3]	Met: 1000 mg bid Lina 2.5 mg + Met 500 mg, bid Lina 2.5 mg + Met 1000 mg, bid	567[8]	Met1000: 147[5] Lina2.5+Met500: 143[5] Lina2.5+Met1000: 143[5] total 433[5]

Safety grouping	Study characteristics and objectives	Studies	Phase	Treatment duration	Treatments	Number of patients, N Randomised (total)	Treated
SAF-C7	Double-blind, placebo-controlled study with metformin and SU background; comparing safety of linagliptin plus metformin and SU versus metformin and SU alone	1218.18	III	24 weeks	Lina: 5 mg qd Met: background SU: background	1058	Met+SU: 263 Lina+Met+SU: 792 total 1055
SAF-C8	All studies with linagliptin plus metformin (metformin as background or given as free combination with linagliptin) to assess safety in a large patient population	1218.6[2] 1218.17 1218.18 1218.20 1218.40[4] 1218.46 1218.52 1218.62	II III III III III III III II	≤104 weeks	see SAF-C5 see SAF-C1 see SAF-C7 see SAF-C2 Lina: 5 mg qd; Met,SU:background see SAF-C4, incl. open-label arm[6] see SAF C6 see SAF-C3	333 701 1058 1552 --[4] 791 + 66 567[8] 491	Lina+Met:132 Lina+Met: 523 Lina+Met: 792 Lina+Met: 776 Lina+Met: --[4] Lina+Met: 352 Lina+Met: 286[8] Lina+Met: 447 total 3529
SAF-C9	Studies in healthy subjects[7]	1288.1 1288.2 1288.3 1288.4 1218.4 1218.47	I I I I I I	<2 weeks	Lina 2.5 mg + Met 1000 mg Lina 2.5 mg + Met 500 mg Lina 2.5 mg + Met 850 mg Lina 2.5 mg / Met 1000 mg Lina 10 mg qd + Met 850 mg tid Lina 2.5 mg + Met 1000 mg	96 95 96 32 16 20	FDC: 96, free: 95 FDC: 94, free: 95 FDC: 96, free: 96 32 16 FDC: 20, free: 20 total 354

7.1.1. Pivotal efficacy studies

In the pivotal efficacy Study 1218.46, the following safety data were collected:

- General adverse events (AEs) were collected, documented and reported to the sponsor from inclusion at screening until 7 days following the last drug exposure. Patients were asked to report AEs to the investigator spontaneously and this was followed by specific questioning. AE intensity was classified as mild, moderate or severe and causality was assigned by the investigator. Changes in blood pressure, heart rate, electrocardiogram (ECG) and physical examination were recorded as AEs if they were not already associated with an already reported AE.
- AEs of particular interest included hypersensitivity reactions, renal adverse reactions, increased liver function test (LFT) >3x upper limit of normal (ULN), severe cutaneous AEs and pancreatitis and they were reported in the same manner as SAEs to the sponsor.
- Hypoglycaemic events were recorded as AE and graded according to pre-defined plasma glucose levels and symptom severity.

- Laboratory tests, including standard haematology, biochemistry and urine panels, were performed at three Covance central laboratories.
- An independent external committee (CEC) regularly reviewed events suspected to be stroke, cardiac ischaemia, myocardial infarction and cardiac death. The CEC adjudicated these events based on pre-specified criteria.

7.1.2. Pivotal studies that assessed safety as a primary outcome

Studies that assessed safety as a primary outcome are tabulated above.

7.1.3. Dose-response and non-pivotal efficacy studies

The dose-response and non-pivotal efficacy studies which provided safety data are tabulated above.

7.1.4. Pivotal studies that assessed safety as a primary outcome

Not applicable.

7.2. Patient exposure

In placebo-controlled studies, 1183 patients received placebo and 2566 patients received linagliptin 5 mg. Study duration ranged from 12 days to 24 weeks. Mean exposure was 133.9 days in placebo patients and 148.2 days for patients treated with linagliptin 5 mg. The duration of exposure in the linagliptin 5 mg group was 1041.4 patient years. In long-term follow-up studies of linagliptin monotherapy, 336 patients received linagliptin 5 mg and 523 patients received linagliptin 5 mg + metformin as background therapy for up to 102 weeks. The mean exposure was 617 days in patients receiving linagliptin and 623 days for patients receiving linagliptin + metformin. The duration of exposure was 567.9 patient years in patients receiving linagliptin and 891.5 patient years in patients receiving linagliptin + metformin.

In the placebo-controlled trial 1218.17 (SAF-C1, see tabulated studies above), 177 patients received metformin and 523 patients received linagliptin + metformin for a planned duration of 24 weeks. Mean exposure was comparable between groups (165 days met and 167 days Lina + Met). In the active-controlled Study 1218.20 (SAF-C2), 776 patients received linagliptin + metformin and 775 patients received linagliptin + glimepiride (Glim) for a planned duration of 104 weeks. Mean exposure was 627 days for Lina + Met patients and 625 days for Glim + Met patients. In the placebo-controlled trial with different linagliptin dosing regimens (1218.62, SAF-C3), 44 patients received metformin and 447 patients received linagliptin + metformin for a planned duration of 12 weeks. Mean exposure was comparable between groups (84 days Met and 83 days Lina + Met). In the pivotal efficacy study of free combination linagliptin + metformin (1218.46, SAF-C4), 72 patients received placebo, 142 patients received linagliptin 5 mg, 291 patients received metformin monotherapy, and 286 patients received linagliptin + metformin combination therapy for a planned duration of 24 weeks. The mean exposure was comparable across the treatment groups (144 days placebo, 158 days Lina, 159 days Met and 161 days Lina + Met).

In the pooled metformin-controlled studies (SAF-C5), 583 patients received metformin and 1388 patients received linagliptin + metformin and the planned study durations ranged from 12 to 24 weeks. The mean exposure was 146 days in the Met group and 130 days in the Lina + Met group. In the SAF-C6 long-term safety group, 147 patients received metformin 1000 mg, 143 patients received linagliptin 2.5 mg + metformin 500, and 143 patients received linagliptin 2.5 mg + metformin 1000 mg with a planned study duration of at least 24 weeks. The planned duration of the extension Study 1218.52 was 54 weeks but at the time of the interim analysis about 50% had an exposure of 24 weeks or more. Mean exposure was comparable across the groups (327 days Met 1000, 333 days Lina 2.5 + Met 500 and 335 days Lina 2.5 + Met 1000). In SAF-C7, the 263 patients received Met + SU and 792 patients received Lina + Met + SU. The

mean exposure in both treatment groups was 170 days. In SAF-C8 (all Phase II and III trials), 3529 patients received linagliptin + metformin with planned study durations ranging from 12 to 54 weeks. The mean exposure was 545 days. In SAF-C9, 354 healthy subjects were treated with linagliptin + metformin. The studies ranged from one to nine days and the mean exposure was two days.

7.3. Adverse events

7.3.1. All adverse events (irrespective of relationship to study treatment)

7.3.1.1. Pivotal study 1218.46

In the randomised TS, the proportion of patients who reported AEs was comparable between treatment groups, ranging from 49.0% in the Lina + Met group to 56.6% in the Lina 2.5 + Met 1000 group (Table 22). Most AEs were mild to moderate. Severe AEs were infrequent, ranging from 0.7% in the Met 500 group to 3.4% in the Met 1000 group. Pre-defined significant AEs were reported by 3.5% to 5.6% of patients. There were no patients with renal events, severe cutaneous adverse reactions or pancreatitis in any treatment group and only one patient (0.7%) in the Lina 5 group had a hypersensitivity reaction. In the open-label arm (Lina 2.5 + Met 1000), 53.0% of patients reported an AE, 3.0% reported AEs of severe intensity, and significant AEs were reported by 6.1% of patients. There were no cases of renal events, severe cutaneous reactions or pancreatitis.

Table 22. Study 1218.46 Adverse events. Overall Summary. Treated set.

