15 December 2016
EMA/ /215439/2017
Committee for Medicinal Products for Human Use (CHMP)

Variation assessment report

Procedure No. EMEA/H/C/WS0915

Medicinal products authorised through the centralised procedure

Invented name:	International non-proprietary name/Common name:	Product-specific application number
Trajenta	linagliptin	EMEA/H/C/002110/WS0915/0022
Jentadueto	linagliptin / metformin	EMEA/H/C/002279/WS0915/0030

Worksharing applicant (WSA): Boehringer Ingelheim International GmbH

Note

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

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List of abbreviations

AE	Adverse event
AESI	Acute pancreatitis
ALT	Alanine aminotransferase
ANCOVA	analysis of covariance
AST	Aspartate aminotransferase
BIcMQs	BI-customised MedDRA queries
BMI	body mass index
BP	blood pressure
CI	confidence interval
DBP	diastolic blood pressure
DPP	dipeptidyl-peptidase
eCCr	estimated creatinine clearance
eGFR	(Estimated) glomerular filtration rate
EMA	European Medicines Agency
Empa	empagliflozin
FAS	full analysis set
FDA	Food and Drug Agency
FDC	fixed dose combination
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GLP	glucagon-like peptide
Hb	haemoglobin
IPV	important protocol violation
ITT	intention to treat
Lina	linagliptin
LOCF	analysis of covariance
MAA	marketing authorisation application
MAH	marketing authorisation holder
MACE	Major adverse cardiovascular events
Met	metformin
MDRD	modification of diet in renal disease
mITT	modified intention to treat
MMRM	mixed model repeated measures
NCF	noncompleters considered failure
OC	observed cases
OL	open-label
OLFAS	open-label full analysis set
OR	original result
PIP	paediatric investigation plan
PPS	per protocol set
PSUR	periodic safety update report
PT	Post-treatment
REML	restricted maximum likelihood
RMP	Risk Management Plan
RS	randomised set
SBP	systolic blood pressure
SD	standard deviation
SGLT	Sodium-dependent glucose co-transporter
SmPC	Summary of the medicinal product characteristics
SMQ	Standardised MedDRA Queries
SU	Sulphonylurea
TS	treated set
TZD	Thiazolidinedione
T2DM	type 2 diabetes mellitus
ULN	Upper limit of normal

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Boehringer Ingelheim International GmbH submitted to the European Medicines Agency on 9 February 2016 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following variation was requested:

Variation requested		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include use of Trajenta as combination therapy with metformin and an SGLT-2 inhibitor and use of Jentadueto as combination therapy with an SGLT-2 inhibitor; as a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated based on studies 1245.30, 1275.10 and 1275.1. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to make minor editorial changes in the SmPC for Jentadueto only. Moreover, the updated RMP version 10 (for Trajenta) and version 12 (for Jentadueto) have been submitted.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/114/2009 and P/3/2010 on the agreement of a paediatric investigation plan (PIP) for Trajenta and the granting of a product-specific waiver for Jentadueto, respectively.

At the time of submission of the application, the PIP P/114/2009, was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The applicant did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

Appointed Rapporteur for the WS procedure:

Johann Lodewijk Hillege

Timetable	Actual dates
Submission date	9 February 2016
Start of procedure:	27 February 2016
CHMP Rapporteur Assessment Report	25 April 2016
PRAC Rapporteur Assessment Report	25 April 2016
PRAC Outcome	13 May 2016
CHMP members comments	17 May 2016
Updated CHMP Rapporteur(s) (Joint) Assessment Report	20 May 2016
Request for supplementary information (RSI)	26 May 2016
Submission of MAH's responses	12 August 2016
Re-start date of the procedure	15 August 2016
CHMP Rapporteur Assessment Report	21 September 2016
CHMP members comments	3 October 2016
Updated CHMP Rapporteur Assessment Report	7 October 2016
Request for Supplementary information	13 October 2016
MAHs submission of responses	14 October 2016
Restart of the procedure	16 November 2016
CHMP Rapporteur Assessment Report	28 November 2016
CHMP members comments	N/A
Updated CHMP Rapporteur Assessment Report	N/A
Opinion	15 December 2016

2. Scientific discussion

2.1. Introduction

In August 2011, linagliptin (Trajenta) film-coated tablets 5 mg were approved in the European Union (EU/1/11/707) for the treatment of adult patients with type 2 diabetes mellitus. Approval of an indication extension was granted in October 2012 for the use of Trajenta in combination with insulin when insulin and metformin do not provide adequate glycaemic control.

In July 2012, a fixed-dose combination (FDC) of linagliptin and metformin (Jentadueto) film-coated tablets (2.5 mg linagliptin/850 mg metformin bid and 2.5 mg linagliptin/1000 mg metformin bid) was approved in the European Union (EU/1/12/780) for the treatment of adult patients with type 2 diabetes mellitus. Approval of an indication extension was granted in January 2014 for the use of Jentadueto in combination with insulin when insulin and metformin do not provide adequate glycaemic control.

With the present submission, the MAH was applying for the use of Trajenta as combination therapy with metformin and an SGLT-2 inhibitor and for the use of Jentadueto as combination therapy with an SGLT-2 inhibitor. Because the applications for Trajenta and Jentadueto are based on the same set of clinical trials and analyses, the content of the Clinical Overview and the Summaries of Clinical Efficacy cover both products.

2.2. Non-clinical aspects

No new clinical data has been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

2.3.2. Pharmacokinetics

To support this indication extension the company has also submitted an interaction study1245.30. This interaction study has been submitted previously during the clinical development programme for the FDC empagliflozin/ linagliptin EMEA/H/C/003833/0000. In this study it was shown that there is no significant interaction between empagliflozin and linagliptin.

Further in procedure EMEA/H/C/003833/0000 the company has shown that the FDC empagliflozin/ linagliptin used in studies 1275.10 and 1275.1 is bioequivalent with the mono-components in study 1275.3. Therefore the bridging of the results of study 1275.10 and 1275.1, with the FDC, to the mono-components is appropriately justified.

A short description of interaction study 1245.30 can be found below.

Study 1245.30

Study 1245.30 investigated the relative bioavailability of multiple doses empagliflozin 50 mg and linagliptin 5 mg after concomitant administration compared to multiple doses of empagliflozin 50 mg and linagliptin 5 mg administered alone to 16 healthy male volunteers

The subjects received the following treatments:

Treatment AB_C	A: Empagliflozin once daily for 5 days B: Empagliflozin and linagliptin in combination for 7 days Washout 35 days C: Linagliptin once daily for 7 days	8 subjects
Treatment C_AB	C: Linagliptin once daily for 7 days Washout 35 days A: Empagliflozin once daily for 5 days B: Empagliflozin and linagliptin in combination for 7 days	8 subjects

The concentration of empagliflozin 50 mg and linagliptin were determined in plasma an urine samples. Further DPP-4 inhibition was assessed as a surrogate marker of the effect of linagliptin and glucose excretion was analysed the glucose excretion was assessed as a surrogate marker of the effect of empagliflozin.

The $AUC_{\tau,ss}$ of empagliflozin was similar when the drug was given alone and in combination with linagliptin but the $C_{max,ss}$ of empagliflozin was reduced by approximately 12% when the drug was given with linagliptin. Median $t_{max,ss}$ of empagliflozin was slightly longer when the drug was given with linagliptin (1.5 h) than when given alone (1.0 h). The urinary secretion of empagliflozin and linagliptin was similar between the treatments.

Table 1 Analysis of relative bioavailability of Empagliflozin and linagliptin

	Geometric means			Two-sided 90% confidence interval		
	Treatment A Empagliflozin 50mg	Treatment B Empagliflozin and linagliptin in combination	Treatment C Linagliptin 5mg	gMean ratio [%]	Lower limit [%]	Upper limit [%]
Empagliflozin				A/B		
AUCtau, ss (nmol*h/L)	9230	9390		101.7	96.5	107.2
Cmax, ss (nmol/L)	1440	1270		88.3	78.8	98.9
Fe0-24,ss [%]	20.7	20.4				
CLR,0-24,ss [mL/min]	41.4	40.1				
Linagliptin				C/B		
AUCtau, ss (nmol*h/L)		158	152	103.3	96.1	111.1

Cmax, ss (nmol/L)	11.2	11.0	101.5	86.9	118.5
Fe0-24,ss [%]	4.77	4.26			
CLR,0-24,ss [mL/min]	53.2	49.6			

Trough DPP-4 inhibition (E24,ss) was similar when linagliptin was administered with BI 10773 compared with linagliptin alone. Empagliflozin alone had no effect on DPP-4 activity. (Table 2)

Table 2 Inhibition of DPP-4 after multiple oral administration of 5 mg linagliptin q.d. and 50 mg BI 10773 q.d., alone and in combination

	Linagliptin 5 mg q.d. (Reference) (N=16)	Empagliflozin 50 mg q.d. (Reference) (N=16)	Linagliptin 5 mg q.d. and Empagliflozin 50 mg q.d. (Test) (N=16)
	Median (range)	Median (range)	Median (range)
E24,ss [%]	83.7 (76.5 to 86.6)	-0.576 (-15 to 13.4)	83.9 (71.9 to 90.1)

Urinary glucose excretion over 24 h was assessed as a surrogate marker of the effect of Empagliflozin. The mean (± SD) cumulative amount of glucose excreted in urine over 24 h (Ae0-24) was approximately 18% lower when BI 10773 was administered with linagliptin (54.8 ± 11.2 g) than when the drug was given alone (67.2 ± 14.6 g). When linagliptin was given alone, urinary glucose excretion was negligible. The rate of glucose excretion was also slightly decreased. The combination of 50 mg Empagliflozin and 5 mg linagliptin q.d. was safe and well tolerated in all patients .

The mild decrease of the urinary glucose excretion does not appear to be related to the slightly decreased Empagliflozin C_{max} , as around $t_{max,ss}$ of Empagliflozin (1.5 hours) the decrease of the urinary glucose excretion rate was similar to other time-intervals. Furthermore, no change in total exposure of empagliflozin (AUC) was found after linagliptin co-administration. As the rate of glucose excretion is it is mainly driven by concentration gradient of blood glucose, other factors, such as disease status, meals and antidiabetic medication may have caused the small and variable effect on the glucose excretion

Therefore it can be concluded that no clinical significant interaction between empagliflozin and linagliptin was observed and that the drugs can be coadministered without dose adjustment.

2.4. Clinical efficacy

Linagliptin (Trajenta) is a selective, orally administered, xanthine-based dipeptidyl-peptidase-4 (DPP-4) inhibitor. Linagliptin lowers blood glucose by extending the half-life of glucagon-like peptide 1 (GLP-1), which is secreted in response to a meal. GLP-1 lowers blood glucose by augmenting the glucose-stimulated insulin release and limiting glucagon secretion to slow gastric emptying and to induce satiety. DPP-4 inhibitors are associated with a low risk of hypoglycaemia because GLP-1 activity ceases when plasma glucose concentration falls below 55 mg/dL.

The combination of linagliptin with metformin provides treatment benefits by lowering glucose and reducing glycosylated haemoglobin (HbA1c) further than monotherapy with either component. Combining linagliptin with metformin in a fixed dose combination tablet simplifies the antidiabetic therapy by decreasing the number of tablets to be taken and should improve the adherence of patients with their antidiabetic treatment.

Empagliflozin is a potent and selective inhibitor of the sodium-dependent glucose co-transporter-2 (SGLT-2), which is expressed in the renal proximal tubules and accounts for approximately 90% of renal glucose reabsorption. Inhibition of SGLT-2 decreases the renal reabsorption of glucose, thereby promoting glucose excretion in the urine with a consequent reduction in blood glucose levels. The mechanism of action of empagliflozin is independent of β-cell function and of the insulin pathway, which contributes to a low risk of hypoglycaemia. SGLT-2 inhibition is associated with weight loss and a reduction in blood pressure.

Because linagliptin, metformin, and SGLT-2 inhibitors improve glycaemic control via different mechanisms, their combination represents a potentially therapeutic option for patients with type 2 diabetes. This assessment report provides an overview of the clinical efficacy and safety of linagliptin as add-on therapy to metformin and the SGLT-2 inhibitor empagliflozin.

2.4.1. Dose response studies

The optimum daily linagliptin dose of 5 mg was determined in dose finding trials of the linagliptin development programme. In the entire Phase III programme, linagliptin 5 mg once daily was shown to be safe and efficacious and is the approved dose.

2.4.2. Main studies

The pivotal data on the efficacy of linagliptin as add-on therapy to empagliflozin and metformin in patients with type 2 diabetes was derived from the double-blind, placebo-controlled, Phase III trial 1275.10. These data were also submitted as part of the MAA for Glyxambi, the FDC of linagliptin empagliflozin (EMEA/H/C/003833).

The efficacy analyses were conducted independently for each of the 2 empagliflozin background doses; 1275.10(met+empa25) and 1275.10(met+empa10). The superiority of linagliptin vs. placebo as add-on therapy to empagliflozin and metformin was tested after 24 weeks of double-blind treatment in patients who met the HbA1c inclusion criterion (HbA1c ≥7.0% and ≤10.5%) following 16 weeks of open-label treatment with the corresponding empagliflozin dose on a metformin background. The analyses were based on a mixed model repeated measures approach (MMRM), using observed cases (OC), in which missing data were not imputed prior to the analyses, but handled directly by the analysis model itself. Sensitivity analyses, including an analysis of covariance (ANCOVA) in which missing values were imputed by the last observation carried forward (LOCF) technique, were also performed.

Evidence of the long-term efficacy of the combination of linagliptin and empagliflozin as add-on therapy to metformin is provided by 52-week data from the factorial design trial 1275.1(met).

Table 3 Overview of the Phase III clinical studies included in the evaluation of efficacy

Study	Short description of study design and analysis strategy	No. of patients[1]
Add-on studies investigating linagliptin as add-on to empagliflozin and metformin		
1275.10*(met+empa25)*	16 weeks open-label treatment with the SGLT-2 inhibitor empa 25 on metformin background therapy,	354 (open-label)
	24 weeks double-blind treatment, lina[3] vs. placebo, add-on therapy to the SGLT-2 inhibitor empa 25 and metformin background therapy	224 (double-blind)
1275.10*(met+empa10)*	16 weeks open-label treatment with the SGLT-2 inhibitor empa 10 on metformin background therapy,	352 (open-label)
	24 weeks double-blind treatment, lina[3] vs. placebo, add-on therapy to the SGLT-2 inhibitor empa 10 and metformin background therapy	254 (double-blind)
Factorial design study		
1275.1*(met)*	52 weeks double-blind treatment empa/lina FDCs[3] vs. individual components[4] on metformin background therapy primary analysis at Week 24, exploratory analyses at Week 52	686

Methods

Study 1275.10 was an add-on study that investigated the efficacy, safety, and tolerability of linagliptin as add-on therapy to the SGLT-2 inhibitor empagliflozin and metformin (***Figure 1***). Patients with type 2 diabetes mellitus and inadequate glycaemic control despite metformin background therapy were randomised to an initial 16-week open-label treatment period with empagliflozin 25 mg (empa 25 OL, study population 1275.10(met+empa25)) or empagliflozin 10 mg (empa 10 OL, study population 1275.10(met+empa10)). Patients who met the inclusion criterion of HbA1c values between 7.0 and 10.5% after 16 weeks of open-label empagliflozin therapy on a metformin background were eligible for randomisation into 1 of 2 possible treatment groups in the 24-week double-blind period of each open-label patient population, following an additional 1-week open-label placebo run-in period: lina 5 (given as FDC empa 25/lina 5 or FDC empa 10/lina 5) or placebo (given in addition to empa 25 or empa 10). Within each study population, the hierarchical testing sequences were independent of each other. All patients continued treatment with metformin throughout the double-blind period.

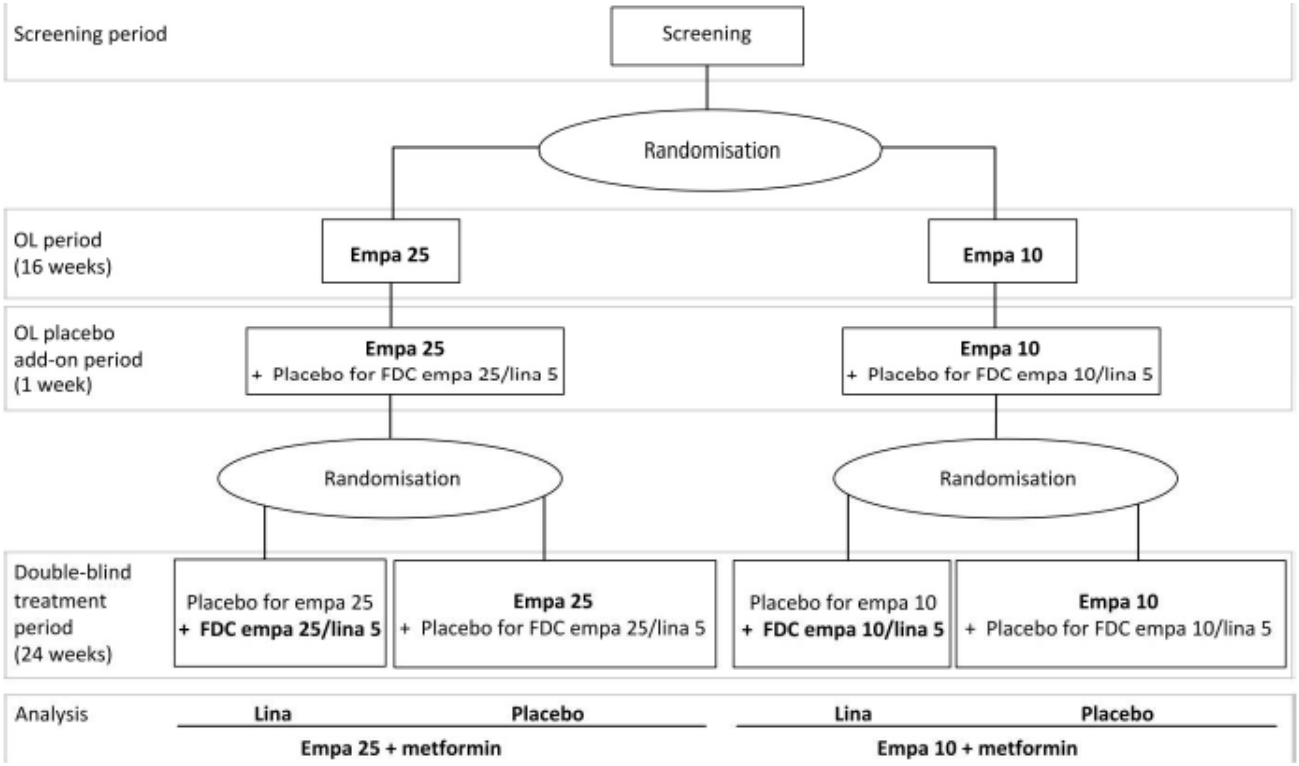

Figure 1 Trial design Study 1275.10

Study 1275.1 was a factorial design study conducted according to the FDA guideline on FDCs in patients with type 2 diabetes mellitus and insufficient glycaemic control despite diet and exercise (***Figure 2***). The study population 1275.1(met) included patients with a metformin background therapy and the study population 1275.1(naïve) included patients with no prior antidiabetic medication. In each population, after a 2-week placebo run-in period, patients were randomised into 5 treatment groups: FDC empa 25/lina 5, FDC empa 10/lina 5, empa 25, empa 10, and lina 5. The superiority of each FDC in terms of reducing HbA1c levels was tested against its respective individual components after 24 weeks of double-blind treatment independently in each study population (primary endpoint). Efficacy and safety were evaluated over the entire 52-week study period. The study population taking metformin background therapy (denoted as 1275.1(met)) is relevant for the current application and is presented in this document.

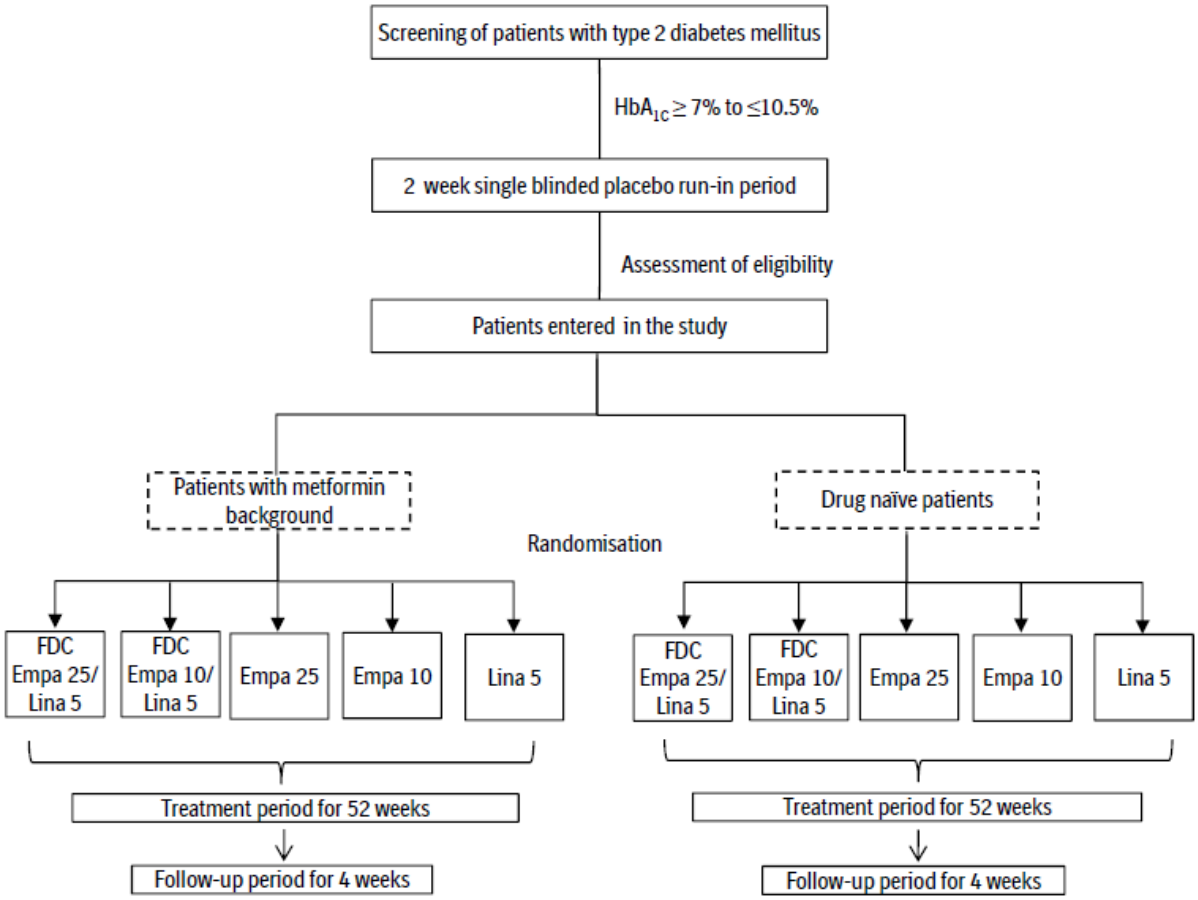

Figure 2 Trial design Study 1275.1

- **Study participants**

All Phase III studies included male and female patients with type 2 diabetes mellitus, insufficient glycaemic control despite diet and exercise counselling, a BMI of 45 kg/m2 or below, who were at least 18 years old. All patients in studies 1275.10, and 1275.1(met) were taking metformin as background medication. Patients were to take an unchanged dose of ≥1500 mg/day (or maximum tolerated dose, or maximum dose as per local label) of immediate release metformin for at least 12 weeks prior to screening (study 1275.10) or randomisation (study 1275.1(met)) and to continue at this dose throughout the duration of the study. No other prior antidiabetic medications were allowed within 12 weeks prior to screening (study 1275.10) or randomisation (1275.1(met)). Study 1275.1(naïve) included patients without prior antidiabetic treatment (defined as absence of any oral antidiabetic therapy, GLP-1 analog, or insulin for 12 weeks prior to randomisation).

Study 1275.10 recruited patients with HbA1c between 8.0% and 10.5% into the open-label parts of the study. Patients who had insufficient glycaemic control, defined as HbA1c between 7.0% and 10.5%, after 16 weeks of open-label treatment with empagliflozin monotherapy and who still met the entry criteria were eligible for the double-blind treatment period. Study 1275.1 recruited patients with HbA1c between 7.0% and 10.5% directly into the double-blind treatment period.

Patients were not eligible to participate in any trial if any of the following criteria applied:

- Uncontrolled hyperglycaemia after an overnight fast during the open-label treatment period and open-label placebo add-on period (study 1275.10) or during the placebo run-in (study 1275.1)

and confirmed by a second measurement. Uncontrolled hyperglycaemia was defined as a glucose level >270 mg/dL (>15 mmol/L) in the study 1275.10 and >240 mg/dL (>13.3 mmol/L) in study 1275.1

- Indication of liver disease, defined by serum levels of either alanine transaminase (ALT, serum glutamic pyruvic transaminase [SGPT]), aspartate transaminase (AST, serum glutamic oxaloacetic transaminase [SGOT]), or alkaline phosphatase above 3x the upper limit of normal at screening (all studies) or after the open-label period (study 1275.10 only)
- Treatment with anti-obesity drugs within 3 months prior to informed consent or any other treatment at the time of screening (e.g. surgery or an aggressive diet regimen) leading to unstable body weight
- Treatment with systemic steroids at the time of informed consent or change in dosage of thyroid hormones within 6 weeks prior to informed consent

Patients were also excluded from participation in any trial if they were drug- or alcohol dependent or intolerant to any ingredient of the trial medications or the background medication. Female patients could not participate if they were pregnant or breast feeding or if they did not use adequate contraceptive methods. Patients were also excluded from participation in a trial if they had any other clinical condition that would jeopardise their safety. Patients with impaired renal function, defined as eGFR <60 mL/min/1.73m2 (MDRD formula) were not eligible to participate in the studies. Patients were not eligible to participate in any study if they had a history of acute coronary syndrome, stroke, or transient ischaemic attack within 3 months prior to informed consent.