	Placebo	Lina 5	Met 500	Met 1000	Lina 2.5 + Met 500	Lina 2.5 + Met 1000
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Number of patients	72 (100.0)	142 (100.0)	144 (100.0)	147 (100.0)	143 (100.0)	143 (100.0)
Patients with any AE	39 (54.2)	80 (56.3)	75 (52.1)	74 (50.3)	70 (49.0)	81 (56.6)
Patients with severe AEs	1 (1.4)	2 (1.4)	1 (0.7)	5 (3.4)	4 (2.8)	2 (1.4)
Patients with investigator defined drug-related AEs	10 (13.9)	15 (10.6)	14 (9.7)	13 (8.8)	16 (11.2)	13 (9.1)
Patients with significant AEs[1]	4 (5.6)	8 (5.6)	5 (3.5)	7 (4.8)	5 (3.5)	8 (5.6)
Patients with 'other significant' AEs (ICH E3)	5 (6.9)	4 (2.8)	2 (1.4)	3 (2.0)	5 (3.5)	2 (1.4)
Patients with AEs leading to discontinuation of trial drug	5 (6.9)	6 (4.2)	3 (2.1)	6 (4.1)	5 (3.5)	3 (2.1)
Patients with serious AEs	1 (1.4)	3 (2.1)	3 (2.1)	6 (4.1)	2 (1.4)	2 (1.4)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Disabling	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Requiring hospitalisation	1 (1.4)	3 (2.1)	3 (2.1)	5 (3.4)	2 (1.4)	1 (0.7)
Prolonging hospitalisation	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	1 (0.7)	1 (0.7)	1 (0.7)	0 (0.0)	1 (0.7)
Patients with hypoglycaemic events[2]	1 (1.4)	0 (0.0)	2 (1.4)	5 (3.4)	5 (3.5)	0 (0.0)
Patients with adjudicated AEs[3]	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	2 (1.4)	1 (0.7)

Note: if combined with metformin 500 mg or 1000 mg, linagliptin was administered as 2.5 mg b.i.d.
[1] i.e. hypersensitivity reactions, renal AEs, increased liver enzymes (all based on investigator reporting); note that severe cutaneous adverse reactions and pancreatitis are not included.
[2] As reported by the investigator.
[3] Confirmed cardiac and cerebrovascular events.

The most frequently reported AEs were gastrointestinal (ranging from 9.7% to 19.6%), infections (ranging from 16.3% to 23.1%), metabolic disorders (ranging from 4.9% to 16.7%) and nervous system disorders (ranging from 3.4% to 13.9%, Table 23). The AE profile in the OLS was broadly similar. Gastrointestinal (GI) disorders were least frequent in the Met 500 group (9.7%) and most frequent in the Lina 2.5 + Met 1000 group (19.6%). Diarrhoea was the

most frequently reported individual GI AE in all treatment groups with the highest frequency in the Lina 2.5 + Met 1000 group (7.7%). For metabolic disorders, patients in the placebo group had the highest frequency of AE (16.7%) compared with 4.9% in the Lina 2.5 + Met group. The difference was driven largely by an excess of hyperglycaemic episodes in the placebo group.

Table 23. Study 1218.46. Frequency of patients with AEs occurring at an incidence of more than 2% in either treatment group on preferred term level, sorted by overall frequency and System Organ Class. Treated set.

	Placebo N (%)	Lina 5 N (%)	Met 500 N (%)	Met 1000 N (%)	Lina 2.5 + Met 500 N (%)	Lina 2.5 + Met 1000 N (%)
Number of patients	72 (100.0)	142 (100.0)	144 (100.0)	147 (100.0)	143 (100.0)	143 (100.0)
Number of patients with any AE	39 (54.2)	80 (56.3)	75 (52.1)	74 (50.3)	70 (49.0)	81 (56.6)
Blood and lymphatic system disorders	2 (2.8)	1 (0.7)	3 (2.1)	1 (0.7)	2 (1.4)	3 (2.1)
Eosinophilia	2 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	0 (0.0)	4 (2.8)	4 (2.8)	1 (0.7)	2 (1.4)	1 (0.7)
Vertigo	0 (0.0)	2 (1.4)	3 (2.1)	1 (0.7)	0 (0.0)	1 (0.7)
Gastrointestinal disorders	10 (13.9)	17 (12.0)	14 (9.7)	23 (15.6)	20 (14.0)	28 (19.6)
Constipation	1 (1.4)	2 (1.4)	3 (2.1)	0 (0.0)	2 (1.4)	1 (0.7)
Diarrhoea	2 (2.8)	5 (3.5)	3 (2.1)	8 (5.4)	7 (4.9)	11 (7.7)
Gastritis	2 (2.8)	1 (0.7)	1 (0.7)	0 (0.0)	4 (2.8)	3 (2.1)
Hyperchlorhydria	0 (0.0)	0 (0.0)	3 (2.1)	1 (0.7)	1 (0.7)	1 (0.7)
Nausea	0 (0.0)	1 (0.7)	0 (0.0)	5 (3.4)	4 (2.8)	3 (2.1)
Vomiting	1 (1.4)	2 (1.4)	0 (0.0)	1 (0.7)	3 (2.1)	0 (0.0)
General disorders and administration site conditions	5 (6.9)	9 (6.3)	14 (9.7)	12 (8.2)	3 (2.1)	10 (7.0)
Fatigue	1 (1.4)	4 (2.8)	1 (0.7)	5 (3.4)	1 (0.7)	1 (0.7)
Pyrexia	2 (2.8)	3 (2.1)	5 (3.5)	2 (1.4)	0 (0.0)	6 (4.2)
Infections and infestations	16 (22.2)	26 (18.3)	29 (20.1)	24 (16.3)	31 (21.7)	33 (23.1)
Gastroenteritis	1 (1.4)	3 (2.1)	2 (1.4)	1 (0.7)	1 (0.7)	1 (0.7)
Influenza	3 (4.2)	6 (4.2)	7 (4.9)	5 (3.4)	6 (4.2)	1 (0.7)
Nasopharyngitis	1 (1.4)	8 (5.6)	4 (2.8)	4 (2.7)	12 (8.4)	6 (4.2)
Pharyngitis	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.0)	0 (0.0)	3 (2.1)
Pharyngitis bacterial	1 (1.4)	1 (0.7)	0 (0.0)	0 (0.0)	3 (2.1)	1 (0.7)
Respiratory tract infection	3 (4.2)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.4)
Upper respiratory tract infection	2 (2.8)	1 (0.7)	6 (4.2)	0 (0.0)	3 (2.1)	6 (4.2)
Urinary tract infection	2 (2.8)	2 (1.4)	4 (2.8)	3 (2.0)	2 (1.4)	7 (4.9)
Investigations	4 (5.6)	10 (7.0)	13 (9.0)	11 (7.5)	8 (5.6)	12 (8.4)
ALT increased	0 (0.0)	3 (2.1)	2 (1.4)	5 (3.4)	2 (1.4)	2 (1.4)
Blood amylase increased	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	0 (0.0)	3 (2.1)
Glomerular filtration rate decreased	4 (5.6)	5 (3.5)	4 (2.8)	3 (2.0)	2 (1.4)	6 (4.2)

Table 23. Continued.