- **Treatments**

Study 1275.10:

16-week open-label period with empa 25 OL or empa 10 OL
1-week open-label period with empa 25 OL plus placebo matching lina 5 or empa 10 OL plus placebo matching lina 5
24-week double-blind double-dummy treatment period with FDC empa 25/ lina 5 or placebo+empa 25; FDC empa 10/lina 5, or placebo+empa 10

Study 1275.1:

2-week single-blinded placebo run-in period before randomisation.
52-week double-blinded period with FDC empagliflozin 25 mg/linagliptin 5 mg or FDC empagliflozin 10 mg/linagliptin 5 mg or Empagliflozin 25 mg or Empagliflozin 10 mg or Linagliptin 5 mg

- **Objectives**

Study 1275.10

The objective of this trial was to investigate the efficacy, safety, and tolerability of linagliptin 5 mg (lina 5) compared with placebo, each administered as add-on therapy to empagliflozin (25 mg [empa 25] or 10 mg [empa 10]) and metformin, over 24 weeks in patients with type 2 diabetes (T2DM), who had met the HbA1c inclusion criterion (HbA1c ≥7% and ≤10.5%) after 16 weeks of open-label (OL) treatment with empa 25 OL or empa 10 OL and metformin background treatment.

Study 1275.1

The objective of the study was to investigate the efficacy, safety, and tolerability of the fixed-dose combination (FDC) empagliflozin 25 mg/linagliptin 5 mg and of the FDC empagliflozin 10 mg/linagliptin 5 mg compared with the individual components (empagliflozin 25 mg or 10 mg, and linagliptin 5 mg) given once daily (q.d.) for 52 weeks in treatment naïve and metformin-treated patients with type 2 diabetes mellitus with insufficient glycaemic control. The study was designed to show superiority of the empagliflozin/linagliptin FDCs over the respective dose of empagliflozin and linagliptin alone, which was analysed separately in treatment naïve and metformin-treated patients. The primary analysis was conducted after 24 weeks of treatment using data collected until the cut-off date 12 Feb 2013, and is presented in this report along with the final analysis after 52 weeks of treatment. The study population taking metformin background therapy (denoted as 1275.1(met)) is relevant for the current application and is presented in this document.

- **Outcomes / endpoints**

Primary

The primary efficacy endpoint in all studies was the change from baseline in glycated haemoglobin (HbA1c) after 24 weeks of double-blind treatment. In all studies, blood samples for the determination of HbA1c were to be taken at almost all trial visits. At the first visit in a particular trial, the blood sample could have been taken at any time during the visit, irrespective of fasting. At all other visits, the blood sample was to be taken before breakfast and before administration of the trial drug. The samples for all trials were analysed in central laboratories that held a National Glycohemoglobin Standardization Program Level I certificate.

Key secondary

The change from baseline in fasting plasma glucose (FPG) after 24 weeks of double-blind treatment was a key secondary endpoint in all studies. In all trials, blood samples for the determination of FPG were to be taken at nearly all trial visits, after an overnight fast and before breakfast and trial drug administration. The samples were measured at a central laboratory using validated assays.

The change from baseline in body weight after 24 weeks of double-blind treatment was a key secondary endpoint in study 1275.1 and a further endpoint in study 1275.10. In all trials, body weight was to be measured on the same scale for each patient.

The categorical efficacy response analysis for HbA1c (response defined as HbA1c<7.0%) after 24 weeks of treatment was a further endpoint in study 1275.10 and a key secondary endpoint in study 1275.1. The proportion of patients who achieved HbA1c values <7.0% following the 16-week open-label period was a further endpoint in study 1275.10.

Additional

Additional further endpoints are the change from baseline in HbA1c by visit over time, the change from pre-treatment in HbA1c after 16 weeks of the open-label period of study 1275.10, the change from baseline in blood pressure (BP) after 24 weeks, and use of rescue medication. Blood pressure (systolic blood pressure [SBP] and diastolic blood pressure [DBP]) were to be measured after 5 minutes of rest in a seated position.

Rescue medication could be initiated provided trial-specific criteria for hyperglycaemia were fulfilled. The use of rescue medication as an indicator of lack of efficacy was defined as either an increase in the dose of antidiabetic background medication above the baseline dose for 7 or more days or the use of additional antidiabetic medication for 7 or more days. In addition, patients who prematurely discontinued trial medication due to lack of efficacy and increased the dose of background medication or started additional antidiabetic medication on the next day were regarded as having taken rescue medication. The proportion of patients requiring rescue medication and the time to first use of rescue medication were calculated.

- **Sample size**

Trial 1275.10:

The following effect sizes were assumed for the calculation of the sample size.

- Trial Population A (lina 5 added-on to empa 25+metformin): Effect of lina 5 vs. placebo: 0.5%
- Trial Population B (lina 5 added-on to empa 10+metformin): Effect of lina 5 vs. placebo: 0.5%

Based on previous experiences with linagliptin, the difference in HbA1c change from baseline after 24 weeks was assumed for the purpose of planning the trial to be 0.5% for lina 5 relative to placebo and that the standard deviation (SD) of the differences was 1.1%. The alpha (Type I error) was assumed to be 2.5% (1-sided).

The overall power for each dose combination is calculated in Table 4. The total number of randomised patients was calculated to be 103 per treatment arm to have 90% power to test the primary endpoint. Assuming a 7% loss of randomised patients from the final analysis set, 9 additional patients were to be randomised per arm. As such, sample size was 112 per arm. A total of 448 patients needed to be randomised into the double-blind period of the trial.

Table 4 Overall power for each trial population

Sample size per double-blind treatment arm	Power for individual test	Sample size including assumed discontinuation rate 7.0%
88	0.85	95
103	**0.90**	**112**
127	0.95	136

Source: Software nQuery Advisor® 6.01 - MTT0 – 1 Two group t-test of equal means.

Trial 1275.1:

An effect size of 0.5% was assumed for the sample size calculation in this trial, with a standard deviation of 1.05% based on previous experience with empagliflozin studies. The power for a hypothesis test of the primary endpoint within a population (naïve or metformin experienced) is summarised below:

Sample size	Power
110	0.94
120	0.96
130	0.97
140	0.98

With a sample size of 130 patients, the power for testing the 4 hypotheses of FDC combination vs. individual components was to be 89% with a population, assuming the hypotheses were independent. Assuming that 2% patients did not have an on-treatment measurement of HbA1c and they were not to be included in the FAS (full analysis set), the number of randomised patients was 133 to achieve the overall power of 89%. Therefore, a sample size for each treatment arm would be 266 (133 treatment naïve and 133 on metformin background therapy). Hence, for the 5 arms in this trial, 1330 patients were to be randomised in total, giving 665 randomised patients per population. This sample size was considered as sufficient for the confirmatory evaluation of safety, tolerability, efficacy, and pharmacokinetics.

- **Randomisation**

When a patient was confirmed eligible, treatment was assigned by a third-party phone/webbased system involving the use of an IXRS system.

In trial 1275.10 patients were randomised to treatment at 2 different times during the trial. At Visit 2 the patient was either randomised to open-label treatment with empa 25 OL or empa 10 OL in a 1:1 ratio.

After the open-label treatment period, the patients were randomised at a 1:1 (trial 1275.10) ratio to double-blind treatment. After the run-in period of trial 1275-1, patients were randomised in a 1:1:1:1:1 ratio.

Patient assignment to the treatment groups was determined by a computer generated random sequence using a block size of 4 (trial 1275.10) or 10 (1275.1). Access to the randomisation code was controlled and documented. Randomisation was stratified by 3 factors:

- Pre-randomisation HbA1c (<8.5% or ≥8.5%) using the Visit 4 HbA1c values.
- Pre-randomisation renal function (mild renal impairment: 60 ≤eGFR ≤89 mL/min/1.73m2 or normal renal function: eGFR ≥90 mL/min/1.73m2) using integer values of eGFR from the Visit 4 creatinine values.
- Region (Europe, North America or Latin America). Patients from any sites in Australia were grouped with Europe for this purpose

- **Blinding (masking)**

Trial 1275.10 employed a double-dummy design, i.e. during the double-blind treatment period patients received 2 (trial 1275.10) or 5 (trial 1275.1) tablets per day, containing active substances or matching placebos).

- **Statistical methods**

To ensure a balanced distribution of patients with different levels of glycaemic control across the randomised treatment groups, randomisation into the double-blind treatment period was stratified by the pre-baseline HbA1c value (<8.5% versus ≥8.5%) in all Phase III studies. Randomisation was also stratified by renal function (normal renal function: estimated glomerular filtration rate [eGFR] modification of diet in renal disease [MDRD] formula ≥90 mL/min/1.73m2; mild impairment: eGFR 60 to 89 mL/min/1.73m2) and geographical region (Europe, North America, Latin America, and Asia [latter not in study 1275.10]).

Analysis sets

The sets used for the analyses of efficacy described in this report are defined below:

The randomised set (RS) consisted of all patients who were randomised to double-blind study drug, regardless of whether any study drug was taken. The treated set (TS) consisted of all patients who were randomised and treated with at least one dose of study drug during the double-blind part of the trial. The disposition of patients is described based on this analysis set.

The full analysis set (FAS) consisted of all patients treated with at least one dose of study drug during the double-blind part of the trials who had a baseline HbA1c assessment and at least one on-treatment HbA1c assessment during the double-blind part of the trial. The FAS represents the primary population used for analyses of the efficacy endpoints.

The FAS-completers set included all patients in the FAS who completed a minimum of 23 weeks treatment in the double-blind part of the trial and who did not prematurely discontinue from the trial prior to the Week

24 visit. The date of last intake of trial medication had to be on or after the start of the time window for the Week 24 visit and an HbA1c value had to be available within the time window for this visit.

The per protocol set (PPS) consisted of all patients in the FAS who had no important protocol violations (IPVs) for efficacy leading to exclusion. The definition of trial-specific IPVs was specified in each trial statistical analysis plan. These IPV definitions included consideration of important violations of entry criteria, treatment non-compliance, prohibited concomitant medication, and premature unblinding. The final decision on which patients were included in the PPS was made prior to unblinding.

The open-label full analysis set (OLFAS) consisted of all patients who received at least 1 dose of open-label treatment during the trial and who had a pre-treatment HbA1c assessment and at least 1 on-treatment HbA1c assessment during the open-label part of the trial (excluding placebo add-on period). The OLFAS was the basis for the efficacy analyses of the open-label period in study 1275.10.

Handling of missing data

For the main analyses of the primary, key secondary, and most of the further efficacy endpoints in study 1275.10, an observed cases (OC) approach was used. All available data were analysed as observed, missing data were not directly imputed prior to analysis and were handled implicitly by the statistical model used (mixed model repeated measures [MMRM]). Further, all values observed after a patient started rescue medication were excluded.

For study 1275.1, a last observation carried forward (LOCF) approach was used in the main analyses of the primary and most of the key secondary and further endpoints. Missing values within a course of measurements on treatment were interpolated based on the last observed value before the missing visit and the first observed value after the missing visit. Baseline values were carried forward if there was no post-baseline value available. Values measured after a patient had taken rescue medication were excluded and imputed using the LOCF method.

Sensitivity analyses with alternative methods of accounting for missing data and rescue medication use were performed in order to assess the robustness of the primary and key secondary analysis results (described below).

For the sensitivity analysis of the primary and key secondary efficacy endpoints in study 1275.10, an LOCF approach was used to replace missing data by the last observed measurement on treatment. The LOCF technique was only implemented for analyses of the double-blind period; data from the open-label period were not carried forward into the double-blind period. For study 1275.1, OC was used in sensitivity analyses of the primary and the key secondary efficacy endpoints (FPG and body weight).

For all studies, a multiple imputation approach, which imputed missing data assuming a relationship with baseline HbA1c, baseline renal impairment, region, treatment, as well as any previously observed on-treatment HbA1c values, was performed for the primary endpoint; this approach also took into consideration the variability of the imputed estimates.

For the primary and key secondary endpoints in study 1275.10, sensitivity analyses were also performed with the OC data but including values that were obtained following rescue medication (OC-IR) in the analysis.

For study 1275.1 only, which according to the protocol, allowed for the collection of efficacy data even after patient withdrawal from treatment, additional sensitivity analyses were performed including also those measurements that were collected after treatment discontinuation or after rescue medication (OC-AD and LOCF-AD).

An original results (OR) analysis was performed for the use of rescue therapy and for the time to start of rescue therapy in all studies. Missing data were not directly imputed for the OR analysis.

For the categorical responder analysis of HbA1c, missing values were imputed using the noncompleters considered failure (NCF) approach, i.e. missing data due to premature discontinuation of a patient or values obtained after the introduction of rescue medication were considered as failure to attain response (HbA1c <7.0%) up to the last planned visit.

Definition of baseline and analysis periods

In all Phase III studies, baseline was defined as the last observation prior to the first intake of any double-blind randomised trial medication. Thus, in study 1275.10, the term 'baseline' was not used to refer to measurements prior to the administration of open-label medication. Such measurements are referred to as 'pre-treatment'.

Measurements of HbA1c values were regarded as 'on-treatment' if they were taken after the first dose of double-blind trial medication and up to 7 days after the last dose of trial medication had been administered. For the other efficacy variables, measurements taken after the first dose up to 1 day after the last dose of trial medication were regarded as on-treatment values.

Hypotheses testing

In study 1275.10, the superiority of linagliptin as add-on to empagliflozin and metformin (study 1275.10) was tested against placebo using a hierarchical testing procedure which allowed each individual hypothesis test to be performed at a two-sided $\alpha = 0.05$ level of significance, whilst controlling the overall probability of a type I error at 0.05 (two-sided).

Study 1275.10 was powered separately for each of the background empagliflozin doses and the statistical inference was therefore carried out for studies 1275.10(met+empa25) and 1275.10(met+empa10) separately. The order of endpoints in the hierarchical testing procedure was the primary endpoint, followed by the key secondary endpoint.

In study 1275.1, the superiority of the FDCs to their individual components was tested separately in the metformin-treated and in the treatment-naïve populations. Within each FDC dose level, there were 2 hypotheses which evaluated whether the FDC was superior to the 2 individual components on the primary endpoint and these were tested simultaneously at a two-sided $\alpha = 0.05$ level of significance. Only if both null hypotheses at the higher FDC dose level were rejected, were the hypotheses at the lower FDC dose level tested, thereby controlling the overall probability of a type I error at 0.05 (two-sided). The order of the key secondary endpoints in the hierarchical testing procedure was the change from baseline in FPG after 24 weeks, the change from baseline in body weight after 24 weeks, followed by the categorical efficacy response analysis for HbA1c (<7%) at Week 24.

Analysis of the primary endpoint

The primary analysis in study 1275.10 was performed on the FAS (OC), using a restricted maximum likelihood (REML)-based MMRM approach on the change from baseline in HbA1c (in units of %) after 24 weeks of double-blind treatment. The statistical approach modelled the change from baseline in HbA1c at each on-treatment visit, and included fixed classification effects for treatment, region, baseline renal function, visit, and treatment-by-visit interaction, and a linear covariate for baseline HbA1c. An unstructured covariance approach was used to model the within-patient errors. The differences between treatment groups were presented with a two-sided 95% confidence interval (CI) and the p-value of the hypothesis tests referred to in Section 1.3.4.

The clinical trial protocols of study 1275.10 originally included an analysis of covariance (ANCOVA) as the primary model. The model was changed to MMRM via global amendments to the protocols. An ANCOVA-based model, with factors for treatment, baseline renal function and region and a continuous covariate for baseline HbA1c, using an LOCF approach, was used as a sensitivity analysis.

Further sensitivity analyses, using the same model as defined in the primary analysis, were performed on the PPS (to determine the impact of protocol violations on the observed treatment effect), on the FAS-completers (to determine the impact of early withdrawals on the observed treatment effect), and on the FAS including values obtained after rescue medication (OC-IR). The primary analysis was also repeated on the FAS (OC) but additionally including the baseline HbA1c-by-visit interaction. Furthermore, an ANCOVA analysis using a multiple imputation approach to account for missing data at Week 24 was done. The primary analysis was also repeated using a subset of the FAS, including only patients from sites located in European countries, Australia, New Zealand, Canada, or USA.

In study 1275.10, a post-hoc assessment of the overall linagliptin versus placebo effect on the primary endpoint was done by combining data from both study populations (1275.10(met+empa25) and 1275.10(met+empa10)).

In study 1275.1, the primary analysis was an ANCOVA on the FAS (LOCF), including treatment, region, and baseline renal function as fixed effects and baseline HbA1c as a linear covariate.

In addition, an MMRM approach on the FAS (OC) was used. Further sensitivity analyses on different analysis sets and including post-treatment as well as post-rescue measurements, termed 'after discontinuation or after rescue medication' (AD) were also performed. A sensitivity analysis on the primary endpoint using a multiple imputation approach on the FAS (OC) was performed. Additionally, the change from baseline in HbA1c was analysed based on the FAS (OC and OC-AD) at 52 weeks using an MMRM approach.

Analysis of the key secondary and further endpoints

The changes from baseline in FPG, body weight, and blood pressure (SBP and DBP) were analysed in a similar way as the change from baseline in HbA1c within the respective study, with the relevant value at baseline included as an additional covariate in the analysis model.

The frequencies of patients who achieved the target levels of HbA1c <7% were analysed. A logistic regression model, based on the FAS (NCF), was applied with factors for treatment, region, baseline renal function, and a linear covariate for HbA1c at baseline.

A logistic regression, with treatment as a factor and continuous baseline HbA1c as a covariate, was also performed using the FAS (OR) on the proportion of patients who used rescue therapy. In addition, the Kaplan-Meier method and a log-rank test were used to analyse the time to first use of rescue medication for the FAS (OR).

Subgroup analyses

Subgroup analyses were performed for the primary and the key secondary endpoints in study 1275.10. In study 1275.1, subgroup analyses were performed for the primary endpoint while for the key secondary endpoints, only selected subgroups were assessed. The presentation of subgroups in this SCE focuses on selected primary endpoint analyses. Further subgroup analyses can be found in the clinical trial reports of the individual studies.

In study 1275.10, subgroups were analysed using a similar MMRM model as for the primary endpoint, with additional terms for subgroup, subgroup-by-visit, subgroup-bytreatment, and visit-by-treatment-by-subgroup interactions. Note that any subgroup category that had any cell with fewer than 5 observations per treatment and visit combination was excluded from the MMRM analyses.

In study 1275.1, subgroups were analysed using a similar ANCOVA model as for the primary endpoint, with additional terms for subgroup and treatment-by-subgroup interaction. Subgroups with fewer than 35 patients in total were excluded from the ANCOVA analyses.

In all studies, a p-value for the treatment-by-subgroup interaction term at Week 24 of <0.1 was considered to indicate a potential interaction effect.

The influence of demographic factors was evaluated in subgroups based on age, gender, weight, race, ethnicity, and geographical region. The influence of the duration and severity of diabetes was investigated in subgroups for time since diagnosis of diabetes and baseline HbA1c. The possible effect of renal impairment was evaluated in subgroups by renal function (eGFR, using the MDRD formula). An overview of all subgroup analyses that are presented in this SCE is provided in

Table 5.

Table 5 Selected subgroups analysed in the Phase III studies

	Subgroup categories	Endpoints analysed		
		1275.9	1275.10	1275.1
Age (years)	Version 1: <65; 65 to <75; 75 to <85; ≥85	HbA_{1c}, FPG, body weight	HbA_{1c}, FPG	NA
	Version 2: <50; 50 to <65; 65 to <75; ≥75	HbA_{1c}, FPG, body weight	HbA_{1c}, FPG	HbA_{1c}, FPG, body weight
Gender	Male; Female	HbA_{1c}, FPG, body weight	HbA_{1c}, FPG	HbA_{1c}, FPG, body weight
Race	White; Black/African American; Asian; Other	HbA_{1c}, FPG, body weight	HbA_{1c}, FPG	HbA_{1c}, FPG, body weight
Ethnicity	Hispanic/Latino; Not Hispanic/Latino	HbA_{1c}, FPG, body weight	HbA_{1c}, FPG	HbA_{1c}, FPG, body weight
Geographical region[1]	Version 1: Europe; North America; Latin America	NA	HbA_{1c}, FPG	NA
	Version 2: Europe; Asia; North America; Latin America	HbA_{1c}, FPG, body weight	NA	HbA_{1c}, FPG, body weight
Weight (kg)	≤70; >70 to ≤80; >80 to ≤90; >90	HbA_{1c}, FPG, body weight	HbA_{1c}, FPG	HbA_{1c}, FPG, body weight
Baseline HbA_{1c} (%)	<8.5; ≥8.5	HbA_{1c}, FPG, body weight	HbA_{1c}, FPG	HbA_{1c}, FPG, body weight, HbA_{1c} response (<7%) rate
Time since diagnosis of diabetes (years)	≤1; >1 to 5; >5 to 10; >10	HbA_{1c}	HbA_{1c}	HbA_{1c}
Renal impairment (eGFR [MDRD]; mL/min/1.73m^2)	Version 1: ≥90; 60 to <90; 45 to <60; <45	HbA_{1c}, FPG, body weight	HbA_{1c}, FPG	NA
	Version 2: ≥90; 60 to <90; 30 to <60; <30	NA	NA	HbA_{1c}, FPG, body weight

NA: Not applicable

Results

- **Participant flow**

Trial 1275.10

This trial was an international, multi-centre trial. A total of 1324 patients were screened by 114 centres in 10 countries across Europe, North America, Latin America, and Australia. Of the screened patients, 706 patients were treated with open-label treatment; 354 patients were treated with empa 25 OL and 352 patients with empa 10 OL. A total of 482 patients (68.3% of the patients treated with open-label treatment) entered the double blind treatment period. Reasons for not entering double-blind treatment were mostly that patients did not meet the inclusion criterion HbA1c ≥7.0% and ≤10.5% (20.6% of patients in the OLS); most of these patients had achieved glycaemic control (HbA1c <7.0%) at Visit 4. It was planned to randomise 448 patients, but 482 patients were actually randomised to double-blind trial treatment in a 1:1 ratio for the trial

population A (lina 5 or placebo added-on to metformin+empa 25; 226 patients overall) and in a 1:1 ratio for the trial population B (lina 5 or placebo added-on to metformin+empa 10; 256 patients overall).

At Visit 4, 114 patients were randomised to treatment with lina 5 and 112 patients to placebo treatment (Table 6). Of the patients randomised to and treated with double-blind treatment, 207 patients (92.4%) completed the 24-week treatment period; 102 (91.1%) in the lina 5 group and 105 (93.8%) in the placebo group. The percentage of patients prematurely discontinuing trial medication was higher in the lina 5 group (8.9%) compared with the placebo group (6.3%), which was mostly due to more patients being lost to follow-up in the lina 5 group compared with the placebo group (4.5% vs. 1.8%). Discontinuations due to AEs occurred in 2.7% of the patients in the lina 5 group and 1.8 % of the patients in the placebo group; none were due to a worsening of T2DM. Discontinuation due to lack of efficacy was reported for 1 patient in the placebo group. The proportions of patients who prematurely discontinued trial medication were higher in North America (lina 5: 11.1%, placebo: 14.8%) than in Europe (lina 5: 9.8%, placebo: 3.8%), or Latin America (lina 5: 5.9%, placebo: 3.0%). Three patients discontinued due to other reasons.

Table 6 Disposition of patients trial 1275.10

	Metformin+empa 25		
	Lina 5 N (%)	Placebo N (%)	Total N (%)
Entered double blind treatment	114	112	226
Treated	112 (100.0)	112 (100.0)	224 (100.0)
Not prematurely discontinued trial medication	102 (91.1)	105 (93.8)	207 (92.4)
Prematurely discontinued trial medication	10 (8.9)	7 (6.3)	17 (7.6)
Adverse event	3 (2.7)	2 (1.8)	5 (2.2)
Study disease worsening	0	0	0
Other pre-existing disease worsening	0	0	0
Other AE	3 (2.7)	2 (1.8)	5 (2.2)
Lack of efficacy[1]	0	1 (0.9)	1 (0.4)
Lost to follow-up	5 (4.5)	2 (1.8)	7 (3.1)
Refused to continue trial medication	0	1 (0.9)	1 (0.4)
Other reason	2 (1.8)	1 (0.9)	3 (1.3)

[1] Introduction of rescue medication due to hyperglycaemia did not lead to sufficient efficacy, i.e. rescue medication criteria were still met.

Trial 1275.1

Disposition of patients in study 1275.1(met)

In study 1275.1(met), a total of 686 metformin-treated patients were randomised in a 1:1:1:1:1 ratio to FDC empa 25/lina 5, empa 25, FDC empa 10/lina 5, empa 10, or lina 5. All randomised patients were treated. Overall, 8.5% of the treated patients prematurely discontinued study medication up to Week 24 and 12.4% prematurely discontinued study medication up to Week 52 (Table 7). The frequency of patients who prematurely discontinued study medication was low and comparable in all treatment groups at Week 24 and 52.

Table 7 Disposition of patients in study 1275.1 week 24 (met)

	Empa 25 mg / Lina 5 mg N (%)	Empa 10 mg / Lina 5 mg N (%)	Empa 25 mg N (%)	Empa 10 mg N (%)	Lina 5 mg N (%)	Total
Entered	137	136	141	140	132	686
Treated [1]	137 (100.0)	136 (100.0)	141 (100.0)	140 (100.0)	132 (100.0)	686 (100.0)
Not prematurely discontinued trial medication	126 (92.0)	129 (94.9)	131 (92.9)	124 (88.6)	118 (89.4)	628 (91.5)
Prematurely discontinued trial medication	11 (8.0)	7 (5.1)	10 (7.1)	16 (11.4)	14 (10.6)	58 (8.5)
Adverse event	3 (2.2)	3 (2.2)	2 (1.4)	5 (3.6)	4 (3.0)	17 (2.5)
Worsening of study disease	0	0	0	0	1 (0.8)	1 (0.1)
Other pre-existing disease worsening	1 (0.7)	0	0	1 (0.7)	0	2 (0.3)
Other adverse events	2 (1.5)	3 (2.2)	2 (1.4)	4 (2.9)	3 (2.3)	14 (2.0)
Lack of efficacy	0	0	0	0	0	0
Non compliant with protocol	1 (0.7)	0	0	2 (1.4)	0	3 (0.4)
Lost to follow-up	1 (0.7)	2 (1.5)	4 (2.8)	4 (2.9)	4 (3.0)	15 (2.2)
Patient refusal to continue, not due to AE	3 (2.2)	1 (0.7)	1 (0.7)	3 (2.1)	2 (1.5)	10 (1.5)
Other	3 (2.2)	1 (0.7)	3 (2.1)	2 (1.4)	4 (3.0)	13 (1.9)
Not prematurely discontinued from trial	131 (95.6)	133 (97.8)	136 (96.5)	132 (94.3)	125 (94.7)	657 (95.8)
Prematurely discontinued from trial	6 (4.4)	3 (2.2)	5 (3.5)	8 (5.7)	7 (5.3)	29 (4.2)
Lost to follow-up	1 (0.7)	1 (0.7)	2 (1.4)	4 (2.9)	2 (1.5)	10 (1.5)
Consent withdrawn	5 (3.6)	1 (0.7)	3 (2.1)	4 (2.9)	5 (3.8)	18 (2.6)
Death	0	1 (0.7)	0	0	0	1 (0.1)

[1] 'Treated' is the number of entered patients who received at least one dose of study medication.

- **Baseline data**

Demographic characteristics in study 1275.10 (met+empa10)

Demographic data at baseline in study 1275.10 (met+empa10) were generally similar across the 2 treatment groups. Overall, 56.3% of patients were male. The majority of patients were White (96.8%). The mean (SD) age in the treatment groups was 56.7 (9.5) years and the mean BMI was 31.01 (5.07) kg/m2. The majority of patients (57.5%) had been diagnosed with type 2 diabetes for >5 years. Based on eGFR (MDRD formula) values, most of the patients (97.2%) had either normal renal function or mild renal impairment (48.6% each) at baseline.

Table 8 Demographic data in study 1275.10

	Metformin+empa25		Metformin+empa10	
	Lina 5	**Placebo**	**Lina 5**	**Placebo**
Number of patients, N (%)	110 (100.0)	110 (100.0)	122 (100.0)	125 (100.0)
Gender, N (%)				
Male	52 (47.3)	63 (57.3)	69 (56.6)	70 (56.0)
Female	58 (52.7)	47 (42.7)	53 (43.4)	55 (44.0)
Race, N (%)				
White	107 (97.3)	106 (96.4)	120 (98.4)	119 (95.2)
Black / African American	3 (2.7)	4 (3.6)	2 (1.6)	3 (2.4)
Asian	0	0	0	1 (0.8)
Other	0	0	0	2 (1.6)
Region, N (%)				
Europe	50 (45.5)	52 (47.3)	62 (50.8)	62 (49.6)
North America	26 (23.6)	25 (22.7)	22 (18.0)	26 (20.8)
Latin America	34 (30.9)	33 (30.0)	38 (31.1)	37 (29.6)
Age, mean (SD) [years]	56.6 (9.8)	56.1 (10.6)	56.6 (9.5)	56.8 (9.4)
Age categories, N (%)				
<65 years	87 (79.1)	92 (83.6)	98 (80.3)	100 (80.0)
65 to <75 years	22 (20.0)	15 (13.6)	20 (16.4)	21 (16.8)
75 to <85 years	1 (0.9)	2 (1.8)	4 (3.3)	4 (3.2)
≥85 years	0	1 (0.9)	0	0
BMI, mean (SD) [kg/m^2]	30.79 (4.63)	32.01 (5.25)	31.26 (5.39)	30.76 (4.75)
Time since diagnosis of diabetes, N (%)				
≤1 year	8 (7.3)	9 (8.2)	7 (5.7)	16 (12.8)
>1 to 5 years	31 (28.2)	33 (30.0)	42 (34.4)	40 (32.0)
>5 to 10 years	40 (36.4)	39 (35.5)	40 (32.8)	37 (29.6)
>10 years	31 (28.2)	29 (26.4)	33 (27.0)	32 (25.6)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	88.97 (18.48)	91.06 (19.68)	91.95 (19.47)	89.80 (19.60)
eGFR (MDRD)[1], N (%)				
≥90 mL/min/1.73m^2	47 (42.7)	54 (49.1)	66 (54.1)	54 (43.2)
60 to <90 mL/min/1.73m^2	59 (53.6)	53 (48.2)	51 (41.8)	69 (55.2)
45 to <60 mL/min/1.73m^2	4 (3.6)	2 (1.8)	4 (3.3)	2 (1.6)
<45 mL/min/1.73m^2	0	1 (0.9)	1 (0.8)	0

Demographic characteristics in study 1275.1 (met)

The key demographic characteristics in study 1275.1 (met) were similar across the treatment groups. Overall, more than half (53.7%) of the patients were male. The majority of patients in this population were White (73.9%). The mean (SD) age of all patients was 56.2 (10.2) years and the mean (SD) BMI was 31.0 (5.5) kg/m2. More than half (55.2%) of the patients had been diagnosed with type 2 diabetes for >5 years. Based on eGFR (MDRD formula) values, most of the patients (97.3%) had either normal renal function (43.9%) or mild renal impairment (53.4%) at baseline. The demographic characteristics at baseline in study 1275.1(met) are shown in Table 9.

Table 9 Demographic data in study 1275.1 (met)

	FDC empa 25/lina 5	Empa 25	FDC empa 10/lina 5	Empa 10	Lina 5
Number of patients, N (%)	134 (100.0)	140 (100.0)	135 (100.0)	137 (100.0)	128 (100.0)
Gender, N (%)					
Male	72 (53.7)	65 (46.4)	83 (61.5)	78 (56.9)	64 (50.0)
Female	62 (46.3)	75 (53.6)	52 (38.5)	59 (43.1)	64 (50.0)
Race, N (%)					
White	97 (72.4)	100 (71.4)	102 (75.6)	103 (75.2)	96 (75.0)
Asian	22 (16.4)	20 (14.3)	18 (13.3)	20 (14.6)	14 (10.9)
Black / African American	7 (5.2)	13 (9.3)	12 (8.9)	8 (5.8)	9 (7.0)
Other	8 (6.0)	7 (5.0)	3 (2.2)	6 (4.4)	9 (7.0)
Region, N (%)					
North America	59 (44.0)	65 (46.4)	63 (46.7)	62 (45.3)	54 (42.2)
Europe	39 (29.1)	37 (26.4)	37 (27.4)	39 (28.5)	39 (30.5)
Latin America	18 (13.4)	20 (14.3)	18 (13.3)	19 (13.9)	18 (14.1)
Asia	18 (13.4)	18 (12.9)	17 (12.6)	17 (12.4)	17 (13.3)
Age, mean (SD) [years]	57.1 (10.2)	55.5 (10.0)	56.2 (10.3)	56.1 (10.5)	56.2 (10.0)
Age categories, N (%)					
<65 years	102 (76.1)	115 (82.1)	110 (81.5)	111 (81.0)	101 (78.9)
65 to <75 years	28 (20.9)	21 (15.0)	21 (15.6)	19 (13.9)	24 (18.8)
75 to <85 years	4 (3.0)	4 (2.9)	4 (3.0)	6 (4.4)	3 (2.3)
≥85 years	0	0	0	1 (0.7)	0
BMI, mean (SD) [kg/m^2]	30.61 (5.69)	31.80 (5.28)	30.79 (5.60)	31.02 (5.27)	30.59 (5.41)
Time since diagnosis of diabetes, N (%)					
≤1 year	10 (7.5)	10 (7.1)	19 (14.1)	13 (9.5)	10 (7.8)
>1 to 5 years	46 (34.3)	50 (35.7)	49 (36.3)	51 (37.2)	44 (34.4)
>5 to 10 years	46 (34.3)	50 (35.7)	41 (30.4)	39 (28.5)	43 (33.6)
>10 years	32 (23.9)	30 (21.4)	26 (19.3)	34 (24.8)	31 (24.2)
eGFR (MDRD), mean (SD) [mL/min/1.73m^2]	87.28 (17.15)	90.23 (18.31)	89.10 (18.38)	91.12 (19.52)	90.03 (20.14)
eGFR (MDRD)[1], N (%)					
≥90 mL/min/1.73m^2	58 (43.3)	60 (42.9)	57 (42.2)	64 (46.7)	57 (44.5)
60 to <90 mL/min/1.73m^2	72 (53.7)	78 (55.7)	77 (57.0)	68 (49.6)	65 (50.8)
30 to <60 mL/min/1.73m^2	3 (2.2)	2 (1.4)	1 (0.7)	5 (3.6)	6 (4.7)
<30 mL/min/1.73m^2	1 (0.7)	0	0	0	0

- Baseline efficacy variables

Baseline efficacy variables in the Phase III study 1275.10

Baseline efficacy variables in study 1275.10(met+empa25)

The efficacy variables at baseline were generally similar between the treatment groups. The overall mean (SD) baseline values were: 7.85 (0.81)% for HbA1c, 8.54 (1.85) mmol/L for FPG, 87.79 (16.53) kg for body

weight, 129.0 (13.3) mmHg for SBP, and 77.7 (7.7) mmHg for DBP. Baseline efficacy variables in study 1275.10(met+empa25) are summarised in Table 10.

Baseline efficacy variables in study 1275.10(met+empa10)

The efficacy variables at baseline were generally similar between the treatment groups. The overall mean (SD) baseline values were: 8.03 (0.91)% for HbA1c, 8.78 (2.08) mmol/L for FPG, 86.99 (17.47) kg for body weight, 127.9 (12.7) mmHg for SBP, and 77.3 (8.3) mmHg for DBP. Baseline efficacy variables in study 1275.10(met+empa10) are summarised in Table 10.

Table 10 Baseline efficacy variables in study 1275.10

	Metformin+empa25		Metformin+empa10	
	Lina 5	Placebo	Lina 5	Placebo
Number of patients, N (%)	110 (100.0)	110 (100.0)	122 (100.0)	125 (100.0)
HbA_{1c}, mean (SD) [%]	7.81 (0.71)	7.88 (0.90)	8.04 (0.96)	8.03 (0.85)
HbA_{1c} category, N (%)				
<8.5%	90 (81.8)	88 (80.0)	91 (74.6)	90 (72.0)
≥8.5%	20 (18.2)	22 (20.0)	31 (25.4)	35 (28.0)
FPG, mean (SD) [mmol/L]	8.44 (1.60)	8.63 (2.07)	8.85 (2.22)	8.72 (1.93)
Body weight, mean (SD) [kg]	85.66 (16.73)	89.91 (16.12)	88.43 (16.84)	85.59 (18.02)
SBP, mean (SD) [mmHg]	129.7 (13.2)	128.4 (13.4)	127.5 (12.9)	128.2 (12.6)
DBP, mean (SD) [mmHg]	78.2 (7.8)	77.2 (7.6)	77.1 (8.2)	77.4 (8.4)

Baseline efficacy variables in study 1275.1(met)

The baseline efficacy variables in trial 1275.1(met) were similar across the treatment groups. The overall mean (SD) baseline values were: 7.98 (0.85)% for HbA1c, 8.76 (1.91) mmol/L for FPG, 86.2 (18.7) kg for body weight, 130.1 (14.3) mmHg for SBP, and 79.1 (8.9) mmHg for DBP. Baseline efficacy variables in study 1275.1(met) are summarised in Table 11.

Table 11 Baseline efficacy variables in trial 1275.1(met)

	FDC empa 25/lina 5	Empa 25	FDC empa 10/ lina 5	Empa 10	Lina 5
Number of patients, N (%)	134 (100.0)	140 (100.0)	135 (100.0)	137 (100.0)	128 (100.0)
HbA_{1c}, mean (SD) [%]	7.90 (0.79)	8.02 (0.83)	7.95 (0.80)	8.00 (0.93)	8.02 (0.90)
HbA_{1c} category, N (%)					
<8.5%	102 (76.1)	104 (74.3)	105 (77.8)	102 (74.5)	95 (74.2)
≥8.5%	32 (23.9)	36 (25.7)	30 (22.2)	35 (25.5)	33 (25.8)
FPG, mean (SD) [mmol/L]	8.58 (1.85)	8.87 (2.10)	8.70 (1.91)	8.97 (1.93)	8.68 (1.70)
Body weight, mean (SD) [kg]	85.47 (20.36)	87.68 (17.61)	86.57 (19.01)	86.14 (18.19)	85.01 (18.34)
SBP, mean (SD) [mmHg]	130.9 (15.7)	129.2 (13.4)	130.5 (15.2)	131.6 (14.4)	128.4 (12.5)
DBP, mean (SD) [mmHg]	78.6 (9.2)	79.9 (8.7)	79.0 (8.5)	80.2 (9.6)	77.7 (8.5)

- **Main efficacy results**

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application (Table 12). These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12 Tabulated summaries of the studies included in the evaluation of efficacy

Title: A phase III, randomised, double-blind, parallel group study to evaluate efficacy and safety of linagliptin 5 mg compared to placebo, administered as oral fixed dose combinations with empagliflozin 10 mg or 25 mg for 24 weeks, in patients with type 2 diabetes mellitus and insufficient glycaemic control after 16 weeks treatment with empagliflozin 10 mg or 25 mg once daily on metformin background therapy.			
Study identifier	1275.10, EudraCT No.: 2012-002271-34, CTR c02714511		
Design	This was a randomised, double-blind, parallel group comparison study. Patients were recruited and randomised at a 1:1 ratio to treatment with linagliptin 5 mg (lina 5) or placebo, each as add-on therapy to empagliflozin 25 mg (empa 25) and metformin (study population 1275.10$_{(met+empa25)}$) or empagliflozin 10 mg (empa 10) and metformin (study population 1275.10$_{(met+empa10)}$). Randomisation was stratified by baseline $HbA_{1c,}$ renal function, and geographical region. The main objective of the trial was to investigate the efficacy and safety of lina 5 compared with placebo, as add-on to empa (25 or 10) and metformin, administered once daily for 24 weeks in patients with type 2 diabetes mellitus and insufficient glycaemic control after the preceding 16 weeks of open-label treatment with empagliflozin and metformin.		
	Duration of main phase:		16 weeks open-label active treatment, 24 weeks double-blind randomised treatment, 1 week follow-up period
	Duration of Run-in phase:		1 week open-label placebo, before double-blind period
	Duration of Extension phase:		not applicable
Hypothesis	Superiority of linagliptin 5 mg vs. placebo, add-on therapy to empagliflozin (25 or 10 mg) and metformin, tested independently in 2 study populations denoted 1275.10$_{(met+empa25)}$ and 1275.10$_{(met+empa10)}$		
Treatments groups	FDC empa 25/lina 5		Fixed-dose combination empagliflozin 25 mg/linagliptin 5 mg after 17 weeks of open-label treatment (16 weeks with empa 25 and 1 week with placebo) on a metformin background, denoted lina 5 in Results, 24 weeks, 114 patients randomised
	Placebo+empa 25		Placebo and empa 25 after 17 weeks of open-label treatment (16 weeks with empa 25 and 1 week with placebo) on a metformin background, denoted placebo in Results, 24 weeks, 112 patients randomised
	FDC empa 10/lina 5		Fixed-dose combination empagliflozin 10 mg/linagliptin 5 mg after 17 weeks of open-label treatment (16 weeks with empa 10 and 1 week with placebo) on a metformin background, denoted lina 5 in Results, 24 weeks, 126 patients randomised
	Placebo+empa 10		Placebo and empa 10 after 17 weeks of open-label treatment (16 weeks with empa 10 and 1 week with placebo) on a metformin background, denoted placebo in Results, 24 weeks, 130 patients randomised
Endpoints and definitions	Primary endpoint	Glycated haemo-globin (HbA_{1c})	Change from baseline in HbA_{1c} after 24 weeks of treatment
	Key secondary endpoint	Fasting plasma glucose (FPG)	Change from baseline in FPG after 24 weeks of treatment
Database lock	08 April 2015		
Results and Analysis 1275.10$_{(met+empa25)}$			
Analysis description	**Primary Analysis**		

Analysis population and time point description	The full analysis set (FAS) included all patients randomised and treated with at least one dose of study drug during the double-blind part of the trial who had a baseline HbA_{1c} assessment and at least one on-treatment HbA_{1c} assessment during the double-blind period. An observed cases (OC) approach was used. All available data were analysed as observed, missing data were not directly imputed prior to analysis and were handled implicitly by the statistical model used (mixed model repeated measures [MMRM]). Further, all values observed after a patient started rescue medication were excluded. Confirmatory tests for the superiority of lina 5 add-on to empa 25 and metformin vs. placebo for the primary and key secondary endpoints followed a hierarchical testing procedure that allowed each test to be done at a two-sided alpha = 0.05 level of significance, whilst controlling the overall probability of a type I error at 0.05 (two-sided). The procedure started with the primary endpoint and continued with the key secondary endpoint. 24 weeks		
Descriptive statistics and estimate variability	Treatment group	Met + empa 25 **Lina 5**	Met + empa 25 **Placebo**
	Number of subjects	110	110
	Mean HbA_{1c} [%] Baseline (SE)	7.82 (0.07)	7.88 (0.09)
	Week 24 (SE)	7.24 (0.08)	7.67 (0.09)
	Mean FPG [mmol/L] Baseline (SE)	8.45 (0.16)	8.61 (0.20)
	Week 24 (SE)	7.80 (0.18)	8.20 (0.16)
Effect estimate per comparison	**Primary endpoint** Change from baseline in HbA_{1c} [%] after 24 weeks – MMRM FAS (OC)	Comparison vs. placebo	**Lina 5**
		Adjusted mean change in HbA_{1c} [%] (SE)	-0.47 (0.10)
		95% CI	(-0.66, -0.28)
		P-value	<0.0001
	Key secondary endpoint Change from baseline in FPG [mmol/L] after 24 weeks – MMRM FAS (OC)	Comparison vs. placebo	**Lina 5**
		Adjusted mean change in FPG [mmol/L] (SE)	-0.44 (0.22)
		95% CI	(-0.87, -0.01)
		P-value	0.0452

Results and Analysis 1275.10*(met+empa10)*

Analysis description	**Primary Analysis**
Analysis population and time point description	The full analysis set (FAS) included all patients treated with at least one dose of study drug during the double-blind part of the trial who had a baseline HbA_{1c} assessment and at least one on-treatment HbA_{1c} assessment during the double-blind period. An observed cases (OC) approach was used. All available data were analysed as observed, missing data were not directly imputed prior to analysis and were handled implicitly by the statistical model used (mixed model repeated measures [MMRM]). Further, all values observed after a patient started rescue medication were excluded. Confirmatory tests for the superiority of lina 5 add-on to empa 10 and metformin vs. placebo for the primary and key secondary endpoints followed a hierarchical testing procedure that allowed each test to be done at a two-sided alpha = 0.05 level of significance, whilst controlling the overall probability of a type I error at 0.05 (two-sided). The procedure started with the primary endpoint and continued with the key secondary endpoint. 24 weeks

Descriptive statistics and estimate variability		Met + empa 10 **Lina 5**	Met + empa 10 **Placebo**
	Number of subjects	122	125
	Mean HbA_{1c} [%] Baseline (SE)	8.04 (0.09)	8.03 (0.08)
	Week 24 (SE)	7.43 (0.09)	7.79 (0.08)
	Mean FPG [mmol/L] Baseline (SE)	8.76 (0.17)	8.64 (0.15)
	Week 24 (SE)	8.27 (0.20)	8.77 (0.17)
Effect estimate per comparison	**Primary endpoint** Change from baseline in HbA_{1c} [%] after 24 weeks – MMRM FAS (OC)	Comparison vs. placebo	**Lina 5**
		Adjusted mean change in HbA_{1c} [%] (SE)	-0.32 (0.10)
		95% CI	(-0.52, -0.13)
		P-value	0.0013
	Key secondary endpoint Change from baseline in FPG [mmol/L] after 24 weeks – MMRM FAS (OC)	Comparison vs. placebo	**Lina 5**
		Adjusted mean change in FPG [mmol/L] (SE)	-0.65 (0.25)
		95% CI	(-1.15, -0.16)
		P-value	0.0103
Notes (for overall 1275.10 efficacy results)	Treatment with linagliptin 5 mg resulted in clinically meaningful reductions in HbA_{1c} and FPG when administered as add-on treatment to empagliflozin 25 mg or empagliflozin 10 mg and metformin after 24 weeks of treatment in patients with type 2 diabetes mellitus having met the HbA_{1c} inclusion criterion (HbA_{1c}: ≥7.0% and ≤10.5%) after 16 weeks of open-label treatment with either empagliflozin 25 mg and metformin or empagliflozin 10 mg and metformin. The placebo-adjusted treatment differences in HbA_{1c} and FPG after 24 weeks of treatment with linagliptin 5 mg administered as add-on therapy to empagliflozin and metformin were statistically significant. The robustness of the primary analysis was confirmed over a number of sensitivity analyses investigating the influence of use of rescue medication, protocol violations, and premature discontinuations. Subgroup analyses supported the consistency of the primary and key secondary efficacy results across a wide range of subpopulations.		
	The proportion of patients reaching target levels of HbA_{1c}<7% after 24 weeks of treatment, which was a further endpoint in this study, was higher after treatment with linagliptin 5 mg than with placebo. Reductions vs. placebo in body weight and blood pressure (further endpoints) were not noticed with linagliptin 5 mg treatment in the double-blind treatment period, but occured during the initial open-label treatment period with empagliflozin, consistent with the mode of action of the two compounds.		

Title: A phase III randomized, double-blind, parallel group study to evaluate the efficacy and safety of once daily oral administration of BI 10773 25 mg/linagliptin 5 mg and BI 10773 10 mg/linagliptin 5 mg Fixed Dose Combination tablets compared with the individual components (BI 10773 25 mg, BI 10773 10 mg, and linagliptin 5 mg) for 52 weeks in treatment naïve and metformin treated patients with type 2 diabetes mellitus with insufficient glycaemic control	
Study identi-fier	1275.1, Eudra CT No.: 2011-000383-10, CTR U13-2755

Design	This was a 52-week randomised, double-blind, parallel group comparison study. Patients were recruited and randomised at a 1:1:1:1:1 ratio to FDC empa 25/lina 5, FDC empa 10/ lina 5, empa 25, empa 10, or lina 5. Randomisation was stratified by screening HbA_{1c}, renal function at screening, and geographical region. The main objective of the trial was to investigate the efficacy (superiority testing), safety, and tolerability of the 2 FDCs vs. their individual components given as tablets once daily for 52 weeks in metformin-treated (study population 1275.1$_{(met)}$) or drug-naïve patients (study population 1275.1$_{(naïve)}$) with type 2 diabetes mellitus and insufficient glycaemic control. The primary efficacy analysis was done after 24 weeks of treatment.		
	Duration of main phase:		52 weeks, 4 weeks follow-up period
	Duration of Run-in phase:		2 weeks
	Duration of Extension phase:		not applicable
Hypo-thesis	Superiority of the FDCs vs. the individual components, tested in parallel in 2 populations of patients, 1275.1$_{(met)}$ and 1275.1$_{(naïve)}$		
Treat-ment groups	FDC empa25/lina 5		Fixed dose combination empagliflozin 25 mg/ linagliptin 5 mg, 52 weeks, 137 patients randomised in 1275.1$_{(met)}$ and 137 patients randomised in 1275.1$_{(naïve)}$
	FDC empa10/lina 5		Fixed dose combination empagliflozin 10 mg/ linagliptin 5 mg, 52 weeks, 136 patients randomised in 1275.1$_{(met)}$ and 136 patients randomised in 1275.1$_{(naïve)}$
	Empa 25		Empagliflozin 25 mg, 52 weeks, 141 patients randomised in 1275.1$_{(met)}$ and 135 patients randomised in 1275.1$_{(naïve)}$
	Empa 10		Empagliflozin 10 mg, 52 weeks, 140 patients randomised in 1275.1$_{(met)}$ and 134 patients randomised in 1275.1$_{(naïve)}$
	Lina 5		Linagliptin 5 mg, 52 weeks, 132 patients randomised in 1275.1$_{(met)}$ and 135 patients randomised in 1275.1$_{(naïve)}$
End-points and defini-tions	Primary endpoint	Glycated haemoglobin (HbA_{1c})	Change from baseline in HbA_{1c} after 24 weeks of treatment
	First key secondary endpoint	Fasting plasma glucose (FPG)	Change from baseline in FPG after 24 weeks of treatment
	Second key secondary endpoint	Body weight	Change from baseline in body weight after 24 weeks of treatment, confirmatory testing only vs. lina 5
	Third key secondary endpoint	Treat-to-target response	Proportion of patients reaching HbA_{1c} <7% after 24 weeks of treatment among those with HbA_{1c} ≥7% at baseline
Data-base lock	20 March 2013		
Results and Analysis 1275.1$_{(met)}$			
Analysis description	**Primary Analysis**		

Analysis population and time point description	The full analysis set (FAS) included all patients treated with at least one dose of study drug during the double-blind part of the trial who had a baseline HbA_{1c} assessment and at least one on-treatment HbA_{1c} assessment during the double-blind period. An ANCOVA (analysis of covariance) with a last observation carried forward (LOCF) approach was used for the main analyses, excluding values after rescue medication. Confirmatory testing of the superiority of the FDCs vs. their individual components was done separately in each patient population. Within each FDC dose level in study population $1275.1_{(met)}$, 2 hypotheses evaluating whether the FDC was superior to the 2 individual components on the primary endpoint were tested simultaneously at a two-sided alfa = 0.05 level of significance. Only if both null hypotheses at the higher FDC dose level were rejected, were the hypotheses at the lower FDC dose level to be tested, thereby controlling the overall probability of a type I error at 0.05 (two-sided). The 3 key secondary endpoints were to be subsequently tested in a pre-defined order (see results below). For the third key secondary endpoint, logistic regression was used, on the FAS (NCF, non-completers considered failure). Upon a health authority request, an observed cases (OC) approach was also used. All available data were analysed as observed, missing data were not directly imputed prior to analysis and were handled implicitly by the statistical model used (mixed model repeated measures [MMRM]). Further, all values observed after a patient started rescue medication were excluded. 24 weeks					
Descriptive statistics and estimate variability		FDC empa 25/ lina 5	FDC empa 10/ lina 5	Empa 25	Empa 10	Lina 5
	Number of subjects	134	135	140	137	128
	Mean HbA_{1c} [%] Baseline (SE)	7.90 (0.07)	7.95 (0.07)	8.02 (0.07)	8.00 (0.08)	8.02 (0.08)
	Week 24 (SE)	6.74 (0.05)	6.89 (0.07)	7.38 (0.09)	7.33 (0.07)	7.29 (0.09)
	Mean FPG [mg/dL] Baseline (SE)	154.62 (2.89)	156.68 (2.98)	159.89 (3.21)	161.64 (2.98)	156.35 (2.72)
	Week 24 (SE)	121.05 (2.25)	125.31 (2.33)	140.08 (4.12)	138.75 (2.44)	143.96 (2.84)
	Mean body weight [kg] Baseline (SE)	85.47 (1.76)	86.57 (1.64)	87.68 (1.49)	86.14 (1.55)	85.01 (1.62)
	Week 24 (SE)	82.48 (1.71)	83.96 (1.62)	84.46 (1.43)	83.62 (1.55)	84.35 (1.61)
	Patients reaching HbA_{1c} <7% after 24 weeks among those with HbA_{1c} ≥7% at baseline (%)	76 (61.8)	74 (57.8)	43 (32.6)	35 (28.0)	43 (36.1)
Effect estimate per comparison	**Primary endpoint** Change from baseline in HbA_{1c} [%] after	**FDC empa 25/lina 5**		vs. empa 25		vs. lina 5
		Adjusted mean (SE)		-0.58 (0.09)		-0.50 (0.09)
		95% CI		(-0.75, -0.41)		(-0.67, -0.32)