	Placebo N (%)	Lina 5 N (%)	Met 500 N (%)	Met 1000 N (%)	Lina 2.5 + Met 500 N (%)	Lina 2.5 + Met 1000 N (%)
Number of patients	72 (100.0)	142 (100.0)	144 (100.0)	147 (100.0)	143 (100.0)	143 (100.0)
Number of patients with any AE	39 (54.2)	80 (56.3)	75 (52.1)	74 (50.3)	70 (49.0)	81 (56.6)
Metabolism and nutrition disorders	12 (16.7)	10 (7.0)	16 (11.1)	11 (7.5)	16 (11.2)	7 (4.9)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	3 (2.1)
Hyperglycaemia	10 (13.9)	5 (3.5)	12 (8.3)	3 (2.0)	5 (3.5)	2 (1.4)
Hypoglycaemia	1 (1.4)	0 (0.0)	2 (1.4)	4 (2.7)	4 (2.8)	0 (0.0)
Musculoskeletal and connective tissue disorders	5 (6.9)	13 (9.2)	8 (5.6)	13 (8.8)	13 (9.1)	14 (9.8)
Arthralgia	0 (0.0)	2 (1.4)	2 (1.4)	2 (1.4)	2 (1.4)	4 (2.8)
Back pain	2 (2.8)	5 (3.5)	0 (0.0)	5 (3.4)	2 (1.4)	8 (5.6)
Muscle spasms	1 (1.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.1)	0 (0.0)
Pain in extremity	0 (0.0)	2 (1.4)	3 (2.1)	2 (1.4)	1 (0.7)	2 (1.4)
Nervous system disorders	3 (4.2)	11 (7.7)	20 (13.9)	5 (3.4)	15 (10.5)	13 (9.1)
Diabetic neuropathy	1 (1.4)	1 (0.7)	1 (0.7)	0 (0.0)	2 (1.4)	3 (2.1)
Headache	1 (1.4)	6 (4.2)	7 (4.9)	3 (2.0)	4 (2.8)	4 (2.8)
Paraesthesia	1 (1.4)	1 (0.7)	3 (2.1)	1 (0.7)	4 (2.8)	2 (1.4)
Psychiatric disorders	3 (4.2)	2 (1.4)	5 (3.5)	1 (0.7)	2 (1.4)	0 (0.0)
Anxiety	2 (2.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Insomnia	0 (0.0)	0 (0.0)	4 (2.8)	1 (0.7)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (1.4)	2 (1.4)	4 (2.8)	3 (2.0)	4 (2.8)	5 (3.5)
Cough	1 (1.4)	1 (0.7)	1 (0.7)	1 (0.7)	2 (1.4)	3 (2.1)
Vascular disorders	4 (5.6)	4 (2.8)	6 (4.2)	5 (3.4)	5 (3.5)	5 (3.5)
Hypertension	4 (5.6)	4 (2.8)	5 (3.5)	4 (2.7)	5 (3.5)	5 (3.5)

The number of patients with AEs in a SOC is based on all AEs within this SOC, not only on the most frequent AEs >2%.
Note: if combined with metformin 500 mg or 1000 mg, linagliptin was administered as 2.5 mg b.i.d.

7.3.1.2. Other studies

In all placebo-controlled trials (SAF-C2) of linagliptin monotherapy, AEs were reported in 53.8% of 1183 placebo patients and 55.0% of 2566 linagliptin 5 mg patients. AE profiles were comparable for severe AEs (1.4% placebo and 1.8% linagliptin 5 mg) and pre-defined AEs of special interest (0.8% placebo, 0.6% linagliptin 5 mg). There were no meaningful differences between the linagliptin and placebo groups with the exception of hypoglycaemia (7.6% linagliptin, 4.1% placebo) and hyperglycaemia (5.0% linagliptin, 10.6% placebo). Cardiac disorders were infrequent (1.4% placebo, 2.4% linagliptin). In the long-term safety study (SAF-M1), AEs were reported in 277 of 336 patients (82.4%) in the Lina group, and in 434 of 523 patients (83.0%) in the Lina + Met group (Table 24). There were no meaningful differences between the groups with the exception of GI disorders (17.3% Lina, 26.2% Lina + Met), hyperglycaemia (36.6% Lina, 29.3% Lina + Met) and hypoglycaemia (2.4% Lina, 6.3% Lina + Met).

Table 24. Adverse events Overall summary for SAF-M1. TS.

	Lina N (%)	Lina+Met N (%)
Number of patients	336 (100.0)	523 (100.0)
Patients with any AE	277 (82.4)	434 (83.0)
Patients with severe AEs	14 (4.2)	27 (5.2)
Patients with investigator-defined drug-related AEs	31 (9.2)	73 (14.0)
Patients with AEs of special interest[1]	11 (3.3)	15 (2.9)
Patients with other significant AEs (based upon ICH E3)	8 (2.4)	15 (2.9)
Patients with AEs leading to discontinuation of trial medication[2]	12 (3.6)	18 (3.4)
Patients with serious AEs	31 (9.2)	67 (12.8)
Fatal	2 (0.6)	0 (0.0)
Immediately life-threatening	0 (0.0)	4 (0.8)
Disability	0 (0.0)	1 (0.2)
Requiring hospitalisation	27 (8.0)	66 (12.6)
Prolonging hospitalisation	1 (0.3)	1 (0.2)
Other	3 (0.9)	6 (1.1)

[1] i.e. hypersensitivity reactions, renal events, and hepatic events (based on investigator-reporting, excluding severe cutaneous adverse reactions and pancreatitis).

In SAF-C8 (all Phase II and III studies), 2603 of 3529 patients (73.8%) reported AEs were infections (including nasopharyngitis and cough) and infestations (36.6%), metabolism and nutrition disorders (29.7%), gastrointestinal disorders (22.4%), musculoskeletal and connective tissue disorders (21.2%) and nervous system disorders (14.7%). The most frequent AEs summarised by preferred term are shown in Table 24. Most AEs were either mild (36.3%) or moderate (31.4%). The frequency of AEs of severe intensity was low (6.1%) and <1% for any organ system. In the post-treatment period, 58 patients (1.9%) reported AEs of mild intensity. The number of events of special interest was low in each SAF. Few patients reported renal events (≤1.3%), hypersensitivity reactions (≤1.2%) and pancreatitis (≤0.2%).

Table 24. Frequency of patients with AEs occurring in more than 1% in either treatment group on the preferred term level, sorted by frequency for SAF-C8 (all Phase II and III studies). TS.

	SAF-C8 Lina+Met N (%)
Number of patients	3529 (100.0)
Patients with any AE	2603 (73.8)
Infections and infestations	1292 (36.6)
Nasopharyngitis	372 (10.5)
Upper respiratory tract infection	267 (7.6)
Urinary tract infection	209 (5.9)
Bronchitis	109 (3.1)
Influenza	111 (3.1)
Gastroenteritis	73 (2.1)
Pharyngitis	48 (1.4)
Sinusitis	49 (1.4)
Metabolism and nutrition disorders	1049 (29.7)
Hypoglycaemia	453 (12.8)
Hyperglycaemia	449 (12.7)
Hypertriglyceridaemia	62 (1.8)
Diabetes mellitus	56 (1.6)
Dyslipidaemia	54 (1.5)
Hyperuricaemia	50 (1.4)
Gastrointestinal disorders	789 (22.4)
Diarrhoea	201 (5.7)
Nausea	97 (2.7)
Constipation	83 (2.4)
Gastritis	80 (2.3)
Dyspepsia	78 (2.2)
Abdominal pain upper	75 (2.1)
Vomiting	61 (1.7)
Abdominal pain	48 (1.4)
Toothache	44 (1.2)
Musculoskeletal and connective tissue disorders	749 (21.2)
Back pain	191 (5.4)
Arthralgia	170 (4.8)
Pain in extremity	108 (3.1)
Musculoskeletal pain	82 (2.3)
Osteoarthritis	75 (2.1)
Muscle spasms	40 (1.1)
Myalgia	40 (1.1)

SAF-C8: Linagliptin was administered as 2.5 mg bid, 5 mg qd, or 10 mg qd in combination with metformin given either as background medication or free combination therapy (500 mg or 1000 mg, bid).

Table 24 Continued.