	24 weeks – ANCOVA FAS (LOCF)	P-value	<0.0001	<0.0001
		FDC empa 10 / lina 5	vs. empa 10	vs. lina 5
		Adjusted mean (SE)	-0.42 (0.09)	-0.39 (0.09)
		95% CI	(-0.59, -0.25)	(-0.56, -0.21)
		P-value	<0.0001	<0.0001
	First key secondary endpoint Change from baseline in FPG [mg/dL] after 24 weeks – ANCOVA FAS (LOCF)	**FDC empa 25 / lina 5**	vs. empa 25	vs. lina 5
		Adjusted mean (SE)	-16.43 (3.54)	-22.20 (3.62)
		95% CI	(-23.37, -9.48)	(-29.30, -15.10)
		P-value	<0.0001	<0.0001
		FDC empa 10 / lina 5	vs. empa 10	vs. lina 5
		Adjusted mean (SE)	-11.34 (3.55)	-19.12 (3.61)
		95% CI	(-18.31, -4.37)	(-26.21, -12.03)
		P-value	0.0015	<0.0001
	Second key secondary endpoint Change from baseline in body weight [kg] after 24 weeks – ANCOVA FAS (LOCF)	**FDC empa 25 / lina 5**		vs. lina 5
		Adjusted mean (SE)		-2.30 (0.44)
		95% CI		(-3.15, -1.44)
		P-value		<0.0001
		FDC empa 10 / lina 5		vs. lina 5
		Adjusted mean (SE)		-1.91 (0.44)
		95% CI		(-2.77, -1.05)
		P-value		<0.0001
	Third key secondary endpoint Patients reaching HbA_{1c} <7% after 24 weeks among those with HbA_{1c} ≥7% at baseline – FAS (NCF)	**FDC empa 25 / lina 5**	vs. empa 25	vs. lina 5
		Odds ratio	4.191	4.500
		95% CI	(2.319, 7.573)	(2.474, 8.184)
		P-value	<0.0001	<0.0001
		FDC empa 10 / lina 5	vs. empa 10	vs. lina 5
		Odds ratio	3.495	2.795
		95% CI	(1.920, 6.363)	(1.562, 5.001)
		P-value	<0.0001	0.0005

Notes	Treatment with the FDCs empagliflozin 25 mg/linagliptin 5 mg and empagliflozin 10 mg/linagliptin 5 mg in patients with metformin background medication led to clinically meaningful reductions in HbA_{1c} with statistically significant differences vs. empagliflozin 25 mg or 10 mg and linagliptin 5 mg after 24 weeks of treatment. Statistically significant and clinically meaningful differences were observed with both FDCs for the change from baseline in FPG, body weight (comparison vs. linagliptin 5 mg only), and for the treat-to-target efficacy response (patients with HbA_{1c}<7.0% among those with HbA_{1c}≥7.0%) after 24 weeks of treatment. A number of sensitivity and subgroup analyses provided consistent results with the primary analyses. Further exploratory endpoints also indicated clinically relevant improvements with the FDCs vs. the individual components. A higher proportion of patients treated with the FDcs than with the individual components reached target HbA_{1c} levels of <6.5% or had an HbA_{1c} reduction of at least 0.5% after 24 weeks of treatment. Clinically meaningful reductions in blood pressure were noted for both FDCs; relevant differences to the linagliptin 5 mg group were shown. Reductions in waist circumference in the FDC and empagliflozin treatment groups were consistent with the observed reduction in body weight after 24 weeks of treatment. The proportions of patients who required rescue medication on-treatment was low in all groups. The clinically revelant improvements in parameters of glycaemic control with FDC treatment were maintained over the entire 52-week treatment period.

Change from baseline in HbA1C

Change from baseline in HbA1c after 24 weeks in the Phase III study 1275.10

Change from baseline in HbA1c after 24 weeks in study 1275.10(met+empa25)

After 24 weeks of double-blind treatment, there was a reduction in HbA1c in the lina 5 group. Based on the MMRM analysis on the FAS (OC), a statistically significant and a clinically relevant difference (p<0.0001) between lina 5 and placebo was seen. The treatment difference versus placebo for the adjusted mean change from baseline to Week 24 in HbA1c was -0.47% (95% CI: -0.66, -0.28). The changes from baseline in HbA1c at Week 24 in study 1275.10(met+empa25) are summarised in

Table **13**.

Figure 3 shows the mean change from baseline in HbA1c over the 24 weeks of double-blind treatment. The treatment effect of lina 5 was seen starting at Week 6; at Week 18, a near-maximum treatment effect of linagliptin was achieved and sustained through Week 24.

Change from baseline in HbA1c after 24 weeks in study 1275.10(met+empa10)

After 24 weeks of double-blind treatment, there was a reduction in HbA1c in the lina 5 group. Based on the MMRM analysis on the FAS (OC), a statistically significant difference (p = 0.0013) between lina 5 and placebo was seen. The treatment difference versus placebo for the adjusted mean change from baseline to Week 24 in HbA1c was -0.32% (95% CI: -0.52, -0.13). The changes from baseline in HbA1c at Week 24 in study 1275.10(met+empa10) are summarised in

Table **13**.

Figure 3 shows the mean change from baseline in HbA1c over the 24 weeks of double-blind treatment. The treatment effect of lina 5 was seen starting at Week 6; at Week 12, a near-maximum treatment effect of linagliptin was achieved and sustained through Week 24.

Table 13 Adjusted mean change from baseline in HbA1c [%] at Week 24 in study 1275.10 - MMRM FAS (OC)

	Metformin+empa25		Metformin+empa10	
	Lina 5	**Placebo**	**Lina 5**	**Placebo**
Patients, N	110	110	122	125
Number of analysed patients, N	109	108	122	125
Mean baseline HbA_{1c} (SE)	7.82 (0.07)	7.88 (0.09)	8.04 (0.09)	8.03 (0.08)
Change from baseline				
Mean HbA_{1c} (SE)	-0.60 (0.07)	-0.13 (0.07)	-0.55 (0.08)	-0.21 (0.07)
Adjusted[1] mean HbA_{1c} (SE)	-0.58 (0.07)	-0.10 (0.07)	-0.53 (0.07)	-0.21 (0.07)
Comparison vs. placebo				
Adjusted[1] mean HbA_{1c} (SE)	-0.47 (0.10)		-0.32 (0.10)	
95% CI	(-0.66, -0.28)		(-0.52, -0.13)	
p-value	<0.0001		0.0013	

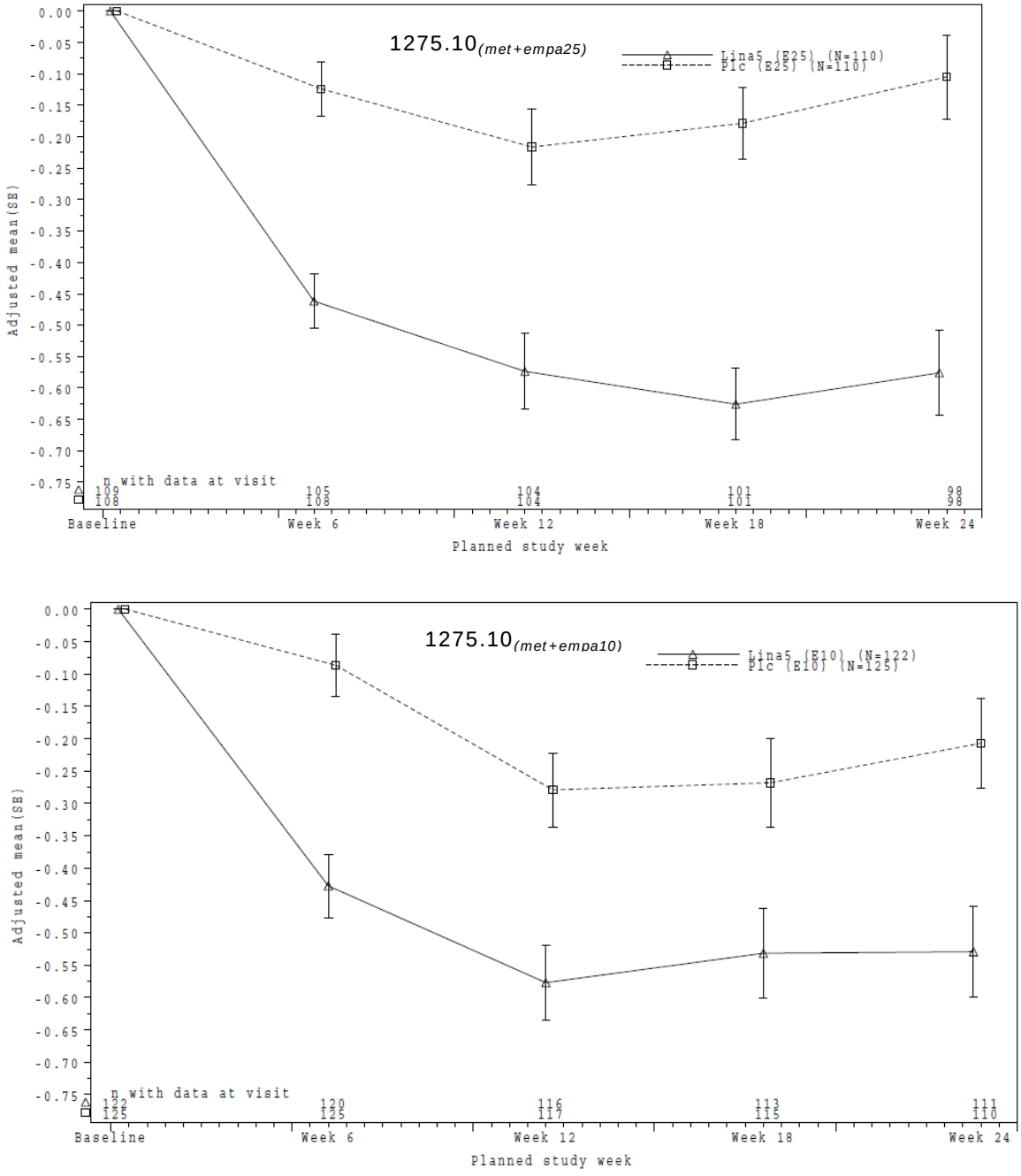

Figure 3 HbA1c [%] change from baseline over time in study 1275.10 - MMRM FAS (OC)

Change from baseline in HbA1c after 24 weeks in study 1275.10(pooled)

In a post-hoc analysis pooling the 2 study populations (metformin plus empa 25 and empa 10 backgrounds), the adjusted mean change from baseline to Week 24 in HbA1c was -0.55% in the lina 5 group and -0.16% in the placebo group, resulting in a treatment difference of -0.40% (95% CI: -0.53, -0.27; p<0.0001) in favour of lina 5.

Patients achieving HbA1c <7.0% after 24 weeks in study 1275.10(met+empa25)

The percentage of patients with a baseline HbA1c of 7.0% or greater with HbA1c <7.0% after 24 weeks of double-blind treatment was higher in the lina 5 group (36.0%) than in the placebo group (15.0%). The results and the associated odds ratio are shown in Table 14.

Patients achieving HbA1c <7.0% after 24 weeks in study 1275.10(met+empa10)

The percentage of patients with a baseline HbA1c of 7.0% or greater with HbA1c <7.0% after 24 weeks of double-blind treatment was higher in the lina 5 group (25.9%) than in the placebo group (10.9%). The results and the associated odds ratio are shown in Table 14.

Table 14 Patients with HbA1c <7.0% at Week 24 in study 1275.10 - FAS (NCF)

	Metformin+empa25		Metformin+empa10	
	Lina 5	**Placebo**	**Lina 5**	**Placebo**
Number of analysed patients[1], N (%)	100 (100.0)	107 (100.0)	116 (100.0)	119 (100.0)
Patients with HbA_{1c} <7.0% at Week 24, N (%)	36 (36.0)	16 (15.0)	30 (25.9)	13 (10.9)
Comparison vs. placebo [2]				
Odds ratio	4.429		3.965	
95% CI	(2.097, 9.353)		(1.771, 8.876)	

Changes in HbA1c in the open-label period of the Phase III study 1275.10

Changes in HbA1c in the open-label period of study 1275.10(met+empa25)

The mean (SD) pre-treatment HbA1c for patients in the open-label period of the study (OLFAS) was 8.96 (0.80)%. The mean change from pre-treatment after 16 weeks of the open-label treatment with empa 25 was -1.42 (0.94)%. Overall, 84 out of 334 patients in the OLFAS (25.1%) reached the glycaemic goal of an HbA1c value <7% after 16 weeks of open-label treatment. Only patients with an HbA1c value between 7.0% and 10.5% (baseline value) after the 16-week open-label period were eligible for double-blind treatment. Out of 99 patients with an HbA1c measurement at Week 16 who did not enter double-blind treatment, 82 patients (82.8%) had HbA1c <7% and 17 patients (17.2%) had HbA1c ≥7.0% and ≤10.5%.

Changes in HbA1c in the open-label period of study 1275.10(met+empa10)

The mean (SD) pre-treatment HbA1c for patients in the open-label period of the study (OLFAS) was 8.91 (0.79)%. The mean change from pre-treatment after 16 weeks of the open-label treatment with empa 10 was -1.12 (1.08)%. Overall, 70 out of 344 patients in the OLFAS (20.3%) reached the glycaemic goal of an HbA1c value <7% after 16 weeks of open-label treatment. Only patients with an HbA1c value between 7.0% and 10.5% (baseline value) after the 16-week open-label period were eligible for double-blind treatment. Out of 83 patients with an HbA1c measurement at Week 16 who did not enter double-blind treatment, 65

patients (78.3%) had HbA1c <7%, 16 patients (19.3%) had HbA1c ≥7.0% and ≤10.5%, and 2 patients (2.4%) had HbA1c >10.5%.

Change from baseline in HbA1c in the Phase III study 1275.1

Change from baseline in HbA1c after 24 weeks in the Phase III study 1275.1(met)

After 24 weeks of treatment in study 1275.1(met), there were reductions in HbA1c in all treatment groups. The primary analysis using an ANCOVA model on the FAS (LOCF) showed statistically significant differences (p<0.0001) between both FDC empagliflozin/linagliptin doses and their individual components. For the FDC empa 25/lina 5 group, the difference for the adjusted mean change from baseline in HbA1c at Week 24 was -0.58% (95% CI: -0.75, -0.41) versus empa 25 and -0.50% (95% CI: -0.67, -0.32) versus lina 5. For the FDC empa 10/lina 5 group, the difference was 0.42% (95% CI: -0.59, -0.25) versus empa 10 and -0.39% (95% CI: -0.56, -0.21) versus lina 5. The changes from baseline in HbA1c at Week 24 in study 1275.1(met) are summarised in Table 15, upper panel.

Table 15 Adjusted mean change from baseline in HbA1c [%] at Week 24 in study 1275.1 - ANCOVA FAS (LOCF)

	FDC empa 25/lina 5	Empa 25	FDC empa 10/lina 5	Empa 10	Lina 5
Study 1275.1*(met)*					
Number of analysed patients[1]	134	140	135	137	128
Mean baseline HbA_{1c} (SE)	7.90 (0.07)	8.02 (0.07)	7.95 (0.07)	8.00 (0.08)	8.02 (0.08)
Change from baseline					
Mean HbA_{1c} (SE)	-1.16 (0.06)	-0.63 (0.09)	-1.06 (0.07)	-0.68 (0.07)	-0.73 (0.07)
Adjusted mean HbA_{1c} (SE)	-1.19 (0.06)	-0.62 (0.06)	-1.08 (0.06)	-0.66 (0.06)	-0.70 (0.06)
Comparison vs. empagliflozin	vs. empa 25		vs. empa 10		
Adjusted mean HbA_{1c} (SE)	-0.58 (0.09)		-0.42 (0.09)		
95% CI	(-0.75,-0.41)		(-0.59,-0.25)		
p-value	<0.0001		<0.0001		
Comparison vs. lina 5					
Adjusted mean HbA_{1c} (SE)	-0.50 (0.09)		-0.39 (0.09)		
95% CI	(-0.67,-0.32)		(-0.56,-0.21)		
p-value	<0.0001		<0.0001		
Study 1275.1*(naïve)*					
Number of analysed patients[1]	134	133	135	132	133
Mean baseline HbA_{1c} (SE)	7.99 (0.08)	7.99 (0.08)	8.04 (0.08)	8.05 (0.09)	8.05 (0.08)
Change from baseline					
Mean HbA_{1c} (SE)	-1.06 (0.09)	-0.94 (0.09)	-1.25 (0.08)	-0.84 (0.08)	-0.69 (0.08)
Adjusted mean HbA_{1c} (SE)	-1.08 (0.07)	-0.95 (0.07)	-1.24 (0.07)	-0.83 (0.07)	-0.67 (0.07)
Comparison vs. empagliflozin	vs. empa 25		vs. empa 10		
Adjusted mean HbA_{1c} (SE)	-0.14 (0.10)		-0.41 (0.10)		
95% CI	(-0.33, 0.06)		(-0.61,-0.21)		
p-value	0.1785		N.A.[2]		
Comparison vs. lina 5					
Adjusted mean HbA_{1c} (SE)	-0.41 (0.10)		-0.57 (0.10)		
95% CI	(-0.61,-0.22)		(-0.76,-0.37)		
p-value	<0.0001		N.A.[2]		

Patients with HbA1c <7.0% after 24 weeks in the Phase III study 1275.1(met)

The percentage of patients with a baseline HbA1c of 7.0% or greater with HbA1c <7.0% after 24 weeks of treatment was higher for both FDC empagliflozin/linagliptin groups than for their individual components. Among patients with baseline HbA1c of 7.0% or greater, 61.8% of the patients in the FDC empagliflozin 25 mg/linagliptin 5 mg group and 57.8% of the patients in the FDC empagliflozin 10 mg/linagliptin 5 mg group attained HbA1c values of less than 7.0% after 24 weeks of treatment, compared with 32.6% of patients in

the empagliflozin 25 mg group, 28.0% of patients in the empagliflozin 10 mg group, and 36.1% of patients in the linagliptin 5 mg group.

Change from baseline in fasting plasma glucose

The change from baseline in FPG after 24 weeks of treatment was a key secondary endpoint in all Phase III studies.

Change from baseline in fasting plasma glucose in the Phase III study 1275.10

Change from baseline in fasting plasma glucose in study 1275.10(met+empa25)

Statistically significant reductions for lina 5 compared with placebo were seen in the MMRM analysis on the FAS (OC) of FPG after 24 weeks of treatment. The adjusted mean difference of lina 5 versus placebo for the mean change from baseline to Week 24 in FPG was -0.44 mmol/L (95% CI: -0.87, -0.01; p = 0.0452). The changes from baseline in FPG in study 1275.10(met+empa25) are shown in Table 16.

Change from baseline in fasting plasma glucose in study 1275.10(met+empa10)

Statistically significant and clinically relevant reductions for lina 5 compared with placebo were seen in the MMRM analysis on the FAS (OC) of FPG after 24 weeks of treatment. The adjusted mean difference of lina 5 versus placebo for the mean change from baseline to Week 24 in FPG was -0.65 mmol/L (95% CI: -1.15, -0.16; p = 0.0103). The changes from baseline in FPG in study 1275.10 (met+empa10) are shown in Table 16.

Table 16 Adjusted mean change from baseline in FPG [mmol/L] at Week 24 in study 1275.10 - MMRM FAS (OC)

	Metformin+empa25		Metformin+empa10	
	Lina 5	**Placebo**	**Lina 5**	**Placebo**
Patients, N	110	110	122	125
Number of analysed patients, N	107	107	120	123
Mean baseline FPG (SE)	8.45 (0.16)	8.61 (0.20)	8.76 (0.17)	8.64 (0.15)
Change from baseline				
Mean FPG (SE)	-0.68 (0.20)	-0.33 (0.18)	-0.55 (0.24)	0.14 (0.16)
Adjusted[1] mean FPG (SE)	-0.68 (0.15)	-0.24 (0.15)	-0.44 (0.18)	0.21 (0.18)
Comparison vs. placebo				
Adjusted[1] mean FPG (SE)	-0.44 (0.22)		-0.65 (0.25)	
95% CI	(-0.87, -0.01)		(-1.15, -0.16)	
p-value	0.0452		0.0103	

Change from baseline in fasting plasma glucose in the Phase III study 1275.1(met)

After 24 weeks of treatment in study 1275.1(met), there were clinically relevant reductions in FPG with both doses of the FDC empagliflozin/linagliptin and also for the empagliflozin groups. In the lina 5 group, the reduction from baseline was smaller. The ANCOVA analysis on the FAS (LOCF) of FPG showed statistically significant and clinically relevant differences between the FDC empa 25/lina 5 group and its individual components (both p<0.0001). The difference for the adjusted mean change from baseline to Week 24 in FPG for the FDC empa 25/lina 5 group was -0.91 mmol/L (95% CI: -1.30, -0.53) versus empa 25 and -1.23 mmol/L (95% CI: -1.63, -0.84) versus lina 5. The analysis also showed clinical and statistical superiority of the FDC empa 10/lina 5 to its individual components empa 10 (p-value = 0.0015) and lina 5 (p<0.0001). The treatment difference for the FDC empa 10/lina 5 group was -0.63 mmol/L (95% CI: -1.02, -0.24) versus empa 10 and -1.06 mmol/L (95% CI: -1.45, -0.67) versus lina 5. The changes from baseline in FPG in study 1275.1(met) are shown in

Table **17**.

Table 17 Adjusted mean change from baseline in FPG [mmol/L] at Week 24 in study 1275.1(met) - ANCOVA FAS (LOCF)

	FDC empa 25/lina 5	Empa 25	FDC empa 10/lina 5	Empa 10	Lina 5
Patients, N	134	140	135	137	128
Number of analysed patients, N	133	139	134	136	127
Mean baseline FPG (SE)	8.58 (0.16)	8.87 (0.18)	8.70 (0.17)	8.97 (0.17)	8.68 (0.15)
Change from baseline					
Mean change in FPG (SE)	-1.86 (0.15)	-1.10 (0.21)	-1.74 (0.14)	-1.27 (0.16)	-0.69 (0.14)
Adjusted[1] mean change in FPG (SE)	-1.96 (0.14)	-1.04 (0.14)	-1.79 (0.14)	-1.16 (0.14)	-0.72 (0.14)
Comparison vs. empa	vs. empa 25		vs. empa 10		
Adjusted[1] mean change in FPG (SE)	-0.91 (0.20)		-0.63 (0.20)		
95% CI	(-1.30, -0.53)		(-1.02, -0.24)		
p-value	<0.0001		0.0015		
Comparison vs. lina 5					
Adjusted[1] mean change in FPG (SE)	-1.23 (0.20)		-1.06 (0.20)		
95% CI	(-1.63, -0.84)		(-1.45, -0.67)		
p-value	<0.0001		<0.0001		

Change from baseline in body weight

Change from baseline in body weight after 24 weeks in the Phase III study 1275.10

Change from baseline in body weight after 24 weeks in study 1275.10(met+empa25)

After 24 weeks of treatment, the changes in body weight were small in both treatment groups, which was expected, based on linagliptin's mechanism of action. Based on the MMRM analysis on the FAS (OC), the adjusted mean (SE) change from baseline to Week 24 in body weight was -0.17 (0.26) kg in the lina 5 group and -0.26 (0.26) kg in the placebo group. The adjusted mean difference between lina 5 and placebo was 0.09 kg (95% CI: -0.63, 0.82).

Change from baseline in body weight after 24 weeks in study 1275.10(met+empa10)

After 24 weeks of treatment, the changes in body weight were small in both treatment groups, which was expected, based on linagliptin's mechanism of action. Based on the MMRM analysis on the FAS (OC), the adjusted mean (SE) change from baseline to Week 24 in body weight was -0.20 (0.25) kg in the lina 5 group and -0.79 (0.25) kg in the placebo group. The adjusted mean difference between lina 5 and placebo was 0.60 kg (95% CI: -0.10, 1.30).

Change from baseline in body weight after 24 weeks in the Phase III study 1275.1(met)

After 24 weeks of treatment in study 1275.1(met), there were clinically relevant reductions in body weight with both of the FDC empagliflozin/linagliptin doses and also for both doses of empagliflozin. There was no relevant change in body weight in the lina 5 group. The ANCOVA analysis on the FAS (LOCF) of body weight showed statistically significant and clinically relevant differences ($p<0.0001$) for both FDC empagliflozin/linagliptin doses compared to lina 5 treatment. The difference versus lina 5 was -2.30 kg (95% CI: -3.15, -1.44) for the FDC empa 25/lina 5 group and -1.91 kg (95% CI: -2.77, -1.05) for the FDC empa 10/lina 5 group. There were no statistically relevant differences in the change from baseline in body weight between the FDCs and the empagliflozin treatment groups. The changes from baseline in body weight in study 1275.1(met) are shown in Table 18.

Table 18 Adjusted mean change from baseline in body weight [kg] at Week 24 in study 1275.1(met) - ANCOVA FAS (LOCF)

	FDC empa 25/lina 5	Empa 25	FDC empa 10/lina 5	Empa 10	Lina 5
Patients, N	134	140	135	137	128
Number of analysed patients, N	134	140	135	137	128
Mean baseline body weight (SE)	85.47 (1.76)	87.68 (1.49)	86.57 (1.64)	86.14 (1.55)	85.01 (1.62)
Change from baseline					
Mean body weight (SE)	-2.99 (0.30)	-3.22 (0.43)	-2.61 (0.27)	-2.51 (0.21)	-0.65 (0.30)
Adjusted[1] mean body weight (SE)	-2.99 (0.31)	-3.18 (0.30)	-2.60 (0.30)	-2.53 (0.30)	-0.69 (0.31)
Comparison vs. empa	vs. empa 25		vs. empa 10		
Adjusted[1] mean body weight (SE)	0.19 (0.43)		-0.07 (0.43)		
95% CI	(-0.65, 1.03)		(-0.91, 0.77)		
p-value	0.6604		0.8757		
Comparison vs. lina 5					
Adjusted[1] mean body weight (SE)	-2.30 (0.44)		-1.91 (0.44)		
95% CI	(-3.15, -1.44)		(-2.77, -1.05)		
p-value	<0.0001		<0.0001		

[1] ANCOVA model included baseline body weight and baseline HbA_{1c} as linear covariates and treatment, baseline eGFR, and region as fixed effects.

Change from baseline in blood pressure

Change from baseline in systolic blood pressure in the Phase III study 1275.10

Change from baseline in systolic blood pressure in study 1275.10(met+empa25)

There were no relevant changes from baseline to Week 24 in SBP in either treatment group. Based on the MMRM analysis on the FAS (OC), the adjusted mean (SE) change from baseline to Week 24 was -0.2 (1.0) mmHg in the lina 5 group and -1.6 (1.0) mmHg in the placebo group.

Change from baseline in systolic blood pressure in study 1275.10(met+empa10)

There were no relevant changes from baseline to Week 24 in SBP in either treatment group. Based on the MMRM analysis on the FAS (OC), the adjusted mean (SE) change from baseline to Week 24 was 0.0 (1.0) mmHg in the lina 5 group and 1.0 (1.0) mmHg in the placebo group.

Change from baseline in systolic blood pressure in the Phase III study 1275.1(met)

After 24 weeks of treatment in study 1275.1(met), there were clinically meaningful reductions in SBP with both doses of the FDC empagliflozin/linagliptin, as well as for both empagliflozin treatment groups. No relevant change was noted in the lina 5 treatment group. The difference to lina 5 for the FDC empa 25/lina 5 group was -4.6 mmHg (95% CI: -7.1, -2.1) and for the FDC empa 10/lina 5 group was -3.0 mmHg (95% CI: -5.6, -0.5). The changes from baseline in SBP in study 1275.1(met) are shown in

Table 19.

Table 19 Adjusted mean change from baseline in systolic blood pressure [mmHg] at Week 24 in study 1275.1(met) - ANCOVA FAS (LOCF)

	FDC empa 25/lina 5	Empa 25	FDC empa 10/lina 5	Empa 10	Lina 5
Patients, N	134	140	135	137	128
Number of analysed patients, N	134	140	135	137	128
Mean baseline SBP (SE)	130.9 (1.4)	129.2 (1.1)	130.5 (1.3)	131.6 (1.2)	128.4 (1.1)
Change from baseline					
Mean SBP (SE)	-5.9 (1.0)	-4.7 (0.9)	-4.2 (1.0)	-4.7 (1.1)	-0.3 (1.1)
Adjusted[1] mean SBP (SE)	-5.6 (0.9)	-5.1 (0.9)	-4.1 (0.9)	-4.0 (0.9)	-1.0 (0.9)
Comparison vs. empa	vs. empa 25		vs. empa 10		
Adjusted[1] mean change in SBP (SE)	-0.6 (1.3)		0.0 (1.3)		
95% CI	(-3.0, 1.9)		(-2.5, 2.4)		
Comparison vs. lina 5					
Adjusted[1] mean change in SBP (SE)	-4.6 (1.3)		-3.0 (1.3)		
95% CI	(-7.1, -2.1)		(-5.6, -0.5)		

Change from baseline in diastolic blood pressure

Change from baseline in diastolic blood pressure in the Phase III study 1275.10

Change from baseline in diastolic blood pressure in study 1275.10(met+empa25)

There were no relevant changes from baseline to Week 24 in DBP in either treatment group. Based on the MMRM analysis on the FAS (OC), the adjusted mean (SE) change from baseline to Week 24 was 0.0 (0.6) mmHg in the lina 5 group and 0.3 (0.6) mmHg in the placebo group.

Change from baseline in diastolic blood pressure in study 1275.10(met+empa10)

There were no relevant changes from baseline to Week 24 in DBP in either treatment group. Based on the MMRM analysis on the FAS (OC), the adjusted mean (SE) change from baseline to Week 24 was 0.4 (0.7) mmHg in the lina 5 group and 1.1 (0.7) mmHg in the placebo group.

Change from baseline in diastolic blood pressure in the Phase III study 1275.1(met)

After 24 weeks of treatment in study 1275.1(met), there were clinically meaningful reductions in DBP with both doses of the FDC empagliflozin/linagliptin, as well as for both empagliflozin treatment groups. Similarly as for SBP, no relevant change was noted in the lina 5 treatment group. As the FDCs and the empagliflozin treatment groups had similar changes from baseline in DBP, there were no relevant differences noted between them. The difference versus lina 5 was -2.5 mmHg (95% CI: -4.1, -0.9) for the FDC empa 25/lina 5 group and -1.4 mmHg (95% CI: -3.0, 0.2) for the FDC empa 10/lina 5 group.

Use of rescue medication

Use of rescue medication in the Phase III study 1275.10

Use of rescue medication in study 1275.10(met+empa25)

Use of antidiabetic rescue medication during 24 weeks of double-blind treatment was reported only for 3 patients (2.7%) in the placebo group; none of the patients in the lina 5 group received rescue medication. Due to the low number of patients with rescue medication no odds ratio was calculated.

Use of rescue medication in study 1275.10(met+empa10)

Use of antidiabetic rescue medication during 24 weeks of double-blind treatment was reported for 2 patients in the lina 5 group (1.6%) and 5 patients in the placebo group (4.0%). Due to the low numbers of patients requiring rescue therapy, the associated odds ratio did not reveal relevant differences between the treatment groups.

Use of rescue medication in the Phase III study 1275.1(met)

Very few patients in study 1275.1(met) required the use of rescue medication during 24 weeks of treatment: 1 patient (0.7%) in the FDC empa 25/lina 5 group, 3 patients (2.2%) in the FDC empa 10/lina 5 group, 6 patients (4.3%) in the empa 25 group, 1 patient (0.7%) in the empa 10 group, and 4 patients (3.1%) in the lina 5 group. Due to the low numbers of patients requiring rescue therapy, the associated odds ratios did not reveal relevant differences between the treatment groups.

Clinical studies in special populations

Comparison of results in subpopulations

Selected subgroup analyses of the primary endpoint in studies 1275.10, and 1275.1 are presented in sections below. For study 1275.1 only subgroups analysed in the metformin-treated population are presented. As the subgroup analyses were conducted on trial level, the number of patients in some of the subgroups was low and thus the results of these analyses should be interpreted with caution.

Age

Subgroup analysis by age in study 1275.10(met+empa25)

The changes from baseline in HbA1c were higher in older patients (p-value for the treatment-by-age interaction: 0.0699). The placebo-adjusted mean changes from baseline to Week 24 in HbA1c for lina 5 were -0.38% (95% CI: -0.58, -0.17) for patients aged <65 years and -0.84% (95% CI: -1.30, -0.38) for patients aged 65 to <75 years. As only 4 patients 75 years or older were included in the FAS, this subgroup was not analysed.

Subgroup analysis by age in study 1275.10(met+empa10)

The changes from baseline in HbA1c were similar across the analysed age groups; no indication of a treatment-by-age interaction was seen (p-value: 0.8851). The placebo-adjusted mean changes from baseline to Week 24 in HbA1c for lina 5 were -0.32% (95% CI: -0.54, -0.11) for patients aged <65 years and -0.36% (95% CI: -0.83, 0.11) for patients aged 65 to <75 years. As only 4 patients 75 years or older were included in each treatment group, this subgroup was not analysed.

Subgroup analysis by age in study 1275.1(met)

The subgroup analysis by age (using categories of patients <50 years, 50 to <65 years, and 65 to <75 years) showed that all age groups had changes in HbA1c after 24 weeks in all treatment groups. In general, the magnitude of treatment difference between FDCs and their individual components decreased with increasing age. The p-value for the treatment-by-age interaction was 0.0058, suggesting that the treatment effect differed across the analysed subgroups. The category ≥75 years was not included in the analysis as it contained fewer than 35 patients.

Gender

Subgroup analysis by gender in study 1275.10(met+empa25)

The treatment effects were of similar magnitude in both genders. There was no evidence of a treatment-by-gender interaction (p-value = 0.8436). The placebo-adjusted mean changes from baseline to Week 24 in HbA1c for lina 5 were -0.45% (95% CI: -0.72, -0.19) in male patients and -0.49% (95% CI: -0.77, -0.22) in female patients

Subgroup analysis by gender in study 1275.10(met+empa10)

The mean changes from baseline in HbA1c after 24 weeks were similar in the lina 5 group in male patients (-0.50%) and female patients (-0.57%). Due to a stronger placebo effect in the male subgroup, the placebo-adjusted mean change from baseline to Week 24 in HbA1c was lower in male patients: -0.19% (95% CI: -0.45, 0.07), compared with female patients: -0.49% (95% CI: -0.78, -0.20). The p-value for the treatment-by-gender interaction was 0.1293.

Subgroup analysis by gender in study 1275.1(met)

The adjusted mean changes in HbA1c after 24 weeks and the associated treatment differences between the FDCs and their single components were generally similar in both genders. There was no indication of a treatment-by-gender interaction (p-value = 0.6657).

Race

Subgroup analysis by race in study 1275.10

As the majority of patients (96.8%) in study 1275.10 were of White race, and the remaining race categories contained fewer than 5 patients per group, this subgroup analysis was not conducted.

Subgroup analysis by race in study 1275.1(met)

The adjusted mean changes in HbA1c after 24 weeks and the associated treatment differences between the FDCs and their single components were generally similar in White, Black/African American, and Asian patients. As the majority of patients in the study were White (73.9%), the subgroups of Black/African American and Asian patients were relatively small. There was no indication of a treatment-by-race interaction (p = 0.6351).

Ethnicity

Subgroup analysis by ethnicity in study 1275.10(met+empa25)

The treatment effects were generally of similar magnitude in patients of Hispanic/Latino and not Hispanic/Latino ethnicity. There was no evidence of a treatment-by-ethnicity interaction (p-value = 0.5053). The placebo-adjusted mean changes from baseline to Week 24 in HbA1c for lina 5 were -0.56% (95% CI: -0.87, -0.24) in Hispanic patients and -0.42% (95% CI: -0.66, -0.19) in non-Hispanic patients.

Subgroup analysis by ethnicity in study 1275.10(met+empa10)

The treatment effects were generally of similar magnitude in patients of Hispanic/Latino and not Hispanic/Latino ethnicity. There was no evidence of a treatment-by-ethnicity interaction (p-value = 0.6879). The placebo-adjusted mean changes from baseline to Week 24 in HbA1c for lina 5 were -0.37% (95% CI: -0.69, -0.05) in Hispanic patients and -0.29% (95% CI: -0.53, -0.04) in non-Hispanic patients.

Subgroup analysis by ethnicity in study 1275.1(met)

The adjusted mean changes in HbA1c after 24 weeks and the associated treatment differences between the FDCs and their single components were generally similar in patients of Hispanic/Latino and not Hispanic/Latino ethnicity. There was no evidence of a treatment-by-ethnicity interaction (p-value = 0.3394).

Geographical region

Subgroup analysis by geographical region in study 1275.10(met+empa25)

The treatment effects were of similar magnitude across geographical regions. There was no evidence of a treatment-by-region interaction (p-value = 0.7317). The placebo-adjusted mean changes from baseline to Week 24 in HbA1c for lina 5 were -0.43% (95% CI: -0.71, -0.16) in Europe, -0.62% (95% CI: -1.02, -0.21) in North America, and -0.43% (95% CI: -0.77, -0.10) in Latin America. A sensitivity analysis of the primary

endpoint including patients from Europe, Australia, Canada, and USA gave results that were consistent with the primary analysis, with treatment effect estimates similar to those of the primary analysis.

Subgroup analysis by geographical region in study 1275.10(met+empa10)

The treatment effects were of similar magnitude across geographical regions. There was no evidence of a treatment-by-region interaction (p-value = 0.8124). The placebo-adjusted mean changes from baseline to Week 24 in HbA1c for lina 5 were -0.28% (95% CI: -0.56, -0.01) in Europe, -0.29% (95% CI: -0.74, 0.16) in North America, and -0.42% (95% CI: -0.77, -0.07) in Latin America. A sensitivity analysis of the primary endpoint including patients from Europe, Australia, Canada, and USA gave results that were consistent with the primary analysis, with treatment effect estimates similar to those of the primary analysis.

Subgroup analysis by geographical region in study 1275.1(met)

The treatment effects were generally of similar magnitude across Europe, North America, Latin America, and Asia. Differences between the regions included higher adjusted mean changes from baseline in HbA1c after 24 weeks in the FDC groups in Asia and lower changes from baseline in HbA1c in the monotherapy groups in North America. However, there was no indication of a treatment-by-region interaction, as evidenced by the interaction p-value of 0.4759.

Baseline body weight

Subgroup analysis by baseline body weight in study 1275.10(met+empa25)

The subgroup analysis by baseline body weight showed larger treatment effects in patients with baseline body weight ≤80 kg compared with patients with higher body weight; however, no indication for a treatment-by-baseline body weight interaction was seen (p-value = 0.3481). The placebo-adjusted mean changes from baseline to Week 24 in HbA1c for lina 5 were -0.66% (95% CI: -1.21, -0.12) for patients with a baseline weight ≤70 kg, -0.67% (95% CI: -1.05, -0.28) for patients with a baseline weight >70 to ≤80 kg, -0.21% (95% CI: -0.59, 0.18) for patients with a baseline weight >80 to ≤90 kg, and -0.44% (95% CI: -0.76, -0.13) for patients with a baseline weight >90 kg.

Subgroup analysis by baseline body weight in study 1275.10(met+empa10)

The subgroup analysis by baseline body weight showed larger treatment effects in patients with baseline body weight ≤70 kg compared with the other subgroups; however, no indication for a treatment-by-baseline body weight interaction was seen (p-value = 0.3029). The placebo-adjusted mean changes from baseline to Week 24 in HbA1c for lina 5 were -0.77% (95% CI:-1.27, -0.26) for patients with a baseline weight ≤70 kg, -0.18% (95% CI:-0.61, 0.24) for patients with a baseline weight >70 to ≤80 kg, -0.24% (95% CI:-0.63, 0.15) for patients with a baseline weight >80 to ≤90 kg, and -0.30% (95% CI:-0.61, 0.02) for patients with a baseline weight >90 kg.

Subgroup analysis by baseline body weight in study 1275.1(met)

The adjusted mean changes in HbA1c after 24 weeks and the associated treatment differences between the FDCs and their single components were generally similar in groups of patients with different baseline weight. There was no indication of a treatment-by-weight interaction (p-value = 0.6014).

Baseline HbA1c

Subgroup analysis by baseline HbA1c in study 1275.10(met+empa25)

The subgroup analysis by baseline HbA1c showed similar treatment effects in both subgroups; no indication for a treatment-by-baseline HbA1c interaction was seen (p-value = 0.4115). The placebo-adjusted mean changes from baseline to Week 24 in HbA1c for lina 5 were -0.43% (95% CI: -0.63, -0.22) for patients with a baseline HbA1c <8.5% and -0.62% (95% CI: -1.05, -0.19) for patients with a baseline HbA1c ≥8.5%.

Subgroup analysis by baseline HbA1c in study 1275.10(met+empa10)

The subgroup analysis by baseline HbA1c showed similar treatment effects in both subgroups; no indication for a treatment-by-baseline HbA1c interaction was seen (p-value = 0.9869). The placebo-adjusted mean changes from baseline to Week 24 in HbA1c for lina 5 were -0.34% (95% CI: -0.57, -0.11) for patients with a baseline HbA1c <8.5% and -0.33%(95% CI: -0.72, 0.05) for patients with a baseline HbA1c ≥8.5%.

Subgroup analysis by baseline HbA1c in study 1275.1(met)

The subgroup analysis by baseline HbA1c showed higher mean adjusted changes from baseline in HbA1c after 24 weeks of treatment in patients with a baseline HbA1c ≥8.5% compared with patients with a baseline HbA1c <8.5% in all treatment groups. The treatment-by-baseline HbA1c interaction p-value was 0.1142.

Time since diagnosis of diabetes

Subgroup analysis by time since diagnosis of diabetes in study 1275.10(met+empa25)

The treatment effects were generally of similar magnitude across the analysed subgroups. There was no indication of a treatment-by-time since diagnosis interaction (p-value = 0.8046). Note that the group of patients diagnosed a year or less before the study was small (total of 17 patients) and thus the results of its analysis should be interpreted with particular caution. The placebo-adjusted mean changes from baseline to Week 24 in HbA1c for lina 5 were -0.23% (95% CI: -0.88, 0.43) in patients diagnosed ≤1 year, -0.51% (95% CI: -0.86, -0.15) in patients diagnosed >1 to 5 years, -0.56% (95% CI: -0.88, -0.24) in patients diagnosed >5 to 10 years, and -0.41% (95% CI: -0.76, -0.05) in patients diagnosed >10 years before the study.

Subgroup analysis by time since diagnosis of diabetes in study 1275.10(met+empa10)

The treatment effects were generally of similar magnitude across the analysed subgroups. There was no indication of a treatment-by-time since diagnosis interaction (p-value = 0.8717). Note that the group of patients diagnosed a year or less before the study was small (total of 23 patients) and thus the results of its analysis should be interpreted with particular caution. The placebo-adjusted mean changes from baseline to Week 24 in HbA1c for lina 5 were -0.38% (95% CI: -1.05, 0.30) in patients diagnosed ≤1 year, -0.43% (95% CI: -0.77, -0.09) in patients diagnosed >1 to 5 years, -0.31% (95% CI: -0.66, 0.04) in patients diagnosed >5 to 10 years, and -0.21% (95% CI: -0.60, 0.17) in patients diagnosed >10 years before the study.

Subgroup analysis by time since diagnosis of diabetes in study 1275.1(met)

In both FDC and both empagliflozin dose groups, the largest mean adjusted changes from baseline in HbA1c after 24 weeks were observed for the group of recently diagnosed patients and in general treatment effects decreased with increasing time since diagnosis. The differences between the subgroups of patients diagnosed at different times were not apparent in the lina 5 group. The treatment-by-time since diagnosis interaction p-value was 0.2417.

Renal function

Subgroup analysis by renal function in study 1275.10(met+empa25)

The treatment effect was higher in patients with normal renal function (eGFR [MDRD]: ≥90 mL/min/1.73 m2) than in patients with mild renal impairment (60 to <90 mL/min/1.73 m2); the treatment-by-baseline renal function interaction p-value was 0.1416. The placebo-adjusted mean changes from baseline to Week 24 in HbA1c for lina 5 were -0.62% (95% CI: -0.89, -0.35) for patients with normal renal function and -0.34% (95% CI: -0.60, -0.08) for patients with mild renal impairment. As there were fewer than 5 patients per group with baseline eGFR of 45 to <60 mL/min/1.73 m2 and only 1 patient with baseline eGFR <45 mL/min/1.73 m2, these categories were not analysed.

Subgroup analysis by renal function in study 1275.10(met+empa10)

The treatment effect was higher in patients with normal renal function (eGFR [MDRD]: ≥90 mL/min/1.73 m2) than in patients with mild renal impairment (60 to <90 mL/min/1.73 m2); the treatment-by-baseline renal function interaction p-value was 0.1962. The placebo-adjusted mean changes from baseline to Week 24 in HbA1c for lina 5 were -0.47% (95% CI: -0.75, -0.18) for patients with normal renal function and -0.20% (95% CI: -0.49, 0.08) for patients with mild renal impairment. As there were fewer than 5 patients per group with baseline eGFR of 45 to <60 mL/min/1.73 m2 and only 1 patient with baseline eGFR <45 mL/min/1.73 m2, these categories were not analysed.

Subgroup analysis by renal function in study 1275.1(met)

The adjusted mean changes from baseline in HbA1c were in general similar between patients with normal renal function and patients with mild renal impairment. There was no indication of a treatment-by-baseline renal function interaction (p-value = 0.4942).

PERSISTENCE OF EFFICACY AND/OR TOLERANCE EFFECTS

CHANGE FROM BASELINE IN HBA1C AFTER 52 WEEKS IN THE PHASE III STUDY 1275.1

The change from baseline in HbA1c and the efficacy response measured as HbA1c <7.0% after 52 weeks of treatment were further endpoints in study 1275.1.

The adjusted mean change from baseline in HbA1c over time in study 1275.1(met)

The adjusted mean change from baseline in HbA1c over time in study 1275.1(met), based on the ANCOVA analysis on the FAS (LOCF), is shown below. The maximal treatment effect in all treatment groups was seen at Week 12 and was maintained thereafter through Week 52 (Figure 4).

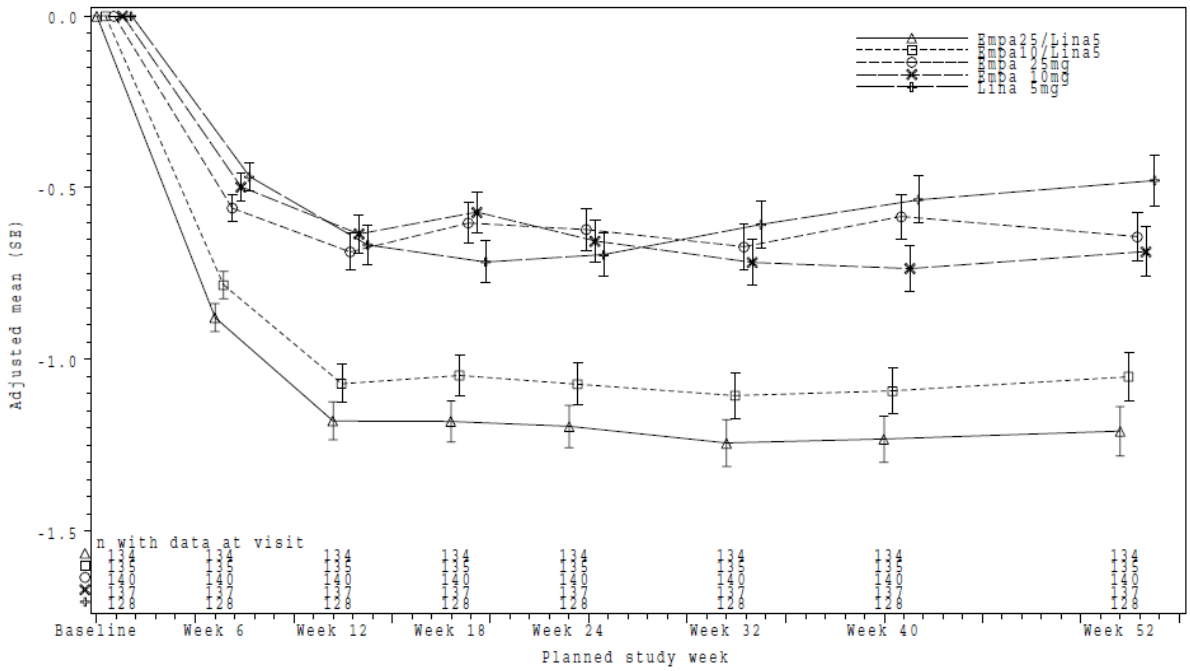

Figure 4 Change from baseline in HbA1c [%] over 52 weeks in study 1275.1(met) - ANCOVA FAS (LOCF)

The ANCOVA analysis of the change from baseline in HbA1c after 52 weeks of treatment showed consistent results with the primary analysis after 24 weeks, see Table 20. For the FDC empa 25/lina 5 group, the treatment difference at Week 52 was -0.57% (95% CI: -0.77, -0.37) versus empa 25 and -0.73% (95% CI:

-0.93, -0.53) versus lina 5. For the FDC empa 10/lina 5 group, the difference was -0.36% (95% CI: -0.56, -0.17) versus empa 10 and -0.57% (95% CI: -0.77, -0.37) versus lina 5.

Table 20 Adjusted mean change from baseline in HbA1c [%] at Week 52 in study 1275.1(met) -ANCOVA FAS (LOCF)

	FDC empa 25/lina 5	Empa 25	FDC empa 10/lina 5	Empa 10	Lina 5
Patients, N	134	140	135	137	128
Number of analysed patients, N	134	140	135	137	128
Mean baseline HbA_{1c} (SE)	7.90 (0.07)	8.02 (0.07)	7.95 (0.07)	8.00 (0.08)	8.02 (0.08)
Change from baseline					
Mean HbA_{1c} (SE)	-1.17 (0.07)	-0.66 (0.10)	-1.03 (0.09)	-0.70 (0.08)	-0.51 (0.07)
Adjusted[1] mean HbA_{1c} (SE)	-1.21 (0.07)	-0.64 (0.07)	-1.05 (0.07)	-0.69 (0.07)	-0.48 (0.07)
Comparison vs. empa	vs. empa 25		vs. empa 10		
Adjusted[1] mean HbA_{1c} (SE)	-0.57 (0.10)		-0.36 (0.10)		
95% CI	(-0.77, -0.37)		(-0.56, -0.17)		
Comparison vs. lina 5					
Adjusted[1] mean HbA_{1c} (SE)	-0.73 (0.10)		-0.57 (0.10)		
95% CI	(-0.93, -0.53)		(-0.77, -0.37)		

CHANGE FROM BASELINE IN THE PERCENTAGE OF PATIENTS WITH HbA1c <7.0% AFTER 52 WEEKS IN THE PHASE III STUDY 1275.1

Patients with HbA1c <7.0% after 52 weeks in study 1275.1(met)

Similarly as seen in the 24-week analysis, the percentage of patients who attained HbA1c <7.0% after 52 weeks was higher in the FDC treatment groups than in the monotherapy groups (

Table **21**): 48.0% of the patients in the FDC empa 25/lina 5 group and 51.6% of the patients in the FDC empa 10/lina 5 group attained HbA1c values of less than 7.0% after 52 weeks of treatment, compared with 32.6% of patients in the empa 25 group, 32.0% of patients in the empa 10 group, and 28.6% of patients in the lina 5 group.

Table 21 Patients with HbA1c <7.0% at Week 52 in study 1275.1(met) - FAS (NCF)

	FDC empa 25/lina 5	Empa 25	FDC empa 10/lina 5	Empa 10	Lina 5
Number of analysed patients[1], N (%)	123 (100.0)	132 (100.0)	128 (100.0)	125 (100.0)	119 (100.0)
Patients with HbA_{1c} <7.0% at Week 52, N (%)	59 (48.0)	43 (32.6)	66 (51.6)	40 (32.0)	34 (28.6)
Comparison vs. empa [2]	vs. empa 25		vs. empa 10		
Odds ratio	1.962		2.364		
95% CI	(1.126, 3.417)		(1.353, 4.130)		
Comparison vs. lina 5 [2]					
Odds ratio	2.458		2.915		
95% CI	(1.378, 4.387)		(1.645, 5.166)		

CHANGE FROM BASELINE IN FASTING PLASMA GLUCOSE AFTER 52 WEEKS IN THE PHASE III STUDY 1275.1

The change from baseline in FPG after 52 weeks of treatment in study 1275.1 (met).