	SAF-C8 Lina+Met N (%)
Number of patients	3529 (100.0)
Patients with any AE	2603 (73.8)
Nervous system disorders	519 (14.7)
Headache	186 (5.3)
Dizziness	136 (3.9)
Diabetic neuropathy	42 (1.2)
Hypoaesthesia	41 (1.2)
Investigations	432 (12.2)
Glycosylated haemoglobin increased	68 (1.9)
Blood creatine phosphokinase increased	59 (1.7)
ALT increased	45 (1.3)
Blood amylase increased	38 (1.1)
General disorders and administration site conditions	383 (10.9)
Asthenia	63 (1.8)
Pyrexia	63 (1.8)
Fatigue	55 (1.6)
Oedema peripheral	56 (1.6)
Chest pain	49 (1.4)
Injury, poisoning and procedural complications	338 (9.6)
Fall	44 (1.2)
Joint sprain	40 (1.1)
Skin and subcutaneous tissue disorders	308 (8.7)
Pruritus	54 (1.5)
Respiratory, thoracic and mediastinal disorders	301 (8.5)
Cough	143 (4.1)
Oropharyngeal pain	44 (1.2)
Vascular disorders	260 (7.4)
Hypertension	166 (4.7)
Renal and urinary disorders	228 (6.5)
Microalbuminuria	43 (1.2)
Eye disorders	201 (5.7)
Cataract	42 (1.2)
Blood and lymphatic system disorders	129 (3.7)
Anaemia	85 (2.4)

SAF-C8: Linagliptin was administered as 2.5 mg bid, 5 mg qd, or 10 mg qd in combination with metformin given either as background medication or free combination therapy (500 mg or 1000 mg, bid).

An analyses of AEs in sub-groups was performed in SAF-C2 and C5 and showed that in the Lina + Met groups there were no clinically meaningful differences in the frequency of AEs based on age, gender, race, ethnicity, geographical region, renal function, hepatic impairment or metformin dose.

7.3.2. Treatment-related adverse events (adverse drug reactions)

7.3.2.1. Pivotal study 1218.46

The number of patients with AEs reported as drug-related ranged from 8.8% in the Met 1000 group to 13.9% in the placebo group. In the OLS, 9.1% of AEs were assessed and as drug-related.

7.3.2.2. Other studies

In SAF-C2, drug-related AEs were reported in 8.5% of placebo patients and 10.4% in the linagliptin 5 mg group. The most frequently reported events were hypoglycaemia (2.4% placebo, 5.0% linagliptin), and hyperglycaemia (1.5% placebo, 0.5% linagliptin). In SAF-MI, drug-related AEs were more common in the Lina + met group (14.0%) than in the Lina group (9.2%). In SAF-C8, drug-related AEs were reported in 17% of all patients receiving Lina + Met.

7.3.3. Deaths and other serious adverse events

7.3.3.1. Pivotal study 1218.46

The number of SAEs was low, ranging from 1.4% to 4.1%. There was only one death (due to MI) which occurred in the Met 1000 group and was considered unrelated. In the OLS, there were no deaths and only one SAE (an elective abortion).

7.3.3.2. Other studies

In SAF-C2, the frequency of SAEs was low (2.5% placebo, 2.7% linagliptin) with no meaningful differences between groups. In SAF-M1, the frequency of SAEs was low (4.2% Lina, 5.2% Lina + Met) with no meaningful differences between the groups. In SAF-C8, there were 18 fatal events (14 during treatment and 4 post-treatment). Of the 14 deaths during treatment, nine patients died while receiving linagliptin + metformin, and five deaths were reported in patients receiving metformin (either as monotherapy or in combination with glimepiride). None of the death rates was considered related to study medication. The causes of death were mainly cardiovascular events in patients aged 53 to 72 years.

7.3.4. Discontinuation due to adverse events

7.3.4.1. Pivotal study 1218.46

AEs leading to discontinuation ranged from 2.1% to 6.9% in the double-blind study, and 6.1% in the OLS.

7.3.4.2. Other studies

In SAF-C2, AEs leading to discontinuation occurred in 3.6% of placebo patients and 2.3% of the linagliptin 5 mg group. There were no meaningful differences between the two groups. In SAF-M1, AEs leading to discontinuation were comparable between groups (3.6% Lina, 3.4% Lina + Met). In SAF-C8, AEs leading to discontinuation occurred in 5.2% of patients.

7.4. Laboratory tests

7.4.1. Liver function

7.4.1.1. Pivotal study 1218.46

Overall, there were no clinically relevant LFT findings or differences between the treatment groups. Transitions from low/normal to ALT values >ULN at the end of treatment ranged from 1.9% in the Lina 5 group to 15.7% in the Lina 2.5 + Met 1000 group. In the OLS, transition from low/normal ALT to high values occurred in 11.1% of patients. No patients fulfilled the criteria for Hy's law.

7.4.1.2. Other studies

Overall, the number of LFT abnormalities was low and there was no evidence of hepatic toxicity. In SAF-C8, 27 patients (0.8%) had ALT elevations >3x ULN, nine patients (0.3%) had ALT elevations >5x ULN, two patients had ALT elevations >10x ULN and one patient had ALT elevation >20x ULN. Six patients (0.2%) had elevated total bilirubin levels >2x ULN, 36 patients (1.0%) had ALT/AST levels >3x ULN and 28 patients (0.8%) had elevated ALP levels >1.5x ULN.

7.4.2. Kidney function

7.4.2.1. Pivotal study 1218.46

In randomised patients, the majority of patients in all treatment groups had normal renal function or mild renal impairment. In all treatment groups there was a decrease in the percentage of patients with normal or mildly impaired renal function from baseline to last visit (placebo 98.2% to 96.5%; Lina 5 99.2% to 96.9%; Met 500 97.7% to 97.0%; Met 1000 99.2% to 98.4%; Lina 2.5 + Met 500 99.2 to98.4%; and Lina 2.5 + Met 1000 99.3% to 94.2%. There was a

comparable increase in the percentage of patients with moderate renal impairment from baseline to last visit in all treatment groups. In the OLS, there was an overall increase in the percentage of patients with normal or mildly impaired renal function from baseline to last visit (98.2% to 100%). Renal events reported as AEs occurred in 15 (0.4%) of 3529 patients in SAF-C8 (Table 25).

Table 25. Overview of AEs of special interest. TS.

	Hypersensitivity reactions[1] N (%)	Renal events[2] N (%)	Hepatic events[3] N (%)	Severe cutaneous adverse reactions[4] N (%)	Pancreatitis N (%)
SAF-C1					
Met (N = 177)	0 (0.0)	1 (0.6)	2 (1.1)	0 (0.0)	0 (0.0)
Lina+Met (N = 523)	1 (0.2)	0 (0.0)	4 (0.8)	0 (0.0)	0 (0.0)
SAF-C2					
Lina+Met (N = 776)	8 (1.0)	4 (0.5)	34 (4.4)	0 (0.0)	1 (0.1)
Glim+Met (N = 775)	9 (1.2)	10 (1.3)	35 (4.5)	0 (0.0)	0 (0.0)
SAF-C3					
Met (N = 44)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lina+Met (N = 447)	0 (0.0)	0 (0.0)	4 (0.9)	0 (0.0)	0 (0.0)
SAF-C4					
Placebo (N = 72)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Lina (N = 142)	1 (0.7)	0 (0.0)	5 (3.5)	0 (0.0)	0 (0.0)
Met (N = 291)	0 (0.0)	0 (0.0)	10 (3.4)	0 (0.0)	0 (0.0)
Lina+Met (N = 286)	0 (0.0)	0 (0.0)	4 (1.4)	0 (0.0)	0 (0.0)
SAF-C5					
Met (N = 583)	0 (0.0)	1 (0.2)	12 (2.1)	0 (0.0)	0 (0.0)
Lina+Met (N = 1388)	1 (0.1)	0 (0.0)	14 (1.0)	0 (0.0)	1 (0.1)
SAF-C6					
Met1000 (N = 147)	0 (0.0)	1 (0.7)	12 (8.2)	0 (0.0)	0 (0.0)
Lina2.5+Met500 (N = 143)	0 (0.0)	0 (0.0)	9 (6.3)	0 (0.0)	0 (0.0)
Lina2.5+Met1000 (N = 143)	1 (0.7)	0 (0.0)	6 (4.2)	0 (0.0)	0 (0.0)
SAF-C8					
Lina+Met (N = 3529)	26 (0.7)	15 (0.4)	129 (3.7)	0 (0.0)	6 (0.2)

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

7.4.2.2. Other studies

In SAF-C8, 47.6% of patients had normal renal function at the end of treatment. Of the patients with normal renal function at baseline, 22.4% developed mild renal impairment, 0.7% developed moderate renal impairment and two patients (0.1%) developed severe renal impairment. Of the patients with mild renal impairment at baseline, 16.3% developed normal renal function and 8.0% developed moderate renal impairment. Of the patients with moderate renal impairment at baseline, 25.5% developed mild renal impairment, one patient (0.7%) developed normal renal function and two patients (1.4%) developed severe renal impairment.

7.4.3. Other clinical chemistry

7.4.3.1. Pivotal study 1218.46

Overall, no clinically relevant changes from baseline or significant differences between groups for any other biochemistry parameters were observed. Differences were observed for platelets, ALP, gamma glutamyltransferase (GGT), creatinine kinase, glucose, LDL and triglycerides were

observed but they were not clinically significant. In the OLS, no clinically relevant findings compared to baseline or between treatment groups were noted.

7.4.3.2. Other studies

Laboratory data at baseline, last value on treatment and changes from baseline were analysed descriptively in each SAF group. In general, there were no clinically meaningful differences from baseline to last value on treatment for any clinical chemistry parameters in any treatment group.

Possibly clinically significant abnormalities were low in all SAF groups. In SAF-C8 (all Phase II and III studies) significant events were noted in ≤6.4% of the population, with the exception of triglyceride abnormalities in 14.5%.

7.4.4. Haematology

7.4.4.1. Pivotal study 1218.46

There were no clinically relevant changes from baseline or significant differences between groups for any haematological parameter in the randomised group or the OLS.

7.4.4.2. Other studies

In general, the mean values at baseline and last value for all haematology parameters and differential counts were comparable between the treatment groups.

7.4.5. Hypoglycaemia

7.4.5.1. Pivotal study 1218.46

Symptomatic hypoglycaemic events were reported as AE. Overall, only 13 events were recorded and none were recorded in the Lina 2.5 + Met 1000 group. One patient in the OLS had five hypoglycaemic events while on treatment.

7.4.5.2. Other studies

Overall, the number of hypoglycaemic events was low and comparable in all treatment groups. An exception was SAF-C2 in which there were more events in the Glim + Met group (36.1%) than in the Lina + Met group (7.5%)($p<0.0001$). Most events (67.5%) occurred in the first month of treatment and most patients did not require external assistance. In SAF-C8, 14.0% of patients reported hypoglycaemic events and 3.8% reported severe hypoglycaemic events. One episode was reported by 36.7% of patients, 2-3 episodes by 29.4%, and ≥4 episodes by 34.0%. The number of episodes was similar in all age groups.

7.4.6. Electrocardiograph

7.4.6.1. Pivotal study 1218.46

No formal analysis of ECG changes was reported. The few significant ECG changes were reported as cardiac AE.

7.4.6.2. Other studies

ECGs were evaluated by the investigator and clinically significant abnormalities were reported as AEs. There were no meaningful differences between any of the treatment groups.

7.4.7. Vital signs

7.4.7.1. Pivotal study 1218.46

There were only trivial differences in systolic and diastolic blood pressure and heart rate. Vital signs were comparable in each treatment group at baseline and over time until the end of the randomised period. No meaningful changes over time were observed in the OLS.

7.4.7.2. Other studies

Changes in systolic and diastolic blood pressure and heart rate were analysed descriptively and summarised by treatment group. No clinically meaningful changes were observed from baseline or between the respective groups.

7.5. Postmarketing experience

This is a new drug application and no postmarketing data are available for the FDC. Linagliptin monotherapy has been approved in Australia only recently and no postmarketing data have been submitted in this application. Metformin has been in widespread use for 50 years and extensive post-marketing data are available.

7.6. Safety issues with the potential for major regulatory impact

7.6.1. Liver toxicity

No signals suggestive of liver toxicity were identified. In SAF-C8, there were 129 (3.7%) hepatic events in 3529 patients in the Lina + Met group.

7.6.2. Haematological toxicity

No signals suggestive of haematological toxicity were identified.

7.6.3. Serious skin reactions

No severe cutaneous adverse reactions were identified in any study.

7.6.4. Cardiovascular safety

Cardiovascular safety was assessed in a meta-analysis of eight trials in a total of 5239 diabetic patients. The primary endpoint was the adjudicated composite of cardiovascular death (including fatal stroke and fatal MI), non-fatal MI, non-fatal stroke and angina requiring hospitalisation. Median drug exposures in the linagliptin, placebo and active comparator groups were 175, 367 and 619 days respectively. A total of 11 primary events were observed in the linagliptin group and 23 events in the total comparator group with incidence rates per 1000 years of 5.3 for linagliptin and 16.8 for the comparators. A Kaplan-Meier plot illustrating the timescale of the events is shown in Figure 9. There was a highly significant risk reduction in favour of linagliptin compared with the total comparator group (Figure 10). When all placebo-controlled trials versus linagliptin were plotted, there were trends in favour of linagliptin but the differences in cardiovascular risk were not statistically significant (Figure 11).

Figure 9. Kaplan-Meier plot for time to primary endpoint (linagliptin versus total comparator.

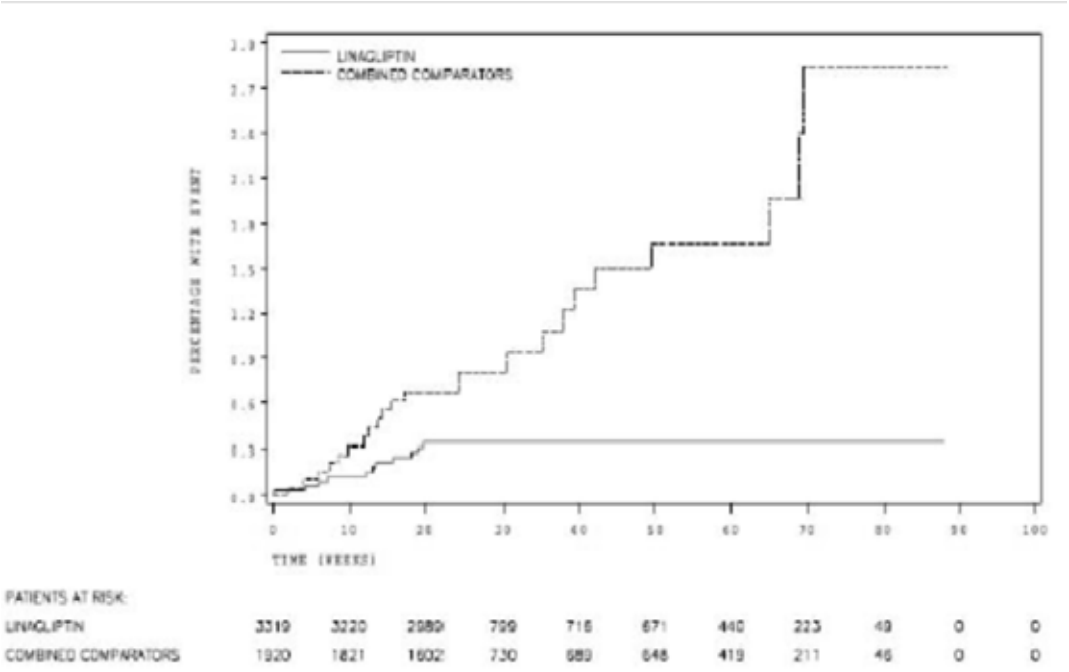


Figure 10. Forest plot of risk of primary end point for linagliptin versus total comparator. a) risk with 95% CI and b) risk with 98% CI