The analysis of the change from baseline in FPG after 52 weeks showed results consistent with the analysis performed after 24 weeks. After 52 weeks of treatment in study 1275.1(met), there were reductions in FPG

with both doses of the FDC empagliflozin/linagliptin and also for both empagliflozin monotherapy groups. In the lina 5 group, the change from baseline in FPG was small (Table 22). The treatment difference for the FDC empa 25/lina 5 group was -1.13 mmol/L (95% CI: -1.60, -0.67) versus empa 25 and -1.59 mmol/L (95.0% CI: -2.07, -1.12) versus lina 5.The difference for the FDC empa 10/lina 5 group was -0.43 mmol/L (95.0% CI: -0.90, 0.03) versus empa 10 and -1.12 mmol/L (95.0% CI: -1.60, -0.65) versus lina 5.

Table 22 Adjusted mean change in FPG [mmol/L] from baseline at Week 52 in study 1275.1(met) - ANCOVA FAS (LOCF)

	FDC empa 25/lina 5	Empa 25	FDC empa 10/lina 5	Empa 10	Lina 5
Patients, N	134	140	135	137	128
Number of analysed patients, N	133	139	134	136	127
Mean baseline FPG (SE)	8.58 (0.16)	8.87 (0.18)	8.70 (0.17)	8.97 (0.17)	8.68 (0.15)
Change from baseline					
Mean change in FPG (SE)	-1.74 (0.14)	-0.76 (0.26)	-1.32 (0.19)	-1.06 (0.18)	-0.21 (0.17)
Adjusted[1] mean change in FPG (SE)	-1.84 (0.17)	-0.70 (0.17)	-1.37 (0.17)	-0.94 (0.17)	-0.25 (0.17)
Comparison vs. empa	vs. empa 25		vs. empa 10		
Adjusted[1] mean change in FPG (SE)	-1.13 (0.24)		-0.43 (0.24)		
95% CI	(-1.60, -0.67)		(-0.90, 0.03)		
Comparison vs. lina 5					
Adjusted[1] mean change in FPG (SE)	-1.59 (0.24)		-1.12 (0.24)		
95% CI	(-2.07, -1.12)		(-1.60, -0.65)		

CHANGE FROM BASELINE IN BODY WEIGHT AFTER 52 WEEKS IN THE PHASE III STUDY 1275.1

The change from baseline in body weight after 52 weeks of treatment in study 1275.1(met).

The reductions observed at Week 24 in body weight with both doses of the FDC empagliflozin/linagliptin and for both empagliflozin doses were maintained at Week 52. There was no relevant change in body weight in the lina 5 group. Based on the ANCOVA analysis on the FAS (LOCF), the adjusted mean (SE) change from baseline in body weight was -3.13 (0.32) kg for the FDC empa 25/lina 5 group and -2.69 (0.32) kg for the FDC empa 10/lina 5 group, compared with -2.80 (0.32) kg for the empa 25 group, -2.93 (0.32) kg for the empa 10 group, and -0.26 (0.33) kg for the lina 5 group. The difference versus lina 5 was -2.87 kg (95% CI: -3.78, -1.97) for the FDC empa 25 /lina 5 group and -2.43 kg (95% CI: -3.34, -1.52) for the FDC empa 10/lina 5 group. There was no relevant difference noted in the change from baseline in body weight between the FDC empagliflozin/linagliptin groups and the empagliflozin treatment groups.

CHANGE FROM BASELINE IN BLOOD PRESSURE AFTER 52 WEEKS IN THE PHASE III STUDY 1275.1

Changes from baseline in blood pressure after 52 weeks of treatment in study 1275.1 (met).

Change from baseline in systolic blood pressure after 52 weeks in study 1275.1(met)

The reductions observed at Week 24 (see Section 3.2.4.1.3) in SBP with both doses of the FDC empagliflozin/linagliptin and for both empagliflozin doses were maintained at Week. There was no relevant change in SBP in the lina 5 group. Based on the ANCOVA analysis on the FAS (LOCF), the adjusted mean (SE) change from baseline in SBP was -3.6 (0.9) mmHg in the FDC empa 25/lina 5 group and -2.8 (0.9) mmHg in the FDC empa 10/lina 5 group, compared with -2.8 (0.9) mmHg in the empa 25 group, -3.5 (0.9) mmHg in the empa 10 group, and 0.3 (1.0) mmHg in the lina 5 group. The difference versus lina 5 was -3.8 mmHg (95% CI: -6.5, -1.2) for the FDC empa 25/lina 5 group and -3.1 mmHg (95% CI: -5.7, -0.4) for the FDC

empa 10/lina 5 group. There were no relevant differences noted in the change from baseline in SBP between the FDC empagliflozin/linagliptin groups and the empagliflozin treatment groups.

CHANGES IN BLOOD PRESSURE AFTER 52 WEEKS IN STUDY 1275.1

Change from baseline in diastolic blood pressure after 52 weeks in study 1275.1(met)

The reductions observed at Week 24 in DBP with both doses of the FDC empagliflozin/linagliptin and for both empagliflozin doses were maintained at Week 52. There was no relevant change in DBP in the lina 5 group. Based on the ANCOVA analysis on the FAS (LOCF), the adjusted mean (SE) change from baseline in DBP was -2.2 (0.6) mmHg in the FDC empa 25/lina 5 group and -2.2 (0.6) mmHg in the FDC empa 10/lina 5 group, compared with -1.9 (0.6) mmHg in the empa 25 group, -1.8 (0.6) mmHg in the empa 10 group, and -0.6 (0.6) mmHg in the lina 5 group. The difference versus lina 5 was -1.6 mmHg (95% CI: -3.2, 0.0) for both the FDC empa 25/lina 5 group and the FDC empa 10/lina 5 group. There were no relevant differences noted in the change from baseline in DBP between the FDC empagliflozin/linagliptin groups and the empagliflozin treatment groups.

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

A complete development program including several Phase III studies was conducted for linagliptin and supported the approval for the treatment of type 2 diabetes. The indication linagliptin as add on to empagliflozin is supported by 2 pivotal studies in patients with type 2 diabetes mellitus: 1 add-on study (1275.10) and one factorial design study (1275.1).

These studies were also part of the marketing authorisation of Glyxambi, the FDC of empagliflozin and linagliptin (EMEA/H/C/003833). Glyxambi was authorised in the EU for use in patients with type 2 diabetes in November 2016.The Phase III add-on study investigated the efficacy, safety, and tolerability of linagliptin as add-on therapy to the SGLT-2 inhibitor empagliflozin (study 1275.10) in patients with type 2 diabetes mellitus and metformin background medication. In this study, the FDC of empa/lina was used. In the factorial design study, patients were randomised into 5 treatment groups: empa 25/lina 5, empa 10/lina 5, empa 25, empa 10, and lina 5 (1275.1). The superiority of each FDC was tested against its respective individual components. Bioequivalence of the FDC with the individual components was established. No drug-drug-interactions between the monocomponents were observed.

Linagliptin is now indicated in the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as monotherapy in patients for whom metformin is inappropriate due to intolerance or contraindicated due to renal impairment. In addition, linagliptin is indicated as combination therapy in combination with metformin, sulphonylurea and metformin, and insulin with or without metformin. According to the Applicant, the linagliptin is also indicated in adults with type 2 diabetes mellitus to improve glycaemic control in adults in combination with an SGLT-2 inhibitor and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control.

In general, design of the new studies is acceptable. The add-on study is pivotal for the indication of linagliptin as add-on to empagliflozin. The factorial design study provides supportive data on the combination of linagliptin and empagliflozin.

Study population and in/exclusion criteria are reasonable. Treatments and objectives are acceptable. Although HbA1c is a surrogate endpoint, it is acceptable.

The study populations can be considered relatively representative of the target population. However, due to the fact that empagliflozin and metformin may not be initiated in patients with a GFR<60 ml/min, only a few patients with eGFR below 60 ml/min were included. In addition, very few subjects ≥75 years old were included. This limits the external validity of the trial to the total population. However, the separate clinical development programs for the monocomponents linagliptin and empagliflozin included more patients within this age category. Although the issue remains that there is limited knowledge on the efficacy and safety of the combination linagliptin and empagliflozin in these patients, this is adequately reflected in the SmPC.

The sample size estimations, randomisation procedures and blinding procedures are considered adequate.

An intention to treat (ITT) analysis for the primary outcome is preferred over a modified intention to treat (mITT) analysis. The mITT analyses can be accepted if the difference in patients between ITT and mITT population is so small that no impact on the overall results are likely. As this is the fact, in this case, the definition of analysis populations and the stratification factors are adequate.

In study 1275.1, the primary analysis was an ANCOVA on the FAS, including treatment, region, and baseline renal function as fixed effects and baseline HbA1c as a linear covariate. Missing data was handled using LOCF. In study 1275.10, an observed cases approach was used. The primary analysis was a longitudinal repeated measures analysis (MMRM), which handled the missing data. Originally ANCOVA was planned, but this was changed to the repeated measures analysis via an amendment to the protocol, before database lock.

MMRM assumes data to be missing at random, and that subjects that discontinue or need rescue medication would have behaved similarly to other subjects in the same treatment group, had they not dropped out. It aims to assess the treatment effect as if the treatment is taken as directed, and obscures the effect of discontinuation or rescue medication. Therefore, the longitudinal repeated measures analysis tends not to be robust in the situation where there is a decreasing treatment effect difference after discontinuation or rescue medication. However, the analysis was accompanied by several sensitivity analyses, using various assumptions. These analyses resulted in similar treatment differences. The primary analyses are considered acceptable.

Continuous secondary endpoints were analysed similarly to the primary endpoint. Categorical secondary endpoints were analysed using logistical regression. Time to rescue medication was analysed using Kaplan-Meier and log-rank test. The methods are standard for these kinds of variables and are acceptable.

In study 1275.10, multiplicity was handled by using a hierarchical testing procedure, with each test performed at alpha = 0.05. In study 1275.1, the FDC empa/lina was tested against both components simultaneously and both had to be statistically significant to proceed testing. These measures ensures control of the overall type I error rate and are acceptable.

Efficacy data and additional analyses

In total, 1164 patients were treated in the double-blind periods of the studies included in the evaluation in this report. These included 478 patients from trial 1275.10; of these 238 patients were treated with linagliptin and 240 patients were treated with placebo. A further 686 patients from trial 1275.1(met) are also included. The baseline characteristics were well balanced across the treatment groups.

Primary endpoint: HbA1c

Linagliptin as add-on therapy to empagliflozin (study 1275.10):

The treatment effects of linagliptin in patients that are treated with empagliflozin were of borderline clinical relevance. The treatment effect of linagliptin on top of empagliflozin 25 mg was -0.47% (95% CI: -0.66, -0.28) and the effect of linagliptin on top of empagliflozin 10 mg was -0.32% (95% CI: -0.52, -0.13). The pooled treatment difference of linagliptin was -0.40% (95% CI: -0.53, -0.27; p<0.0001).

Factorial design study with FDC and individual components (study 1275.1):

The difference between the FDC and monotherapy with empagliflozin were also of borderline clinical relevance. In metformin treated patients, the treatment difference for the FDC empa 25/lina 5 group was -0.58% (95% CI: -0.75, -0.41) versus empa 25 and the treatment difference for the FDC empa 10/lina 5 group was -0.42% (95% CI: -0.59, -0.25) versus empa 10.

Other endpoints: fasting glucose

In general, the results for changes in FPG were consistent with the results for the changes in HbA1c. The effects of linagliptin on top off empagliflozin on fasting plasma glucose in study 1275.10 were small. The adjusted mean difference of lina 5 versus placebo for the mean change in FPG was -0.65 mmol/L (95% CI: -1.15, -0.16; p = 0.0103) in combination with empagliflozin 10 mg and -0.44 mmol/L (95% CI: -0.87, -0.01; p = 0.045) in combination with empagliflozin 25 mg.

The difference in fasting glucose between the FDC empa/lina and empagliflozin were very small. In metformin treated patients, for the FDC empa 25/lina 5, the FPG adjusted mean difference was -0.91 (SE 0.20) mmol/L vs. empa 25 and -1.23 (SE 0.20) mmol/L vs. lina 5. For the FDC empa 10/lina 5, the FPG adjusted mean difference was -0.63 (SE 0.20) mmol/L vs. empa 10 and -1.06 (SE 0.20) mmol/L vs. lina 5. In naïve patients, for the FDC empagliflozin 10/lina 5 group, the FPG adjusted mean difference was -23.63 mg/dL (95.0% CI: -31.06,-16.21) vs empa 25 mg and for the FDC empa 10/lina 5 was -22.29 mg/dL (95.0% CI: -29.71,-14.88) vs empa 10 mg.

Other endpoints: body weight

As could be expected based on linagliptin's mechanism of action, linagliptin in combination with empagliflozin in study 1275.10 was not associated with statistically significant changes in body weight in comparison to placebo. In study 1275.01 (met), linagliptin was also not associated with weight loss.

Other endpoints: blood pressure

In study 1275.10, linagliptin add-on to empagliflozin (25 mg and 10 mg) and metformin provided no reductions in systolic or diastolic blood pressure after 24 weeks of treatment compared with placebo.

In study 1275.1, there were also no changes in blood pressure with linagliptin treatment.

Efficacy after 52 weeks

In general, in study 1275.1, the effects after 52 weeks were in line with the findings after 24 weeks.

2.4.4. Conclusions on clinical efficacy

The contribution of linagliptin as add on to empagliflozin and metformin is small but clinically relevant.

Due to the fact that empagliflozin and metformin may not be initiated in patients with a GFR<60 ml/min, only a few patients with eGFR below 60 ml/min were included. In addition, very few subjects ≥75 years old were included. This is adequately reflected in the SmPC.

2.5. Clinical safety

Introduction

The individual clinical development programme conducted with linagliptin established the safety profile. The main safety aspects are briefly summarised below.

Overall, in clinical studies the frequencies of adverse events, adverse events leading to discontinuation, and serious adverse events were very similar across studies, and similar between linagliptin and placebo groups. Listed side effects of linagliptin are grouped by background treatment regimen. For monotherapy with linagliptin (and all backgrounds) nasopharyngitis, cough, hypersensitivity, pancreatitis, angioedema, urticaria, rash, mouth ulceration, and increased amylase have been identified as listed events. Hypoglycaemia was identified as listed event only when added to a background treatment of metformin plus sulphonylurea. Constipation was identified as listed event only on a background of insulin

The MAH has conducted a large number of clinical studies for linagliptin. This AR will focus only on the add on study of linagliptin to empagliflozin (study 1275.10), and factorial design study with linagliptin and empagliflozin (study 1275.1), and the Phase I studies 1275.3 and 1245.30, see **Table 23**. All studies have been performed according to the Declaration of Helsinki, the ICH Good Clinical Practice (GCP), and the respective national regulatory requirements.

In total, 1164 patients were treated in the double-blind periods of the studies included in the evaluation presented in this document. These included 478 patients from trial 1275.10; of these 238 patients were treated with linagliptin and 240 patients were treated with placebo. A further 686 patients from trial 1275.1(met) are also included.

The treated set (TS) was used for the analysis of safety and comprised all patients who received at least one dose of study medication. Adverse events were coded with the MedDRA coding dictionary current at the time of clinical trial reporting (version 17.1 for study 1275.10 and version 16.0 for study 1275.1(met)).

The analysis of adverse events was based on treatment-emergent adverse events, i.e. those with an onset date between the first and the last intake of study medication plus 7 days. For the analyses of fatal adverse events and malignancy adverse events, data up to the last contact with the patient were included. For the analyses of hepatic injury adverse events and elevated transaminases, data up to 30 days after the last intake of study medication were included.

Adverse event analyses were based on the number of patients with adverse events, not the number of adverse events. Analyses of adverse events adjusted for exposure (incidence rate per 100 patient years of time at risk) used patient-specific time at risk, i.e. the exposure until the onset of the event or, if the patient did not have an event, the entire time of exposure plus 7 days.

Table 23 Overview of clinical studies included in the evaluation of safety

Study	Short description of study design and analysis strategy	
1275.10$_{(met+empa25)}$	16 weeks of open-label treatment with the SGLT-2 inhibitor empa 25 on metformin background therapy, 24 weeks of double-blind treatment, lina[3] vs. placebo, add-on therapy to the SGLT-2 inhibitor empa 25 and metformin background therapy	354 (open-label) 224 (double-blind)
1275.10$_{(met+empa10)}$	16 weeks of open-label treatment with the SGLT-2 inhibitor empa 10 on metformin background therapy, 24 weeks of double-blind treatment, lina[3] vs. placebo, add-on to the SGLT-2 inhibitor empa 10 and metformin background therapy	352 (open-label) 254 (double-blind)
Phase III factorial design study		**No. of patients[1]**
1275.1$_{(met)}$	52 weeks of double-blind treatment empa/lina FDCs[3] vs. individual components[4] on metformin background therapy primary analysis at Week 24, exploratory analyses at Week 52	686

Patient exposure

For all studies, the majority of the patients completed the treatment periods as planned. There were no relevant differences in the percentage of patients prematurely discontinuing from the trial medication between the treatment groups. Overall, the most common reasons for premature discontinuation were either adverse events or patients being lost to follow-up.

Table 24 Treated patients in Phase III studies

1275.10, add-on to empagliflozin and metformin

Add-on to empagliflozin 25 mg and metformin		Add-on to empagliflozin 10 mg and metformin		Total
Lina 5	Placebo	Lina 5	Placebo	
112	112	126	128	478

1275.1$_{(met)}$, add-on to metformin

Empa 25/lina 5	Empa 25	Empa 10/lina 5	Empa 10	Lina 5	Total
137	141	136	140	132	686

* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

Adverse events

In general, only treatment-emergent adverse events, which had an onset between the first and the last intake of double-blind study medication+7 days, are presented in this document. Analyses of adverse events were based on the treated set.

Overview of adverse events in study 1275.10

In study 1275.10, the numbers of patients reported with at least 1 adverse event on treatment were similar between the linagliptin 5 mg (add-on to empagliflozin and metformin) and corresponding placebo groups (**Table 25**). The proportion of patients reported with adverse events leading to treatment discontinuation and serious adverse events was overall low and similar between all treatment groups. No patient died during

the on-treatment phase of the study. For a detailed description of the different types of adverse events, see the sections below.

Table 25 Overview of patients with adverse events in study 1275.10 – TS

	Add-on to empagliflozin 25 mg and metformin		Add-on to empagliflozin 10 mg and metformin	
	Lina 5	**Placebo**	**Lina 5**	**Placebo**
	N (%)	**N (%)**	**N (%)**	**N (%)**
Number of patients	112 (100.0)	112 (100.0)	126 (100.0)	128 (100.0)
Patients with any adverse event	59 (52.7)	66 (58.9)	61 (48.4)	71 (55.5)
Adverse events leading to premature discontinuation of study medication	3 (2.7)	3 (2.7)	4 (3.2)	3 (2.3)
Serious adverse events	3 (2.7)	4 (3.6)	4 (3.2)	5 (3.9)
Fatal adverse event	0	0	0	0
Patients with AESIs				
Decreased renal function[1]	1 (0.9)	1 (0.9)	1 (0.8)	1 (0.8)
Hepatic injury[1]	1 (0.9)	1 (0.9)	1 (0.8)	1 (0.8)
Pancreatitis[1]	0	0	1 (0.8)	0
Urinary tract infection[2]	15 (13.4)	9 (8.0)	12 (9.5)	10 (7.8)
Genital infection[2]	3 (2.7)	9 (8.0)	3 (2.4)	4 (3.1)
Confirmed hypoglycaemic adverse events[3]	0	3 (2.7)	0	0
Bone fracture[2]	1 (0.9)	0	0	1 (0.8)
Volume depletion[2]	0	1 (0.9)	0	1 (0.8)
Malignancy[2]	0	0	0	0
Hypersensitivity reactions[1]	1 (0.9)	2 (1.8)	2 (1.6)	1 (0.8)

Overview of adverse events in study 1275.1(met)

In study 1275.1(met), the proportions of patients reported with at least 1 adverse event on treatment were similar between treatment groups (Table 26). Adverse events leading to treatment discontinuation were reported more frequently in the empagliflozin 10 mg group than in the other treatment groups. The proportion of patients reported with serious adverse events was overall low and similar between all treatment groups. Two cases of deaths were reported on-treatment: 1 patient died in the empagliflozin 10 mg/linagliptin 5 mg (add-on to metformin) treatment group and 1 patient in the empagliflozin 10 mg (add-on to metformin) treatment group. For a detailed description of the different types of adverse events, see the sections below.

Table 26 Overview of patients with adverse events in study 1275.1(met) – TS

	Add-on to metformin				
	Empa 25/ lina 5	**Empa 25**	**Empa 10/ lina 5**	**Empa 10**	**Lina 5**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
Number of patients	137 (100.0)	141 (100.0)	136 (100.0)	140 (100.0)	132 (100.0)
Patients with any adverse event	98 (71.5)	103 (73.0)	94 (69.1)	96 (68.6)	91 (68.9)
Adverse events leading to premature discontinuation of study medication	3 (2.2)	4 (2.8)	2 (1.5)	9 (6.4)	4 (3.0)
Serious adverse events	6 (4.4)	10 (7.1)	9 (6.6)	6 (4.3)	8 (6.1)
Fatal adverse event	0	0	1 (0.7)	1 (0.7)	0
Patients with AESIs					
Decreased renal function[1]	1 (0.7)	0	0	0	1 (0.8)
Hepatic injury[1]	2 (1.5)	1 (0.7)	0	4 (2.9)	0
Pancreatitis[1]	0	0	0	0	1 (0.8)
Urinary tract infection[2]	14 (10.2)	19 (13.5)	13 (9.6)	16 (11.4)	20 (15.2)
Genital infection[2]	3 (2.2)	12 (8.5)	8 (5.9)	11 (7.9)	3 (2.3)
Confirmed hypoglycaemic adverse events[3]	5 (3.6)	5 (3.5)	3 (2.2)	2 (1.4)	3 (2.3)
Bone fracture[2]	1 (0.7)	4 (2.8)	4 (2.9)	0	0
Volume depletion[2]	1 (0.7)	2 (1.4)	2 (1.5)	1 (0.7)	4 (3.0)
Malignancy[2]	3 (2.2)	2 (1.4)	1 (0.7)	2 (1.4)	1 (0.8)
Hypersensitivity reactions[1]	7 (5.1)	4 (2.8)	4 (2.9)	5 (3.6)	5 (3.8)

Common adverse events

Most frequent adverse events

The frequencies of patients with adverse events in the add-on design study 1275.10 were generally slightly lower in the linagliptin (add-on to empagliflozin and metformin) group than in the corresponding placebo group. In the factorial design study 1275.1, the frequencies of patients with adverse events were similar across all treatment groups. Most frequent adverse events in all studies were infections (urinary tract or upper respiratory tract).

Most frequent adverse events in study 1275.10

The frequencies of patients with adverse events in study 1275.10 were lower in each of the linagliptin 5 mg (add-on to empagliflozin and metformin) groups than in their corresponding placebo groups. At PT level, patients were most frequently reported with urinary tract infection, nasopharyngitis, and increased lipase. For most PTs, the frequency was balanced between treatment groups. Patients were less frequently reported with nasopharyngitis and hyperglycaemia in the linagliptin 5 mg (add-on to empagliflozin 25 mg and metformin) group, than in the corresponding placebo group. Patients were more frequently reported with nasopharyngitis in the linagliptin 5 mg (add-on to empagliflozin 10 mg and metformin) group than in the corresponding placebo group (Table 27).

Table 27 Frequency of patients with adverse events with a frequency of >2% in any treatment group at PT level in study 1275.10 – TS

System organ class Preferred term	Add-on to empagliflozin 25 mg and metformin		Add-on to empagliflozin 10 mg and metformin	
	Lina 5 N (%)	Placebo N (%)	Lina 5 N (%)	Placebo N (%)
Number of patients	112 (100.0)	112 (100.0)	126 (100.0)	128 (100.0)
Patients with any adverse event	59 (52.7)	66 (58.9)	61 (48.4)	71 (55.5)
Infections and infestations	26 (23.2)	31 (27.7)	35 (27.8)	29 (22.7)
Urinary tract infection	11 (9.8)	7 (6.3)	10 (7.9)	6 (4.7)
Nasopharyngitis	2 (1.8)	8 (7.1)	8 (6.3)	3 (2.3)
Bronchitis	1 (0.9)	1 (0.9)	4 (3.2)	1 (0.8)
Asymptomatic bacteriuria	3 (2.7)	1 (0.9)	1 (0.8)	1 (0.8)
Cystitis	0	2 (1.8)	2 (1.6)	3 (2.3)
Metabolism and nutrition disorders	2 (1.8)	14 (12.5)	5 (4.0)	15 (11.7)
Hyperglycaemia	0	5 (4.5)	3 (2.4)	4 (3.1)
Hypoglycaemia	0	4 (3.6)	1 (0.8)	0
Dyslipidaemia	1 (0.9)	2 (1.8)	0	4 (3.1)
Psychiatric disorders	2 (1.8)	6 (5.4)	5 (4.0)	3 (2.3)
Depression	2 (1.8)	4 (3.6)	2 (1.6)	0
Nervous system disorders	1 (0.9)	4 (3.6)	8 (6.3)	7 (5.5)
Headache	1 (0.9)	2 (1.8)	4 (3.2)	2 (1.6)
Vascular disorders	3 (2.7)	5 (4.5)	4 (3.2)	3 (2.3)
Hypertension	3 (2.7)	2 (1.8)	3 (2.4)	3 (2.3)
Musculoskeletal and connective tissue disorders	6 (5.4)	7 (6.3)	9 (7.1)	16 (12.5)
Back pain	0	4 (3.6)	5 (4.0)	5 (3.9)
Pain in extremity	3 (2.7)	0	0	1 (0.8)
Arthralgia	1 (0.9)	1 (0.9)	3 (2.4)	2 (1.6)
Reproductive system and breast disorders	2 (1.8)	7 (6.3)	4 (3.2)	1 (0.8)
Balanoposthitis	1 (0.9)	4 (3.6)	1 (0.8)	1 (0.8)
Investigations	9 (8.0)	9 (8.0)	5 (4.0)	10 (7.8)
Lipase increased	7 (6.3)	7 (6.3)	4 (3.2)	1 (0.8)

Most frequent adverse events in study 1275.1(met)

The frequencies of patients with adverse events were similar across all treatment groups. At PT level, patients were most frequently reported with urinary tract infection and upper respiratory tract infection. For most PTs, the frequency was balanced between treatment groups Table 28.