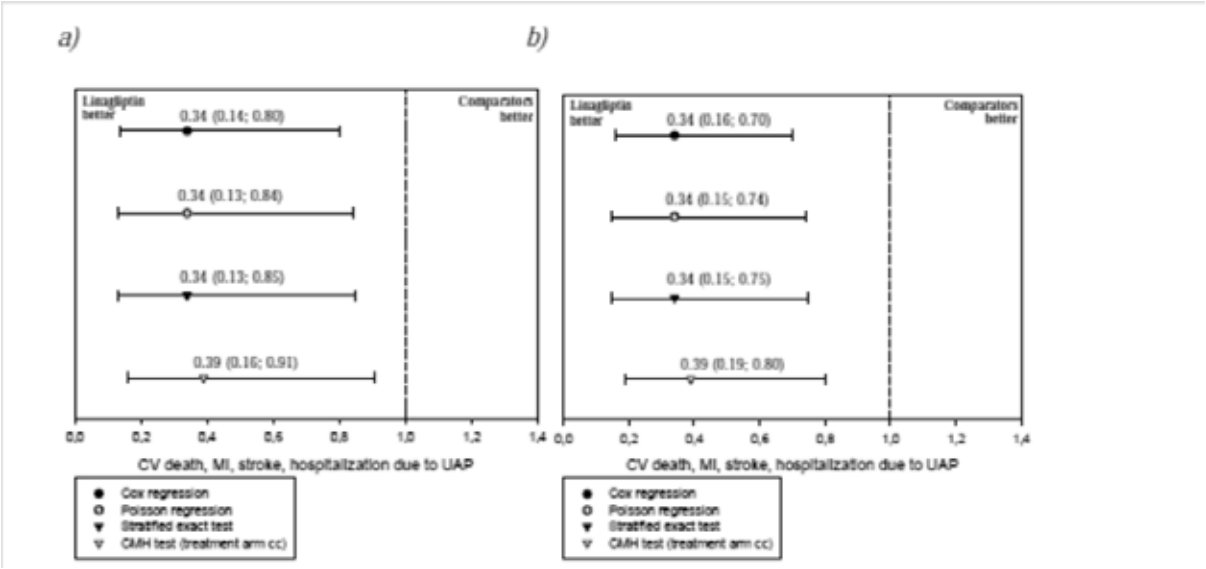
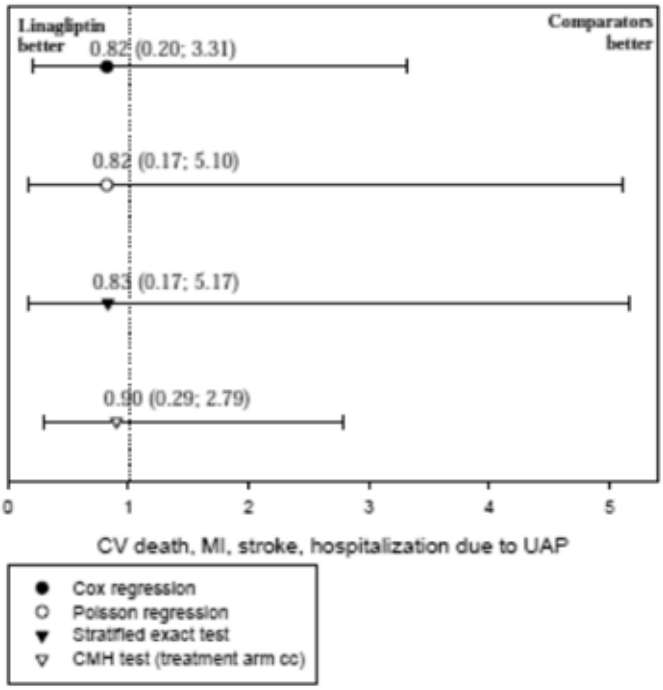


Figure 11. Forest plot of risk of primary end point for all placebo-controlled trials versus linagliptin



7.6.5. Unwanted immunological events

Not applicable.

7.7. Other safety issues

7.7.1. Safety in special populations

There were no meaningful differences in safety in sub-groups defined by race, gender or BMI. Relatively few patients were aged >75 years but their AE profile was similar to younger patients. Patients with severe renal impairment were excluded. However, the AE profiles in patients with normal renal function or mild to moderate renal impairment were comparable.

7.7.2. Safety related to drug-drug interactions and other interactions

No studies have examined the proposed FDC tablets interactions with other drugs.

7.8. Evaluator's overall conclusions on clinical safety

The safety of the combination of linagliptin and metformin was assessed in 3529 patients with type 2 diabetes. Long-term exposure was high with 2694 patients receiving treatment for at least 24 weeks, 2081 patients for at least 52 weeks and 1756 patients for more than 78 weeks. The adverse event profile of the linagliptin/metformin combination was assessed in placebo-controlled studies, in studies against active comparators, in long-term extension studies and in sub-group analyses. In studies of the free combination (SAF-C4), adverse event rates were comparable between treatment groups (52.8% placebo, 54.9% linagliptin, 49.5% metformin and 50.7% linagliptin/metformin). Severe AEs (1.4% placebo and 1.4% linagliptin, 2.1% metformin and 2.1% linagliptin/metformin) and AEs of special interest (2.8% placebo, 4.2% linagliptin, 2.4% metformin, and 1.7% linagliptin/metformin) were also comparable between groups. AEs leading to discontinuation were infrequent, comparable in each group but numerically highest in the placebo group.

In all Phase II and III studies (SAF-C8), SAEs occurred in approximately 10% of patients and were comparable between treatment groups. The incidence by preferred term was less than 1% and there were no trends towards a particular organ system. Serious cardiac disorders were reported in 2% of patients, mainly angina in 0.5% and myocardial infarction in 0.3%. However, a meta-analysis of events per 1000 years showed no increased risk in patients receiving the linagliptin/metformin combination. Events of special interest, including stroke, acute and chronic pancreatitis, serious skin eruptions, renal failure and hypersensitivity reactions, were no more common in patients receiving the combination treatment. There were 14 deaths during the treatment periods in all studies and 4 deaths in post-treatment follow-up periods. Nine deaths occurred in patients receiving linagliptin/metformin and five deaths in patients receiving metformin monotherapy or in combination with glimepiride. None of the deaths was considered drug related and the incidence per 1000 patient years was similar in the combination group compared with metformin monotherapy.

Overall the incidence of significant laboratory abnormalities was low and comparable in each treatment group. There was no trend towards increasing renal impairment during long-term treatment. There was no evidence of liver toxicity and the incidence of significant hepatic events was low in all treatment groups. Analyses in sub-groups showed no effects on safety based on age, gender, race, BMI, ethnicity, hepatic function and degree of renal impairment (although metformin is contra-indicated in patients with hepatic and severe renal failure).

There was an increased incidence of GI disturbance such as nausea, vomiting and diarrhoea in the metformin groups. In the linagliptin groups, there was an increased incidence of nasopharyngitis and cough compared with placebo and a low but increased incidence of pancreatitis. The incidence of these adverse drug reactions was in keeping with the known safety profiles of linagliptin and metformin and there was no evidence to suggest an increased incidence of AEs when used in combination.

The incidence of hypoglycaemia was generally low and similar (<3%) in patients treated with linagliptin and placebo. It was identified as an AE only in patients treated with linagliptin/metformin and SU. In general, the symptomatic hypoglycaemic events were not severe and did not require external intervention.

8. First round benefit-risk assessment

8.1. First round assessment of benefits

The benefits of the linagliptin/metformin FDC in the proposed usage are:

- Increased convenience and compliance (the only potential benefit compared with the free combination).
- Flexible metformin dosage
- A sustained improvement in glycaemic control
- Reduced use of rescue medication
- Good tolerability (including special groups)
- Lipid and weight neutral
- Hypoglycaemic events comparable to placebo
- Reduced dependence on SU (hypoglycaemia and weight gain)
- Potential to delay need for insulin by prolonging OAD therapy (not tested and an arguable benefit)

- Potential for better long-term disease outcomes (e.g. retinopathy, nephropathy) associated with HbA1c reduction

8.2. First round assessment of risks

The risks of the linagliptin/metformin FDC in the proposed usage are:

- Adverse events related to linagliptin (for example, nasopharyngitis, cough)
- Adverse events related to metformin (for example, GI side effects and lactic acidosis)
- Adverse events related to sulphonylureas (for example, hypoglycaemia, weight gain)
- Thoughtless prescribing without due attention to metformin precautions and contra-indications

8.3. First round assessment of benefit-risk balance

The benefit-risk balance of the linagliptin/metformin FDC given for the proposed usage was considered to be favourable.