Table 28 Frequency of patients with adverse events with a frequency of ≥3% in any treatment group at PT level in study 1275.1(met) – TS

System organ class Preferred term	Add-on to metformin				
	Empa 25/ lina 5	Empa 25	Empa 10/ lina 5	Empa 10	Lina 5
	N (%)	N (%)	N (%)	N (%)	N (%)
Number of patients	137 (100.0)	141 (100.0)	136 (100.0)	140 (100.0)	132 (100.0)
Patients with any adverse event	98 (71.5)	103 (73.0)	94 (69.1)	96 (68.6)	91 (68.9)
Infections and infestations	50 (36.5)	50 (35.5)	55 (40.4)	57 (40.7)	55 (41.7)
Urinary tract infection	12 (8.8)	17 (12.1)	12 (8.8)	13 (9.3)	15 (11.4)
Upper respiratory tract infection	11 (8.0)	9 (6.4)	14 (10.3)	11 (7.9)	4 (3.0)
Nasopharyngitis	8 (5.8)	5 (3.5)	11 (8.1)	7 (5.0)	12 (9.1)
Gastroenteritis	8 (5.8)	2 (1.4)	4 (2.9)	2 (1.4)	4 (3.0)
Influenza	1 (0.7)	4 (2.8)	1 (0.7)	7 (5.0)	4 (3.0)
Bronchitis	2 (1.5)	6 (4.3)	5 (3.7)	3 (2.1)	6 (4.5)
Metabolism and nutrition disorders	12 (8.8)	25 (17.7)	15 (11.0)	15 (10.7)	23 (17.4)
Hyperglycaemia	0	8 (5.7)	3 (2.2)	3 (2.1)	10 (7.6)
Hypoglycaemia	5 (3.6)	6 (4.3)	4 (2.9)	4 (2.9)	3 (2.3)
Nervous system disorders	19 (13.9)	22 (15.6)	19 (14.0)	20 (14.3)	16 (12.1)
Headache	7 (5.1)	6 (4.3)	7 (5.1)	10 (7.1)	8 (6.1)
Dizziness	4 (2.9)	5 (3.5)	6 (4.4)	3 (2.1)	5 (3.8)
Vascular disorders	8 (5.8)	3 (2.1)	4 (2.9)	7 (5.0)	11 (8.3)
Hypertension	5 (3.6)	1 (0.7)	1 (0.7)	5 (3.6)	7 (5.3)
Respiratory, thoracic and mediastinal disorders	11 (8.0)	11 (7.8)	12 (8.8)	8 (5.7)	6 (4.5)
Cough	5 (3.6)	2 (1.4)	6 (4.4)	2 (1.4)	2 (1.5)
Gastrointestinal disorders	23 (16.8)	24 (17.0)	31 (22.8)	21 (15.0)	21 (15.9)
Diarrhoea	3 (2.2)	4 (2.8)	9 (6.6)	6 (4.3)	0
Constipation	8 (5.8)	4 (2.8)	7 (5.1)	3 (2.1)	3 (2.3)
Dyspepsia	4 (2.9)	5 (3.5)	1 (0.7)	1 (0.7)	4 (3.0)
Nausea	4 (2.9)	5 (3.5)	4 (2.9)	1 (0.7)	4 (3.0)
Musculoskeletal and connective tissue disorders	17 (12.4)	24 (17.0)	26 (19.1)	23 (16.4)	24 (18.2)
Back pain	6 (4.4)	2 (1.4)	5 (3.7)	9 (6.4)	7 (5.3)
Arthralgia	1 (0.7)	7 (5.0)	6 (4.4)	3 (2.1)	6 (4.5)
Myalgia	3 (2.2)	1 (0.7)	5 (3.7)	4 (2.9)	0
Muscle spasms	1 (0.7)	5 (3.5)	0	2 (1.4)	1 (0.8)
Pain in extremity	1 (0.7)	5 (3.5)	3 (2.2)	2 (1.4)	2 (1.5)
Investigations	13 (9.5)	16 (11.3)	8 (5.9)	11 (7.9)	15 (11.4)
Lipase increased	5 (3.6)	1 (0.7)	0	2 (1.4)	2 (1.5)
Weight decreased	2 (1.5)	4 (2.8)	3 (2.2)	5 (3.6)	0

Serious adverse events and deaths

Deaths

In the add-on trial 1275.10, no patients had a fatal adverse event with an onset date during the open-label or on-treatment periods. However, 1 patient who had been in the placebo group had a fatal adverse event with an onset post-treatment and 1 patient who had been in the linagliptin group had a fatal adverse event with an onset post-study. In both cases, the preferred term for the adverse event was pancreatic carcinoma.

In the factorial design trial 1275.1(met), there were 2 patients who had fatal adverse events with an onset date during the on-treatment period; a patient in the empagliflozin 10 mg/linagliptin 5 mg fixed-dose combination group died of hypertensive heart disease and a patient in the empagliflozin 10 mg group died of lung neoplasm; the latter patient was also reported with the fatal adverse event metastatic non-small cell lung cancer with an onset posttreatment.

None of the deaths were considered as drug-related.

Table 29 Patients with fatal adverse events with onset date on treatment or post treatment by treatment group – TS

Patient No./Study No.	Age [years] / gender	Preferred term	Onset[1]	Drug-related[2]
Placebo (add-on to empagliflozin and metformin), post-treatment				
32424/1275.10	64/M	Pancreatic carcinoma	70	No
Linagliptin (add-on to empagliflozin and metformin), post-study				
31861/1275.10	70/M	Pancreatic carcinoma	312	No
Empagliflozin 10 mg/linagliptin 5 mg (add-on to metformin), on-treatment				
97041/1275.1$_{(met)}$	53/M	Hypertensive heart disease	172	No
Empagliflozin 10 mg (add-on to metformin), on-treatment				
90242/1275.1$_{(met)}$	61/M	Lung neoplasm	365	No
Empagliflozin 10 mg (add-on to metformin), post-treatment				
90242/1275.1$_{(met)}$	61/M	Non-small cell lung cancer metastatic	371	No

[1] Onset of the adverse event leading to death, relative to the first dose of double-blind study medication
[2] As judged by the investigator

Serious adverse events

In this section, an analysis of all serious adverse events is presented in detail.

The frequencies of patients with serious adverse events in the add-on design studies were overall lower in the linagliptin 5 mg (add-on to empagliflozin and metformin) group than in the corresponding placebo group. In the factorial design study, the frequencies of patients with adverse events were overall similar across all treatment groups.

Serious adverse events in study 1275.10

In study 1275.10, the frequencies of patients with serious adverse events were low (<4%) and similar across treatment groups. Three patients (2.7%) were reported with serious adverse events in the linagliptin 5 mg (add-on to empagliflozin 25 mg and metformin), 4 patients (3.6%) in the placebo (add-on to empagliflozin 25 mg and metformin), 4 patients (3.2%) in the linagliptin 5 mg (add-on to empagliflozin 10 mg and metformin), and 5 patients (3.9%) in the placebo (add-on to empagliflozin 10 mg and metformin) group. In the patient population taking linagliptin 5 mg or placebo as add-on to empagliflozin 25 mg and metformin, the highest frequency of serious adverse events at SOC level was infections and infestations (0% of patients in the linagliptin 5 mg and 1.8% of patients in the placebo group). Except for osteomyelitis in the placebo (add-on to empagliflozin 25 mg and metformin) group (reported for 2 patients [1.8%]), serious adverse events at PT level were not reported for more than 1 patient per treatment group. In the patient population taking linagliptin 5 mg or placebo as add-on to empagliflozin 10 mg and metformin, the highest frequency of serious adverse events at SOC level was musculoskeletal and connective tissue disorders (2 patients [1.6%] in each treatment group), infections and infestations (2 patients [1.6%] in the linagliptin 5 mg treatment group), and gastrointestinal disorders (2 patients [1.6%] in the linagliptin 5 mg treatment group). Serious adverse events at PT level were not reported for more than 1 patient per treatment group.

Serious adverse events in study 1275.1(met)

In study 1275.1(met), the frequency of patients with serious adverse events was <8% and similar across treatment groups. Six patients (4.4%) were reported with serious adverse events in the empagliflozin 25 mg/linagliptin 5 mg, 10 patients (7.1%) in the empagliflozin 25 mg, 9 patients (6.6%) in the empagliflozin

10 mg/linagliptin 5 mg, 6 patients (4.3%) in the empagliflozin 10 mg, and 8 patients (6.1%) in the linagliptin 5 mg group. At PT level, for none of the serious adverse events more than 1 patient was reported in any of the treatment groups .

Other significant adverse events

Other significant adverse events, as defined in ICH E3 and reported in this document, are marked haematological and other laboratory abnormalities (other than those meeting the definition of 'serious') and any event that led to an intervention, including withdrawal of test drug treatment, dose reduction, or significant additional concomitant therapy, other than those reported as serious adverse events. Dose reduction was not allowed according to the study protocols. Serious adverse events are not included in 'other significant adverse events'; all adverse events leading to discontinuation of study medication (i.e. including serious events) are presented above.

Overall, less than 6% of the patients per treatment group were reported with other significant adverse events in all Phase III studies. At PT level, each other significant adverse event was reported for not more than 1 patient (0% to 0.9%) per treatment group.

Other significant adverse events in study 1275.10

In study 1275.10, 2 patients (1.8%) were reported with other significant adverse events in the linagliptin 5 mg (add-on to empagliflozin 25 mg and metformin) group (PT urinary tract infection and dysphagia), 2 patients (1.8%) in the placebo (add-on to empagliflozin 25 mg and metformin) group (PT bronchitis, hyperglycaemia, and vulvovaginal pruritus), 2 patients (1.6%) were reported with other significant adverse events in the linagliptin 5 mg (add-on to empagliflozin 10 mg and metformin) group (PT urinary tract infection, amylase increased, and lipase increased), and 3 patients (2.3%) in the placebo (add-on to empagliflozin 10 mg and metformin) group (PT urinary tract infection, cough, and upper abdominal pain).

Other significant adverse events in study 1275.1(met)

In study 1275.1(met), 2 patients (1.5%) each were reported with other significant adverse events in the empagliflozin 25 mg/linagliptin 5 mg, empagliflozin 10 mg/linagliptin 5 mg, and the linagliptin 5 mg group (all as add-on to metformin), 3 patients (2.1%) were reported with other significant adverse events in the empagliflozin 25 mg (add-on to metformin) group, and 7 patients (5.0%) in the empagliflozin 10 mg (add-on to metformin) group.

Analysis of adverse events of special interest

Based on the mode of action and known safety profile of DPP-4 inhibitors, safety data were searched for adverse events of special interest. The search was based on SMQs or, when no appropriate SMQ was available, on BIcMQs (BI-customised MedDRA queries). Adverse events of special interest comprise: renal adverse events, hepatic adverse events, severe cutaneous adverse reactions, hypersensitivity reactions, pancreatitis, and pancreatic cancer. The overview of adverse events of special interest presented by the company is based on the add-on trial 1275.10.

Renal adverse events

Only 2 patients (0.8%) in each treatment group were reported with renal adverse events. There were small fluctuations in mean eGFR and eCCr values over time but no clinically meaningful differences between the linagliptin and placebo groups. There were also no meaningful differences between treatment groups with regard to the proportions of patients who shifted into worse or better renal function categories based on eGFR values.

Hepatic adverse events

No patient had on-treatment central laboratory values consistent with biochemical Hy's law constellation (ALT and/or AST ≥3x ULN with concomitant or subsequent total bilirubin ≥2x ULN within 30 days after ALT/AST elevation; the maximum alkaline phosphatase value in the 30-day period <2x ULN) during the double-blind treatment period. One patient, in the linagliptin 5 mg (add-on to empagliflozin 10 mg and metformin) group, was reported with such a laboratory constellation based on local laboratory data, but these values could not be confirmed by the central laboratory. The adjudication committee classified the event as a mild to moderate hepatic injury with a possible causal relationship with the study medication, but not as a Hy's law case.

The frequency of patients with ALT and/or AST ≥3x and <5x ULN during the double-blind treatment period was low (not more than 1 patient per treatment group; 0 to 0.9%,Table 30). No patient had values above 5x ULN during the double-blind treatment period.

Table 30 Frequency of patients in study 1275.10 with elevated liver enzymes during the treatment period – TS

	Add-on to empagliflozin 25 mg and metformin		**Add-on to empagliflozin 10 mg and metformin**	
	Lina 5 N (%)	**Placebo N (%)**	**Lina 5 N (%)**	**Placebo N (%)**
Number of patients	112 (100.0)	112 (100.0)	126 (100.0)	128 (100.0)
ALT and/or AST ≥3x ULN	0	1 (0.9)	1 (0.8)	1 (0.8)
ALT and/or AST ≥5x ULN	0	0	0	0
ALT and/or AST ≥10x ULN	0	0	0	0
ALT and/or AST ≥20x ULN	0	0	0	0
ALT and/or AST ≥3x ULN with total bilirubin ≥2x ULN[1]	0	0	0	0

One patient, in the placebo (add-on to empagliflozin 10 mg and metformin) group, had an ALT/AST increase of ≥10x ULN from baseline during the 30 days after last dose of study medication. Severe cutaneous adverse reactions.

One patient (0.4%), in the linagliptin group, was reported with a severe cutaneous adverse reaction. The event was bullous dermatitis and led to discontinuation of study medication.

Hypersensitivity

There were 3 patients (1.3%) in each treatment group who were reported with hypersensitivity reactions. In the linagliptin group, the reported events were bullous dermatitis, rash, and urticaria. In the placebo group, the reported events were eczema, hypersensitivity and immune thrombocytopenic purpura.

Pancreatitis

One patient (0.4%) in the linagliptin group was reported with pancreatitis. The event was acute pancreatitis and led to discontinuation of study medication.

Pancreatic cancer

Although no patients were reported with pancreatic cancer during the double-blind treatment period, there were 2 patients reported with pancreatic carcinoma after the end of treatment; 1 patient in the linagliptin group was reported with pancreatic carcinoma in the post-study period and 1 patient in the placebo group was reported with pancreatic carcinoma in the post-treatment period. Both of these events were fatal.

Other adverse events of interest

A number of other adverse events were identified as being of interest for the analyses of safety. The search was based on SMQs or, when no appropriate SMQ was available, on BIcMQs (BI-customised MedDRA queries). The overview of further selected adverse events is based on the add-on trial 1275.10; for malignancies, events from the factorial design trial 1275.1$_{(met)}$ are also included.

Hypoglycaemic adverse events

Hypoglycaemia is a labelled side effect of both linagliptin (when combined with metformin and a sulphonylurea) and empagliflozin (when combined with a sulphonylurea or insulin) and is of general interest in studies on diabetes. In total, 2 patients (0.8%) in the linagliptin group and 4 patients (1.7%) in the placebo group were reported with investigator-defined hypoglycaemia. Confirmed hypoglycaemic adverse events comprised all investigator-reported symptomatic and asymptomatic adverse events that had a plasma glucose value of ≤70 mg/dL or that required the assistance of another person. No patients in the linagliptin group and 3 patients (1.3%) in the placebo group were reported with confirmed hypoglycaemic events. Thus, there is no evidence that treatment with linagliptin as add-on therapy to empagliflozin and metformin increases the risk of hypoglycaemia.

Malignancies

Because type 2 diabetes mellitus may be associated with an increased risk of several types of cancer when compared with the general population, malignancies were considered of interest. An overview of malignancies from both trials 1275.10 and 1275.1$_{(met)}$ is provided here. There were 2 patients with malignancies reported in trial 1275.10; both were pancreatic carcinoma reported after the end of treatment and with fatal outcome. A further 11 patients in trial 1275.1$_{(met)}$ were reported with malignancies; these included 4 patients treated with linagliptin in combination with empagliflozin as add-on therapy to metformin. The reported malignancies were of several different tumour types and locations, without a clear trend for a certain tumour type or location. Out of the 13 patients reported with malignancies, 8 patients had malignancies with the onset date after 6 months of treatment. In accordance with previous regulatory guidance, a search for thyroid cancer in trial 1275.10 was conducted; no patients were reported with thyroid cancer.

Cardiac failure

Cardiac failure is an identified potential risk associated with DPP-4 inhibitors. No patients in trial 1275.10 were reported with cardiac failure.

Lactic acidosis

Lactic acidosis was analysed because it is a risk associated with metformin; the analysis of this selected adverse event is therefore relevant for the fixed-dose combination of linagliptin and metformin. No cases of lactic acidosis were reported in trial 1275.10.

Laboratory findings

The results for study 1275.10 summarised below are generally based on descriptive statistics of laboratory parameters at baseline and last value on treatment, frequency of changes with respect to the reference range from baseline to last value on treatment, and frequency of patients with possibly clinically significant abnormalities.

Standard laboratory parameters (functional groups: haematology, differentials [automatic and absolute], electrolytes, enzymes, substrates [including serum lipids], plasma proteins, and urinalysis) were comparable at baseline and mean changes from baseline to the last value on treatment were generally small without clinically meaningful differences between the linagliptin and placebo groups.

The frequency of shifts from within normal range at baseline to >ULN or to <LLN at last observation on treatment was generally low and similar between the 2 treatment groups. Some differences between the linagliptin and placebo groups for shifts to >ULN were noted for lipase (14.4% and 10.2%), triglycerides (9.0% and 5.2%), and urea (7.2% and 3.7%).

Overall, the frequency of patients reported with possibly clinically significant abnormalities was low and comparable between treatment groups. Relatively high frequencies were reported for bicarbonate (possibly clinically significant low values – linagliptin: 15.9% of patients; placebo: 13.2% of patients), for lipase (possibly clinically significant high values – linagliptin: 11.9%; placebo: 9.2%), and for triglycerides (possibly clinically significant high values – linagliptin: 7.0%; placebo: 4.7%).

Vital signs

Baseline mean values for blood pressure (SBP and DBP) and pulse rate were comparable and changes from baseline to last value on treatment were small and similar in the linagliptin and placebo groups (pulse rate – linagliptin: +0.14 bpm, placebo: 0.27 bpm; systolic blood pressure – linagliptin: 0.10 mmHg, placebo: +0.15 mmHg; diastolic blood pressure – linagliptin: +0.02 mmHg, placebo: +0.79 mmHg

Safety in special populations

The following safety categories were analysed for subgroups of study 1275.10: all adverse events, adverse events leading to treatment discontinuation, serious adverse events, and adverse events assessed as drug-related by the investigator. As the overall number of events was very low for most of these categories, the following summary generally only includes all adverse events and serious adverse events with overall at least 2 patients with events in either treatment group of study 1275.10.

INTRINSIC FACTORS

Age

Only patients at least 18 years of age were included in study 1275.10. About 80% of the patients were younger than 65 years at baseline. Only around 17% were between 65 and 75 years, 3% were older than 75 years, and 1 patient was older than 85 years (**Table 31**). Therefore results of subgroup analyses of patients older than 75 years are mostly inconclusive.

In general, with increasing age, there was an increase in the proportions of patients reported with adverse events. Within each age category, the trends in the frequency of any adverse events and serious adverse events were consistent with those for the overall population.

Table 31 Frequency of patients with adverse events in subgroups by age in study 1275.10 – TS

Age [years]	<65 N (%)	65 to <75 N (%)	≥75 N (%)
Number of patients			
Linagliptin (add-on to empagliflozin and metformin)	190 (100.0)	43 (100.0)	5 (100.0)
Placebo (add-on to empagliflozin and metformin)	196 (100.0)	36 (100.0)	8 (100.0)
Patients with any adverse event			
Linagliptin (add-on to empagliflozin and metformin)	94 (49.5)	22 (51.2)	4 (80.0)
Placebo (add-on to empagliflozin and metformin)	107 (54.6)	24 (66.7)	6 (75.0)
Patients with serious adverse events			
Linagliptin (add-on to empagliflozin and metformin)	5 (2.6)	2 (4.7)	0
Placebo (add-on to empagliflozin and metformin)	8 (4.1)	0	1 (12.5)

Gender

In study 1275.10, about half of the patients were men. Demographic data were largely similar for men and women.

The frequency of patients with any adverse events was higher for women than for men in both treatment groups (**Table 32**). Within each gender, the trends in the frequency of any adverse events and serious adverse events were generally consistent with those for the overall population.

Table 32 Frequency of patients with adverse events in subgroups by gender in study 1275.10 – TS

Gender	Male N (%)	Female N (%)
Number of patients		
Linagliptin (add-on to empagliflozin and metformin)	125 (100.0)	113 (100.0)
Placebo (add-on to empagliflozin and metformin)	137 (100.0)	103 (100.0)
Patients with any adverse event		
Linagliptin (add-on to empagliflozin and metformin)	59 (47.2)	61 (54.0)
Placebo (add-on to empagliflozin and metformin)	77 (56.2)	60 (58.3)
Patients with serious adverse events		
Linagliptin (add-on to empagliflozin and metformin)	3 (2.4)	4 (3.5)
Placebo (add-on to empagliflozin and metformin)	7 (5.1)	2 (1.9)

Renal function

Based on eGFR (MDRD), renal function was categorised as normal (eGFR ≥90 mL/min/1.73m^2), mild renal impairment (60 to <90 mL/min/1.73m^2), moderate A (45 to <60 mL/min/1.73m^2), moderate B (30 to <45 mL/min/1.73m^2), severe (<30 to 15 mL/min/1.73m^2), or end stage (<15 mL/min/1.73m^2).

About half of the patients had normal renal function and the other half had mild renal impairment at baseline. Moderate or severe/end stage renal impairment was an exclusion criterion in study 1275.10. Very few patients (14 with moderate A and 2 with moderate B, none with severe/end stage renal impairment) are included in these subgroups, mostly because study inclusion was based on local calculation of renal function with the Cockcroft-Gault formula (and some discrepancies with MDRD occur at the boundaries of the renal impairment categories). Therefore only patients with normal renal function or mild renal impairment at baseline are described in this section.

Demographic data were overall similar between subgroups. In the placebo group the frequency of patients with any adverse event was higher for patients with mild renal impairment than for patients with normal renal function, whereas no difference was seen in the linagliptin group (**Table 33**). Within each renal impairment category, the trends in the frequency of any adverse events and serious adverse events were generally consistent with those for the overall population.

Table 33 Frequency of patients with adverse events in subgroups by renal function in study 1275.10 – TS

Renal function	**Normal renal function (eGFR ≥90 mL/min/1.73m^2)** **N (%)**	**Mild renal impairment (eGFR 60 to <90 mL/min/1.73m^2)** **N (%)**
Number of patients		
Linagliptin (add-on to empagliflozin and metformin)	115 (100.0)	112 (100.0)
Placebo (add-on to empagliflozin and metformin)	109 (100.0)	126 (100.0)
Patients with any adverse event		
Linagliptin (add-on to empagliflozin and metformin)	58 (50.4)	58 (51.8)
Placebo (add-on to empagliflozin and metformin)	55 (50.5)	78 (61.9)
Patients with serious adverse events		
Linagliptin (add-on to empagliflozin and metformin)	5 (4.3)	1 (0.9)
Placebo (add-on to empagliflozin and metformin)	3 (2.8)	6 (4.8)

In both treatment groups the frequency of patients with any adverse events was higher in the subgroup with mild renal impairment (linagliptin: 56.3%, placebo: 65.3% of patients) than in the subgroup with normal renal function (linagliptin: 50.3%, placebo: 54.3%). Within each renal impairment category, the trends in the frequency of any adverse events and serious adverse events were generally consistent with those for the overall population.

EXTRINSIC FACTORS

Geographical region

Subgroup analyses by region were performed for Europe, Latin America, and North America.

In study 1275.10, nearly 50% of the patients were from Europe, about 20% were from North America and about 30% from Latin America. Demographic data were largely similar among regions. For patients from North America, the overall frequency of adverse events was higher for patients receiving placebo than for patients treated with linagliptin, whereas no treatment difference was seen for patients from Europe or Latin America (**Table 34**).

Within each region, the trends in the frequency of any adverse events and serious adverse events were generally consistent with those for the overall population.

Table 34 Frequency of patients with adverse events in subgroups by region in study 1275.10 – TS

Region	Europe N (%)	Latin America N (%)	North America N (%)
Number of patients			
Linagliptin (add-on to empagliflozin and metformin)	114 (100.0)	74 (100.0)	50 (100.0)
Placebo (add-on to empagliflozin and metformin)	115 (100.0)	71 (100.0)	54 (100.0)
Patients with any adverse event			
Linagliptin (add-on to empagliflozin and metformin)	59 (51.8)	36 (48.6)	25 (50.0)
Placebo (add-on to empagliflozin and metformin)	62 (53.9)	34 (47.9)	41 (75.9)
Patients with serious adverse events			
Linagliptin (add-on to empagliflozin and metformin)	3 (2.6)	1 (1.4)	3 (6.0)
Placebo (add-on to empagliflozin and metformin)	6 (5.2)	1 (1.4)	2 (3.7)

Regions: Europe (Australia, Germany, Italy, Portugal, Russia, Spain, Ukraine); Latin America (Argentina); North America (Canada, USA).

Safety related to drug-drug interactions and other interactions

Interaction studies conducted in healthy volunteers suggest that the pharmacokinetics of linagliptin were not influenced by co-administration with metformin and glibenclamide. Co-administration of linagliptin with ritonavir resulted in a moderate increase in peak linagliptin plasma concentrations area under the concentration-time curve. Co-administration of linagliptin with rifampicin resulted in a moderate decrease and in peak linagliptin plasma concentrations area under the concentration-time curve. These changes were not considered to be clinically meaningful.

The drug-drug interaction of empagliflozin and linagliptin was investigated in study 1245.30. The relative bioavailability of multiple doses of empagliflozin 50 mg and linagliptin 5 mg after their concomitant administration was compared to the bioavailabilities of multiple doses of empagliflozin 50 mg and linagliptin 5 mg administered alone in healthy male volunteers. There was no clinically meaningful effect on the pharmacokinetics of either drug and thus no evidence for a drug-drug interaction.

Discontinuation due to AES

Adverse events leading to premature discontinuation of study medication

The frequency of patients with adverse events leading to premature discontinuation of study medication in the Phase III studies was <7% and similar across all treatment groups. At PT level, each adverse event leading to premature discontinuation of study medication was reported for not more than 1 patient (0 to 0.9%) per treatment group in the add-on study 1275.10.

In study 1275.10, 3 patients (2.7%) in the linagliptin 5 mg (add-on to empagliflozin 25 mg and metformin), 3 patients (2.7%) in the placebo (add-on to empagliflozin 25 mg and metformin), 4 patients (3.2%) in the linagliptin 5 mg (add-on to empagliflozin 10 mg and metformin), and 3 patients (2.3%) in the placebo (add-on to empagliflozin 10 mg and metformin) group were reported with adverse events leading to premature discontinuation of study medication.

In study 1275.1(met), 3 patients (2.2%) in the empagliflozin 25 mg/linagliptin 5 mg, 4 patients (2.8%) in the empagliflozin 25 mg, 2 patients (1.5%) in the empagliflozin 10 mg/ linagliptin 5 mg, 9 patients (6.4%) in the empagliflozin 10 mg, and 4 patients (3.0%) in the linagliptin 5 mg group (all treatments as add-on to metformin) were reported with adverse events leading to premature discontinuation of study medication. At PT level, each adverse event leading to premature discontinuation of study medication was reported for not more than 1 patient (0 to 0.8%) per treatment group, except for increased blood creatinine (2 patients [1.5%] in the empagliflozin 25 mg/linagliptin 5 mg [add-on to metformin] group).

Post marketing experience

At the time of writing, linagliptin and the combination of linagliptin and metformin were not approved as add-on therapy to SGLT-2 inhibitors in the EU. However, the FDC empagliflozin/linagliptin had been approved (30 Jan 2015) and marketed in the US and been approved as Glyxambi on 11 November 2016 in the EU. In the US, no special safety measurements have been agreed with FDA, therefore standard safety monitoring procedures are being followed by the MAH. Several adverse events were reported to the MAH after the US marketing approval, but based on the post-marketing case reports no specific safety signal had been detected at the time of writing this summary.

2.5.1. Discussion on clinical safety

The safety assessment of linagliptin in combination with empagliflozin was based on data from the 2 Phase III clinical studies.

The MAH has conducted a large number of clinical studies for linagliptin. This AR focusses on the add on study of linagliptin to empagliflozin (study 1275.10), and factorial design study with linagliptin and empagliflozin (study 1275.1). In total, 1164 patients were treated in the double-blind periods of the studies. These included 478 patients from trial 1275.10; of these 238 patients were treated with linagliptin and 240 patients were treated with placebo. A further 686 patients from trial 1275.1(met) are also included.

In patients with normal renal function or mild renal impairment, linagliptin as add-on to empagliflozin and metformin background therapy was well tolerated. The frequencies of patients with treatment-emergent adverse events were generally similar across treatment groups in all studies. In the add-on study 1275.10, an overall lower proportion of patients was reported with adverse events in the linagliptin (add-on to empagliflozin and metformin) groups than in the placebo group. In the study 1275.1 patient population, the frequencies of patients reported with at least 1 adverse event on-treatment were similar in the 5 treatment groups.

The frequencies of patients with serious adverse events were lower in the linagliptin treatment groups than in the placebo groups in the add-on study 1275.10, and similar across treatment groups in the factorial design study 1275.1.

For the analyses of adverse events of special interest and other significant adverse events, the MAH summarizes data from study 1275.10. Of course, for the use of linagliptin as add-on to empagliflozin, trial 1275.10 is very relevant. However, the factorial design trial 1275.1(met) also provides information on the additional efficacy of linagliptin in patients that also use empagliflozin. Although this study uses initial combination therapy of linagliptin and empagliflozin, we consider safety data relevant for the safety assessment of the add-on indication.

In the present Phase III studies, the frequency of patients with confirmed hypoglycaemic events was low. However, when taken together with insulin or sulphonylurea, both empagliflozin and linagliptin are associated with hypoglycaemia. In the present studies, empagliflozin and linagliptin were not investigated in combination with insulin or sulphonylurea. These indications were not specifically requested. In addition, it is not expected that combination of empagliflozin and linagliptin with sulfonylurea or insulin will lead to an additionally increased risk of hypoglycaemia because both components do not further reduce glucose in a hypoglycaemic state.

In the SmPC for both linagliptin and empagliflozin, a reduction of the SU dose is recommended when adding these treatments. Based on the mechanism of action and the data provided, no added safety concerns of hypoglycaemia are to be expected when linagliptin and empagliflozin are used together.

The Applicant acknowledges that the combination of empagliflozin and linagliptin has not been studied in patients receiving concomitant GLP-1 analogues or thiazolidinediones. Although the text of the new indication is relatively broad, the studied combinations are clearly described in 5.1 of the SmPC.

The frequency of patients reported with hepatic adverse events or relevant laboratory findings was low and comparable across all treatment groups in each study. As expected, treatment with linagliptin was associated with small increases in lipase. This has been added to the SmPC. In the 2 studies, 1 patient was reported with pancreatitis. This patient was treated with linagliptin. Pancreatitis is identified as a possible risk with DPP-4 inhibitors.

The frequencies of patients with decreased renal function adverse events was small and similar for all groups. There was no clinically relevant difference in the frequencies of patients reported with urinary tract infection across treatment groups in each study.

There were no new signals with respect to hypersensitivity reactions, malignancy, cardiac failure and lactic acidosis were low, with no relevant differences between groups.

There were no relevant effects of gender, race and renal function on adverse events.

2.5.2. Conclusions on clinical safety

In patients with type 2 diabetes mellitus and metformin background therapy, treatment with the add-on therapy of linagliptin to the SGLT-2 inhibitor empagliflozin was well tolerated and the safety profile was generally consistent with the known safety profiles of the individual components. In the factorial design study in patients uncontrolled on metformin monotherapy, the combination of linagliptin with empagliflozin was also well tolerated, with similar safety profiles to the individual components.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the Risk Management Plans **version 10.0 for Trajenta** and **version 12.0 for Jentadueto** are both acceptable.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMPs agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

The CHMP endorsed the Risk Management Plans **version 10.0 for Trajenta** and **version 12.0 for Jentadueto** with the following content:

TRAJENTA

Safety concerns

Important identified risks	Hypoglycaemia Pancreatitis Lactic acidosis Angioedema/urticaria Hypersensitivity reactions
Important potential risks	Skin lesions Infections Worsening of renal function Pancreatic cancer Cardiac failure
Missing information	Paediatric patients (including paediatric off-label use) Elderly patients >80 years Pregnancy/breast-feeding Patients with a history of cardiovascular events Concomitant therapy with P-gp and CYP 3A4 inhibitors Use in combinations not studied or approved Malignancies Idiosyncratic reactions Immunological adverse reactions

Pharmacovigilance plan

Study/activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Long term CV-safety study 1218.74 A multicentre, international, randomised, parallel group, double-blind study to evaluate CV safety of linagliptin versus glimepiride in patients with T2DM at high CV risk (Phase III interventional study, category 3)	To evaluate CV safety of linagliptin versus glimepiride	• Hypoglycaemia • Pancreatitis • Worsening of renal function • Pancreatic cancer • Malignancies • Elderly patients >80 years • Patients with a history of CV events • Cardiac failure	Ongoing	Event driven An independent DMC have made recommendations on continued study conduct based on interim analysis in 2014. A further formal interim analysis is estimated in 2015. Final analysis estimated 2018
CV safety study 1218.22 A multicentre, international, randomised, parallel group, double-blind, placebo-controlled, CV safety and renal microvascular outcome study with linagliptin, 5 mg once daily in patients with T2DM at high vascular risk (Phase IV interventional study, category 3)	CV outcome study in patients with T2DM at high vascular risk	• Hypoglycaemia • Pancreatitis • Worsening of renal function • Pancreatic cancer • Malignancies • Elderly patients >80 years • Patients with a history of CV events • Cardiac failure	Ongoing	Event driven An independent DMC will make recommendations on continued study conduct study based on an interim analysis estimated to be in 2016. Final analysis estimated 2019

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Hypoglycaemia	Appropriate labelling in SmPC sections 4.2 Posology, 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects	Not applicable.
Pancreatitis	Appropriate labelling in SmPC sections 4.4 Special warnings and precautions for use and 4.8 Undesirable effects.	Not applicable.
Angioedema/urticaria	Appropriate labelling in SmPC sections 4.3 Contraindications and 4.8 Undesirable effects	Not applicable.
Hypersensitivity reactions	Appropriate labelling in SmPC sections 4.3 Contraindication and 4.8 Undesirable effects	Not applicable.
Important potential risks		
Skin lesions	None proposed	Not applicable.
Infections	None proposed	Not applicable.
Worsening of renal function	None proposed	Not applicable.
Pancreatic cancer	None proposed	Not applicable.
Cardiac failure	None proposed	Not applicable.
Missing information		
Paediatric patients (incl. paediatric off-label use)	Appropriate labelling in SmPC section 4.2 Posology	Not applicable.
Elderly patients <80 years	Appropriate labelling in SmPC section 4.2 Posology	Not applicable.
Pregnancy/breast-feeding	Appropriate labelling in SmPC section 4.6 Fertility, pregnancy and lactation	Not applicable.
Patients with a history of cardiovascular events	None proposed	Not applicable.
Missing information (cont'd)		
Concomitant therapy with P-gp and CYP3A4 inhibitors	Appropriate labelling in SmPC section 4.5 Interaction with other medicinal products and other forms of interaction	Not applicable.
Use in combinations not studied or approved	Appropriate labelling in SmPC section 4.5 Interaction with other medicinal products and other forms of interaction	Not applicable.
Malignancies	None proposed	Not applicable.
Idiosyncratic reactions	None proposed	Not applicable.
Immunological adverse reactions	Appropriate labelling in SmPC sections 4.3 Contraindication and 4.8 Undesirable effects.	Not applicable.

JENTADUETO

Safety concerns

Important identified risks	Hypoglycaemia
	Pancreatitis
	Lactic acidosis
	Angioedema/urticaria
	Hypersensitivity reactions
Important potential risks	Skin lesions
	Infections
	Worsening of renal function
	Pancreatic cancer
	Cardiac failure
Missing information	Paediatric patients (including paediatric off-label use)
	Elderly patients >80 years
	Pregnancy/breast-feeding
	Patients with a history of cardiovascular events
	Concomitant therapy with P-gp and CYP 3A4 inhibitors
	Use in combinations not studied or approved
	Malignancies
	Idiosyncratic reactions
	Immunological adverse reactions

Pharmacovigilance plan

(Same as for Trajenta)

Study/activity	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports
Long term CV-safety study 1218.74 A multicentre, international, randomised, parallel group, double-blind study to evaluate CV safety of linagliptin versus glimepiride in patients with T2DM at high CV risk (Phase III interventional study, category 3)	To evaluate CV safety of linagliptin versus glimepiride	• Hypoglycaemia • Pancreatitis • Worsening of renal function • Pancreatic cancer • Malignancies • Elderly patients >80 years • Patients with a history of CV events • Cardiac failure	Ongoing	Event driven An independent DMC have made recommendations on continued study conduct based on interim analysis in 2014. A further formal interim analysis is estimated in 2015. Final analysis estimated 2018
CV safety study 1218.22 A multicentre, international, randomised, parallel group, double-blind, placebo-controlled, CV safety and renal microvascular outcome study with linagliptin, 5 mg once daily in patients with T2DM at high vascular risk (Phase IV interventional study, category 3)	CV outcome study in patients with T2DM at high vascular risk	• Hypoglycaemia • Pancreatitis • Worsening of renal function • Pancreatic cancer • Malignancies • Elderly patients >80 years • Patients with a history of CV events • Cardiac failure	Ongoing	Event driven An independent DMC will make recommendations on continued study conduct study based on an interim analysis estimated to be in 2016. Final analysis estimated 2019

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Hypoglycaemia	Appropriate labelling in SmPC sections 4.2 Posology, 4.4 Special warnings and precautions, and 4.8 Undesirable effects.	Not applicable
Pancreatitis	Appropriate labelling in SmPC sections 4.4 Special warnings and precautions and 4.8 Undesirable effects.	Not applicable
Lactic acidosis	Appropriate labelling in SmPC sections 4.2 Posology, 4.3 Contraindications, 4.4 Special warnings and precautions, 4.5 Interactions, 4.8 Undesirable effects, and 4.9 Overdose.	Not applicable
Angioedema/urticaria	Appropriate labelling in SmPC sections 4.3 Contraindications and 4.8 Undesirable effects.	Not applicable
Hypersensitivity reactions	Appropriate labelling in SmPC sections 4.3 Contraindication and 4.8 Undesirable effects.	Not applicable
Important potential risks		
Skin lesions	None proposed.	Not applicable
Infections	None proposed.	Not applicable
Worsening of renal function	None proposed.	Not applicable
Pancreatic cancer	None proposed.	Not applicable
Cardiac failure	None proposed	Not applicable.
Missing information		
Paediatric patients (incl. paediatric off-label use)	Appropriate labelling in SmPC section 4.2 Posology.	Not applicable
Elderly patients >80 years	Appropriate labelling in SmPC sections 4.2 Posology and 4.4 Special warnings and precautions.	Not applicable
Pregnancy/breast-feeding	Appropriate labelling in SmPC section 4.6 Fertility, pregnancy and lactation.	Not applicable
Patients with a history of CV events	Appropriate labelling in SmPC section 4.3 Contraindications.	Not applicable
Concomitant therapy with P-gp and CYP3A4 inhibitors	Appropriate labelling in SmPC section 4.5 Interactions.	Not applicable
Missing information (cont'd)		
Use in combinations not studied or approved	Appropriate labelling in SmPC section 4.5 Interactions.	Not applicable
Malignancies	None proposed.	Not applicable
Idiosyncratic reactions	None proposed.	Not applicable
Immunological adverse reactions	Appropriate labelling in SmPC sections 4.3 Contraindication and 4.8 Undesirable effects.	Not applicable

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.8 and 5.1 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the applicant and has been found acceptable for the following reasons: the changes proposed to the package leaflet can be considered minor and the absence of further user consultation can be justified.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The MAH did apply for an extension of indication for the combined use of linagliptin (a dipeptidylpeptidase [DPP-4] inhibitor) and of linagliptin/metformin with a sodium-dependent glucose cotransporter-2 [SGLT-2] inhibitor for the treatment of adults with type 2 diabetes mellitus. Support for this indication consists of 2 pivotal studies in patients with type 2 diabetes mellitus: 1 add-on study (1275.10) with linagliptin as add on to a combination of metformin and empagliflozin and one factorial design study (1275.1).
These studies were also part of the marketing authorisation of Glyxambi, the FDC of empagliflozin and linagliptin (EMEA/H/C/003833). Glyxambi was authorised in the EU for use in patients with type 2 diabetes in November 2016.

The Phase III add-on study investigated the efficacy, safety, and tolerability of linagliptin as add-on therapy to the SGLT-2 inhibitor empagliflozin (study 1275.10) in patients with type 2 diabetes mellitus and metformin background medication. In the factorial design study, patients were randomised into 5 treatment groups: empa 25/lina 5, empa 10/lina 5, empa 25, empa 10, and lina 5 (1275.1). The superiority of each FDC was tested against its respective individual components. Bioequivalence of the FDC with the individual components was established. No drug-drug-interactions between the monocomponents were observed. Although the factorial design study does not investigate the add-on indication, this study provides information on the combined use of linagliptin and empagliflozin.

Linagliptin had previously been indicated for the treatment of type 2 diabetes mellitus to improve glycaemic control in adults as monotherapy in patients for whom metformin is inappropriate due to intolerance or contraindicated due to renal impairment, and as combination therapy in combination with metformin, sulphonylurea and metformin, and insulin with or without metformin. In this application the MAH requested an extension of the indication, and proposes that linagliptin is also indicated in adults with type 2 diabetes mellitus to improve glycaemic control in adults in combination with an SGLT-2 inhibitor and metformin when diet and exercise plus dual therapy with these medicinal products do not provide adequate glycaemic control. An equivalent extension of indication was requested for the FDC linagliptin/metformin.

In total, 1164 patients were treated in the double-blind periods of the two studies. These included 478 patients from the add-on trial 1275.10; of these 238 patients were treated with linagliptin and 240 patients were treated with placebo. A further 686 patients from the factorial design trial 1275.1(met) are also included. The baseline characteristics were well balanced across the treatment groups.

In the add-on study 1275.10, the treatment effect of linagliptin on top of empagliflozin 25 mg was -0.47% (95% CI: -0.66, -0.28) and the effect of linagliptin on top of empagliflozin 10 mg was -0.32% (95% CI: -0.52, -0.13). The pooled treatment difference of linagliptin was -0.40% (95% CI: -0.53, -0.27; p<0.0001).

In the factorial design study 1275.1 (met), the treatment difference for the FDC empa 25/lina 5 group was -0.58% (95% CI: -0.75, -0.41) versus empa 25 and the treatment difference for the FDC empa 10/lina 5 group was -0.42% (95% CI: -0.59, -0.25) versus empa 10.

In general, the results for changes in FPG were consistent with the results for the changes in HbA1c.

As could be expected based on linagliptin's mechanism of action, linagliptin in combination with empagliflozin in study 1275.10 was not associated with statistically significant changes in body weight in comparison to placebo. In study 1275.01 (met), linagliptin was also not associated with weight loss.

In study 1275.10, linagliptin add-on to empagliflozin (25 mg and 10 mg) and metformin provided no reductions in systolic or diastolic blood pressure after 24 weeks of treatment compared with placebo. In study 1275.1, there were also no changes in blood pressure with linagliptin treatment.

In general, in study 1275.1, the effects after 52 weeks were in line with the findings after 24 weeks.

Uncertainty in the knowledge about the beneficial effects

As described above, the treatment effects of linagliptin on top of empagliflozin were small (1275.10; (-0.47% on top of empa 25 mg and -0.32% on top of empa 10 mg). As requested, the company performed a subgroup analyses in study 1275.10 in patients with HbA1c greater than or equal to 8.5%. In these patients, the adjusted mean treatment differences for linagliptin to placebo in study 1275.10 were clinically relevant (-0.62%) as add-on to empagliflozin 25 mg and metformin, but of borderline clinical relevance (-0.33%) as add-on to empagliflozin 10 mg and metformin.

Additional data showing the efficacy of linagliptin in combination with empagliflozin (on a background of metformin) was provided by the factorial design study 1275.1(met). In this study, the treatment difference between the combination of empagliflozin 25 mg/linagliptin 5 mg and empagliflozin 25 mg was -0.58%). Similarly, the treatment difference between the combination of empagliflozin 10 mg/linagliptin 5 mg and empagliflozin 10 mg was -0.42%. Taken together, the data from study 1275.10 and 1275.1(met) suggest that the additive effect of linagliptin on top of empagliflozin and metformin is on average approximately 0.45% and of clinical relevance.

Study 1275.10 also included an analysis of the proportions of patients who achieved an HbA1c value of 7% or lower at 24 weeks. The analysis showed that more than twice as many patients treated with linagliptin than with placebo achieved HbA1c<7.0% after 24 weeks. For linagliptin as add on to empagliflozin 25 mg, responder percentages were 36% vs. 15%. For linagliptin as add on to empagliflozin 10 mg, responder percentages were 26% vs. 11%.

Similarly, responder analyses in the factorial design study 1275.1(met) demonstrate that linagliptin in combination with empagliflozin was associated with higher responder percentages than with empagliflozin monotherapy (64.9% and 60.0% for linagliptin in combination with empagliflozin 25 mg and 10 mg respectively vs. 35.7% and 34.3% for empagliflozin 25 mg and 10 mg respectively).

Empagliflozin is the only SGLT2-inhibitor for which the combination with linagliptin was investigated. A combination of lina with other SGLT2-inhibitors has not been studied. This is described in SmPC section 5.1.

The study populations can be considered relatively representative of the target population. However, due to the fact that empagliflozin and metformin may not be initiated in patients with a GFR<60 ml/min, only a few patients with eGFR below 60 ml/min were included. In addition, very few subjects ≥75 years old were included.

Risks

Unfavourable effects

The safety assessment of linagliptin in combination with empagliflozin was also based on data from the add on study of linagliptin to empagliflozin (study 1275.10), and factorial design study with linagliptin and empagliflozin (study 1275.1). In total, 1164 patients were treated in the double-blind periods of the studies included in the evaluation presented in this document.

In patients with normal renal function or mild renal impairment, linagliptin as add-on to empagliflozin and metformin background therapy was well tolerated. The frequencies of patients with treatment-emergent adverse events were generally similar across treatment groups in all studies. In the add-on study 1275.10, an overall lower proportion of patients was reported with adverse events in the linagliptin (add-on to empagliflozin and metformin) groups than in the placebo group. In the study 1275.1 patient population, the frequencies of patients reported with at least 1 adverse event on-treatment were similar in the 5 treatment groups.

The frequencies of patients with serious adverse events were lower in the linagliptin treatment groups than in the placebo groups in the add-on study 1275.10, and similar across treatment groups in the factorial design study 1275.1.

The frequencies of patients with decreased renal function adverse events was small and similar for all groups. There was no clinically relevant difference in the frequencies of patients reported with urinary tract infection across treatment groups in each study.

There were no new signals with respect to hypersensitivity reactions, malignancy, cardiac failure and lactic acidosis were low, with no relevant differences between groups.

There were no relevant effects of gender, race and renal function on adverse events.

Uncertainty in the knowledge about the unfavourable effects

In the present Phase III studies, the frequency of patients with confirmed hypoglycaemic events was low. However, when taken together with insulin or sulphonylurea, both empagliflozin and linagliptin are associated with hypoglycaemia. In the present studies, empagliflozin and linagliptin were not investigated in combination with insulin or sulphonylurea. Concomitant use of linagliptin with empagliflozin and glucagon like peptide 1 (GLP-1) analogues or thiazolidinediones has also not been studied.

The frequency of patients reported with hepatic adverse events or relevant laboratory findings was low and comparable across all treatment groups in each study. As expected, treatment with linagliptin was associated with small increases in lipase. This has been added to the text of the SmPC. In the 2 studies, 1 patient was reported with pancreatitis. This patient was treated with linagliptin. Pancreatitis is identified as a possible risk with DPP-4 inhibitors.

Empagliflozin is the only SGLT2-inhibitor for which the combination with linagliptin was investigated. A combination of lina with other SGLT2-inhibitors has not been studied.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The effects of linagliptin as add on to empagliflozin on HbA1c were relatively small, but clinically relevant. In addition, linagliptin was associated with small reductions in fasting plasma glucose. As expected, linagliptin was not associated with reductions in body weight and blood pressure. No information regarding the

modulation of cardiovascular risk with linagliptin is currently known as a cardiovascular outcome trial with linagliptin is ongoing.

The differences between SGLT-2 inhibitors may not be very large. Nevertheless, empagliflozin is the only SGLT2-inhibitor for which the combination with linagliptin was investigatedwhich is described in the SmPC section 5.1.

Due to the fact that empagliflozin may not be initiated in patients with a GFR<60 ml/min, only a few patients with eGFR below 60 ml/min were included. In addition, very few subjects ≥75 years old were included. This may limit the external validity of the studies to the total population.

In patients with type 2 diabetes mellitus and metformin background therapy, treatment with the add-on therapy of linagliptin to the SGLT-2 inhibitor empagliflozin was well tolerated and the safety profile was generally consistent with the known safety profile. In the factorial design study in patients uncontrolled on metformin monotherapy, the combination of linagliptin with empagliflozin was also well tolerated, with similar safety profiles to the individual components.

Patients with type 2 diabetes can be treated with empagliflozin in combination with SU and insulin. The concomitant use of linagliptin with empagliflozin and sulphonylurea derivatives or insulin has not been studied; for which there may be an increased risk of hypoglycaemia. In addition, concomitant use of linagliptin with empagliflozin and glucagon like peptide 1 (GLP-1) analogues or thiazolidinediones has also not been studied.

Benefit-risk balance

Treatment with linagliptin in combination with empagliflozin and metformin was well tolerated and the safety profiles were generally consistent with the known safety profile. The HbA1c lowering effect of linagliptin in combination with empagliflozin and metformin was small, but relevant.

Discussion on the benefit-risk assessment

The clinical relevance of the effect of linagliptin as add on to empagliflozin and metformin is modest, but acceptable. Responder percentages were clearly higher. The combination of linagliptin and empagliflozin might be beneficial for certain patients.

The fact that only a few patients ≥75 years old were included limits the external validity of the trial to the total population. In addition, only a few patients with eGFR below 60 ml/min were included. However, the separate clinical development programs for the monocomponents linagliptin and empagliflozin include more patients within this age category. Although the issue remains that there is limited knowledge on the efficacy and safety of the combination linagliptin and empagliflozin in these patients, this is sufficiently reflected in the SmPC. The concomitant use of linagliptin and empagliflozin was not investigated in combination with insulin, sulphonylurea, glucagon like peptide 1 (GLP-1) analogues or thiazolidinediones . It is not expected that combination of empagliflozin and linagliptin with sulfonylurea or insulin will lead to an additionally increased risk of hypoglycaemia because both components do not further reduce glucose in a hypoglycaemic state.

In the SmPC for both linagliptin and empagliflozin, a reduction of the SU dose is recommended when adding these treatments. Based on the mechanism of action and the data provided, no added safety concerns of hypoglycaemia are to be expected when linagliptin and empagliflozin or another SGLT-2 inhibitor are used together.

Empagliflozin is the only SGLT2-inhibitor for which the combination was investigated. This is described in the SmPC section 5.1.The combination of empagliflozin and linagliptin has not been studied in patients receiving concomitant GLP-1 analogues or thiazolidinediones.

Since the initial authorisation of linagliptin-containing products, the general wording of the indication for medicinal products for the treatment of diabetes has evolved, and in addition more data has been accumulated regarding the combined use of linagliptin with other products for the treatment of diabetes representing the standard of care. Therefore, the wording of the indication in section 4.1 of the SmPC refers now in more general terms to the combined use of linagliptin and linagliptin/metformin with other products for the treatment of diabetes, including insulin. Although the wording of the indication is relatively broad, the combinations studied are clearly described in section 5.1 of the SmPC.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends by consensus the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include the use of Trajenta and Jentadueto in combination with other diabetes medicines; as a consequence, sections 4.1, 4.8 and 5.1 of the SmPC are updated based on studies 1245.30, 1275.10 and 1275.1. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to make minor editorial changes in the PI. Moreover, the RMP version 10 (for Trajenta) and version 12 (for Jentadueto) have been updated. Furthermore, the PI is brought in line with the latest QRD template version 10.0.

The worksharing procedure leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.