9. First round recommendation regarding authorisation

Authorisation is recommended for the linagliptin/metformin FDC for the proposed indications:

a) 'as an adjunct to diet and exercise to improve glycaemic control in adults with T2DM when treatment with both linagliptin and metformin is appropriate, in patients inadequately controlled on metformin alone or those already being treated and well controlled with the free combination of linagliptin and metformin'.

b) (b)'in combination with a sulphonylurea (that is, triple combination therapy)as an adjunct to diet and exercise in patients inadequately controlled on their maximum tolerated dose of metformin and a sulphonylurea'.

10. Clinical questions

10.1. Pharmacokinetics

The accumulation factors for linagliptin AUC and C_{max} were 1.40 and 1.49, respectively, (in Afro-American subjects) with T2DM at steady state. Please confirm that no data were submitted in the dossier regarding the bioequivalence of the free tablets and proposed FDCs formulations at steady-state.

Please confirm that no new information is submitted regarding the drug-drug interaction between the proposed FDC tablets and other drugs.

11. Second round evaluation of clinical data submitted in response to questions

11.1. Sponsor's response to *pharmacokinetics* question listed above (Section 10).

Boehringer Ingelheim confirmed that there were no bioequivalence studies done under steady state conditions with the FDC formulation. The sponsor had not received the clinical evaluation report at this stage and therefore did not have any context as to why this question has been asked, that is, data on the pharmacokinetics characteristics of linagliptin in Afro-American subjects and whether the bioequivalence data on the FDC formulation was performed at steady state.

The sponsor provided the following comments: The linagliptin/metformin FDC is an immediate release tablet that is recommended to be taken as two tablets twice daily. Linagliptin is also an immediate release tablet, but is recommended to be taken as one tablet daily.

The bioequivalence studies conducted with the free tablets and the proposed FDC formulations (Studies 1288.1, 12882 and 1288.3) were single dose studies as recommended for immediate release products. A single dose study is generally considered as most sensitive to detect formulation differences, whereas a multiple dose study is only required for extended release products where the accumulation might depend on the formulation if flip-flop kinetics[8] are present. The primary endpoints for these single dose studies were C_{max} for both linagliptin and metformin, and AUC_{0-72} for linagliptin and AUC_{0-inf} for metformin. Due to the long terminal half-life of linagliptin of more than 100 h, a truncated AUC_{0-72} was used instead of AUC_{0-inf} for linagliptin for the primary endpoint (which is in line with the TGA adopted European Union (EU) *Guideline on the investigation of bioequivalence*[9]).

In contrast, Study 1218.55 was a multiple dose study to determine the pharmacokinetic/pharmacodynamic characteristics of linagliptin (without metformin) in Afro-American subjects. The primary endpoints of $AUC_{\tau,ss}$ and $C_{max,ss}$ were at steady state. In addition, the accumulation factors reported for linagliptin in this study (1.40 for AUC and 1.49 for C_{max}) are similar to the previously reported values.

No dedicated drug-drug interactions studies were performed with the FDC. Extensive data exists on the drug-drug interaction of the individual actives (linagliptin and metformin) of the FDC. Data was provided during the initial evaluation of linagliptin that co-administration with metformin did not impact on the pharmacokinetics of either linagliptin or metformin in healthy volunteers. Therefore in the proposed Australian Product Information, the section "*Interaction with other medicines*" has combined the same information from the linagliptin (Trajenta) PI and metformin (Diabex) PI.

[8] Flip-flop kinetics definition: In pharmacokinetics, flip-flop phenomenon happens when the rate of absorption is slower than the rate of elimination. The decline of the terminal slope during flip-flop pharmacokinetics will depend greatly on how fast absorption is taking place. In this case, the terminal slope is not controlled by the usual clearance and volume of distribution, but instead by bioavailability and the ka.

[9] CPMP/EWP/QWP/1401/98Rev.1/Corr** <http://www.tga.gov.au/pdf/euguide/ewp140198rev1.pdf>
Adopted by TGA with the following notation:
"While this guidance suggests that the design and conduct of the study should follow EU regulations on Good Clinical Practice, sponsors should note that the EU Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) has been adopted in Australia with TGA annotations.
The procedure for abridged applications claiming essential similarity to a reference product (ie, generics), which allows applications to be made to numerous Member States of the EU, based on bioequivalence with a reference product from one Member State, does not apply in Australia. An application for registration of a generic product in Australia should generally include a bioequivalence study versus a leading brand obtained in Australia."

11.2. Evaluator's response to the sponsor

11.2.1. Regarding evaluator's precaution in Afro-American subjects with T2DM

Very little new data were provided by the sponsor in regards to the effects of intrinsic and extrinsic factors on the PK of the new FDC. As the sponsor states in their response Study 1218.55 examined the single dose and steady state PKs of linagliptin 5 mg in patients with T2DM of African-American (AA) origin (Table 26).

Table 26. Study 1218.55. Geometric mean (%gCV) and mean (%CV) noncompartmental PK parameters of linagliptin after single and multiple oral administration of 5 mg linagliptin to AA T2DM patients n(N=41 (single dose) and N=39 (steady state).

	Unit	gMean	gCV[%]	Mean	CV[%]
AUC_{0-24}	[nmol·h/L]	137	32.4	144	33.5
C_{max}	[nmol/L]	10.9	57.6	12.7	63.1
t_{max}^{*}	[h]	1.50	1.00 - 8.00		
fe_{0-24}	[%]	0.504	214	1.16	137
CLR_{0-24}	[mL/min]	6.45	151	11.6	115
$AUC_{\tau,ss}$	[nmol·h/L]	194	25.8	200	26.4
$C_{max,ss}$	[nmol/L]	16.4	40.9	17.8	46.6
$t_{max,ss}^{*}$	[h]	1.50	0.500 - 4.00		
$C_{24,ss}$	[nmol/L]	5.94	25.5	6.12	25.5
$t_{1/2,ss}$	[h]	119	22.4	122	28.0
$Vz/F_{,ss}$	[L]	9400	36.0	10000	40.7
$CL/F_{,ss}$	[mL/min]	911	25.8	940	24.8
$MRT_{po,ss}$	[h]	102	20.3	104	20.6
$fe_{0-24,ss}$	[%]	4.42	45.2	4.82	42.0
$CLR_{0-24,ss}$	[mL/min]	40.3	33.7	42.4	31.7
RA,AUC_{0-24}	[.]	1.40	22.8	1.44	23.6
RA,C_{max}	[.]	1.49	52.8	1.67	47.8
$Accumulation,t_{1/2}$	[h]	13.1	44.0	14.3	42.2

* for tmax and tmax,ss, the median and range (min-max) is given

This study indicates that in patients of AA origin with T2DM the gMean C_{max} and AUC_{0-24} following a single 5 mg dose of linagliptin was 10.9 nM/L (5.15 ng/mL, assuming the molecular weight (MW) of linagliptin = 472.54)and 137 nM.h/L (64.7 ng.h/mL), respectively. At steady-state in these subjects the gMean C_{maxss} and $AUC_{t,ss}$ of linagliptin was 16.4 nM/L (7.74 ng/mL) and 194 nM.h/L (91.67 ng.h/mL), respectively.

By contrast, Study 1218.2, from the initial Category 1 application for linagliptin tablets 5 mg, examined the PKs of linagliptin 5 mg following a single dose and at steady-state in 8 Caucasian subjects with T2DM (Tables 27 and 28). This study demonstrated that in patients of Caucasian origin with T2DM the gMean C_{max} and AUC_{0-24} following a single 5 mg dose of linagliptin was 3.93 ng/mL and 56 ng.h/mL, respectively and at steady-state in these subjects the gMean C_{maxss} and $AUC_{t,ss}$ of linagliptin were 5.24 ng/mL and 74.7 ng.h/mL, respectively.

Table 27. Study 1218.2. Individual noncompartmental PK parameters of linagliptin after single oral administration of 5 mg linagliptin to patients with T2DM with descriptive statistics.

	AUC_{0-24} [ng·h/mL]	$AUC_{0-24,norm}$ [(ng·h/mL)/mg]	AUC_{0-t_z} [ng·h/mL]	t_z [h]	C_{max} [ng/mL]	$C_{max,norm}$ [(ng/mL)/mg]	t_{max} [h]	Ae_{0-24} [µg]	fe_{0-24} [%]	$CL_{R,0-24}$ [mL/min]
	62.7	12.5	61.7	23.5	4.57	0.914	3.00	36.7	0.734	9.76
	46.1	9.21	45.4	23.5	2.53	0.506	6.02	7.22	0.144	2.61
	47.9	9.58	47.1	23.5	2.81	0.562	2.00	6.83	0.137	2.38
	58.1	11.6	57.2	23.5	3.45	0.690	6.00	53.4	1.07	15.3
	46.2	9.23	45.4	23.5	2.65	0.530	1.50	25.1	0.502	9.07
	63.1	12.6	62.0	23.5	6.05	1.21	0.917	30.4	0.609	8.04
	69.2	13.8	68.1	23.5	7.79	1.56	1.50	95.9	1.92	23.1
	59.9	12.0	58.9	23.5	4.07	0.814	1.50	9.73	0.195	2.71
N	8	8	8	8	8	8	8	8	8	8
Mean	56.6	11.3	55.7	23.5	4.24	0.848	2.80	33.2	0.663	9.12
SD	8.84	1.77	8.70	0.0151	1.86	0.371	2.07	30.1	0.602	7.21
Median	46.1	9.21	45.4	23.5	2.53	0.506	0.917	6.83	0.137	2.38
Max	59.0	11.8	58.1	23.5	3.76	0.752	1.75	27.8	0.555	8.55
CV [%]	69.2	13.8	68.1	23.5	7.79	1.56	6.02	95.9	1.92	23.1
gMean	15.6	15.6	15.6	0.0644	43.8	43.8	73.7	90.8	90.8	79.1
gVC [%	56.0	11.2	55.1	23.5	3.93	0.786	2.26	22.6	0.453	6.73
	16.0	16.0	16.0	0.0644	42.4	42.4	78.0	125	125	106

Table 28. Study 1218.2. Individual noncompartmental PK parameters of linagliptin at steady state after multiple oral administration of 5 mg linagliptin to patients with T2DM with descriptive statistics.

	$AUC_{\tau,ss}$ [ng·h/mL]	$AUC_{\tau,ss,norm}$ [(ng·h/mL)/mg]	$C_{max,ss}$ [ng/mL]	$C_{max,ss,norm}$ [(ng/mL)/mg]	$t_{max,ss}$ [h]	$C_{min,ss}$ [ng/mL]	$t_{min,ss}$ [h]	$C_{pre,ss}$ [ng/mL]	$C_{pre,2}$ [ng/mL]	$C_{pre,3}$ [ng/mL]	$C_{pre,4}$ [ng/mL]
	80.1	16.0	5.05	1.01	1.50	2.85	23.5	2.89	2.06	2.04	2.14
	79.6	15.9	4.89	0.978	1.00	2.74	0.00	2.74	1.50	1.85	2.30
	70.5	14.1	4.73	0.946	1.00	2.36	23.5	2.46	1.63	2.07	2.36
	85.0	17.0	4.85	0.970	3.00	2.48	0.00	2.48	1.84	1.85	1.95
	61.4	12.3	3.75	0.750	3.00	1.94	23.5	1.99	1.58	1.62	1.61
	78.2	15.6	7.88	1.58	1.50	2.37	0.00	2.37	2.11	2.16	2.36
	73.3	14.7	5.70	1.14	1.00	2.35	0.00	2.35	2.26	2.53	2.40
	72.0	14.4	5.92	1.18	1.50	2.33	0.00	2.33	2.16	2.22	2.13
N	8	8	8	8	8	8	8	8	8	8	8
Mean	75.0	15.0	5.35	1.07	1.69	2.43	8.81	2.45	1.89	2.04	2.16
SD	7.30	1.46	1.22	0.243	0.843	0.278	12.2	0.273	0.294	0.277	0.269
Median	61.4	12.3	3.75	0.750	1.00	1.94	0.00	1.99	1.50	1.62	1.61
Max	75.7	15.1	4.97	0.994	1.50	2.37	0.00	2.42	1.95	2.06	2.22
CV [%]	85.0	17.0	7.88	1.58	3.00	2.85	23.5	2.89	2.26	2.53	2.40
gMean	9.73	9.73	22.7	22.7	49.9	11.4	138	11.1	15.5	13.6	12.5
gVC [%	74.7	14.9	5.24	1.05	1.53	2.41	---	2.44	1.87	2.03	2.14
	10.1	10.1	21.7	21.7	48.0	11.7	---	11.3	16.0	13.6	13.5

The evaluator's comparison of these results indicated that the exposure to linagliptin is increased following both single doses and at steady-state in Afro-American subjects with T2DM compared to Caucasians with T2DM, for example, at steady state the C_{max} and AUC of linagliptin 5 mg is approximately 1.48 and 1.23 fold higher in Afro-American subjects compared with Caucasians.

Therefore in the absence of a single study that directly compared linagliptin PKs in Afro-American and Caucasian subjects with T2DM, as recommended in the first round, the evaluator suggests that the precautions section of the PI should be modified and a new part should be added stating that:

"Race

Studies in Afro-American and Caucasian subjects with T2DM have identified that at steady state linagliptin AUC and Cmax were approximately 23% and 48% higher, respectively, in Afro-American subjects compared to Caucasians. Although this increase is unlikely to be clinically significant Afro-American subjects may require a reduction in dose."

In addition, the sponsor's *Summary of Clinical Pharmacology Studies* indicates that there is a similar increase in steady-state linagliptin exposure in Japanese and Chinese subjects with T2DM compared to Caucasians with T2DM and although this is unlikely to affect the efficacy of linagliptin in Asian subjects it may result in an increase in adverse drug-drug interactions. Therefore, a similar statement to the one above should be made in regards to Japanese and Chinese subjects.

11.2.2. In regards to drug-drug interaction studies with the FDC

This question was asked to establish whether the effects of drugs like cimetidine on metformin excretion or simvastatin on linagliptin metabolism were potentiated following administration of the FDC or free combination compared with when metformin or linagliptin were administered alone. The evaluator accepted that in the absence of these data then the listing of the drug-drug interactions of the two active components separately as it currently appears in the proposed PI was not ideal but was considered to be satisfactory.

12. Second round benefit-risk assessment

12.1. Second round assessment of benefits

No change in the assessment has occurred as a result of a final review following the sponsor's responses to the clinical questions (see *First Round Assessment of benefits above*).

12.2. Second round assessment of risks

No change in the assessment has occurred as a result of a final review following sponsor's responses to the clinical questions (see *First Round Assessment of risks above*).

12.3. Second round assessment of benefit-risk balance

No change in the assessment has occurred as a result of a final review following sponsor's responses to the clinical questions (see *First Round Assessment of benefit-risk balance above*).

13. Second round recommendation regarding authorisation

Authorisation is recommended for the fixed dose combination tablets containing linagliptin and metformin 2.5/500, 2.5/850 and 2.5/1000 mg as indicated below:

> *Trajentamet is an adjunct to diet and exercise to improve glycaemic control in adults with T2DM when treatment with both linagliptin and metformin is appropriate, in patients inadequately controlled on metformin alone or in those already being treated and well controlled with the free combination of linagliptin and metformin.*
>
> *Trajentamet is indicated in combination with a sulphonylurea (i.e., triple combination therapy) as an adjunct to diet and exercise in patients inadequately controlled on their maximal tolerated dose of metformin and a sulphonylurea.*

14. References

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