15 September 2016
EMA/749639/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Glyxambi

International non-proprietary name: empagliflozin / linagliptin

Procedure No. EMEA/H/C/003833/0000

Note

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

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5520
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Background information on the procedure 7
1.1. Submission of the dossier 7
1.2. Steps taken for the assessment of the product 8

2. Scientific discussion 9
2.1. Introduction 9
2.2. Quality aspects 10
2.2.1. Introduction 10
2.2.2. Active Substances 10
2.2.3. Finished Medicinal Product 15
2.2.4. Discussion on chemical, pharmaceutical and biological aspects 21
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects 21
2.2.6. Recommendations for future quality development 21
2.3. Non-clinical aspects 21
2.3.1. Introduction 21
2.3.2. Pharmacology 22
2.3.3. Pharmacokinetics 23
2.3.4. Toxicology 26
2.3.5. Ecotoxicity/environmental risk assessment 30
2.3.6. Discussion on non-clinical aspects 33
2.3.7. Conclusion on the non-clinical aspects 34
2.4. Clinical aspects 34
2.4.1. Introduction 34
2.4.2. Pharmacokinetics 36
2.4.3. Pharmacodynamics 44
2.4.4. Discussion on clinical pharmacology 45
2.4.5. Conclusions on clinical pharmacology 46
2.5. Clinical efficacy 46
2.5.1. Dose response study 46
2.5.2. Main study(ies) 46
2.5.3. Discussion on clinical efficacy 68
2.5.4. Conclusions on the clinical efficacy 72
2.6. Clinical safety 72
2.6.1. Discussion on clinical safety 93
2.6.2. Conclusions on the clinical safety 94
2.7. Risk Management Plan 95
Summary of safety concerns 95
2.8. Pharmacovigilance 100

2.9. Product information 100
2.9.1. User consultation 100
2.9.2. Additional monitoring 101
3. Benefit-Risk Balance 101
4. Recommendations 106

List of abbreviations

AE	Adverse event
AE	Adverse event of special interest
ALT	Alanine transaminase
ANCOVA	Analysis of covariance
AR	Assessment report
AST	Aspartate transaminase
AUC	Area under the concentration vs. time curve
BCS	Biopharmaceutics classification system
BI	Boehringer Ingelheim
BIcMQ	BI-customised MedDRA query
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CECP	Clinical Events Committee for adjudication of pancreatic events
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CMAs	Critical material attributes
Cmax	Maximum plasma concentration
CNS	Central nervous system
CPP(s)	Critical process parameter(s)
CQA(s)	Critical Quality Attribute(s)
CTD	Common Technical Document
CTR	Clinical trial report
CV	Cardiovascular
CYP3A4	Cytochrome P450 3A4 isoform
DB	Double blind
DBP	Diastolic blood pressure
DILI	Drug-induced liver injury
DPP-4	Dipeptidyl peptidase-4
eCCR	Estimated creatinine clearance
eGFR	Estimated glomerular filtration rate
EMA	European medicines agency
Empa	Empagliflozin
ESRD	End-stage renal disease
FAS	Full analysis set
FDA	Food and drug administration
FDC	Fixed dose combination
FPG	Fasting plasma glucose
GC	Gas chromatography
GLP-1	Glucagon-like peptide 1
HbA_{1c}	Glycaeted haemoglobin

HDL	High-density lipoprotein
hepEAC	Hepatic External Adjudication Committee
HIV	Human immunodeficiency virus
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation
IPC(s)	in-process control(s)
IPV	Important protocol violation
(FT-)IR	(Fourier transform) Infrared
ISS	Integrated safety summary
KF	Karl-Fischer method
Lina	Linagliptin
LC	Liquid chromatography
LDL	Low-density lipoprotein
LDPE	Low-density polyethylene
LLN	Lower limit of normal
LOD	loss on drying
LOCF	Last observation carried forward
MACE	Major adverse cardiac event
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Drug Regulatory Activities
Met	Metformin
MMRM	Mixed model repeated measures
MRHD	Maximum human recommended dose
NCF	Non-completers considered failure
NDA	New Drug Application
(^{1}H or ^{13}C) NMR	(Proton/ carbon) Nuclear magnetic resonance
NOAEL	No observed adverse effect level
NOEL	No observed effect level
OAT	Organic anion transporter
OATP	Organic anion transporter polypeptide
OC	Observed cases
OC-IR	Observed cases including values after rescue medication
OCT	Organic cation transporter
OGTT	Oral glucose tolerance test
OL	Open-label
OLFAS	Open-label full analysis set
OR	Original results
PARs	Proven acceptable ranges
PBT	Persistent, bioaccumulative and toxic
P-gP	P-glycoprotein (permeability glycoprotein)
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
Pooled	Data pooled from the 3 Phase III Glyxambi studies
PPG	Post-prandial glucose
PT	Preferred term
PVC/PVDC	polyvinyl chloride/polyvinylidene chloride

Q1	Lower quartile
Q3	Upper quartile
RH	Relative Humidity
RMP	Risk management plan
SAE	Serious adverse event
SAF-L1	Treated set, all patients on metformin-background therapy
SAF-L2	Treated set, all patients (metformin background + treatment naïve)
SBP	Systolic blood pressure
SCAR	Serious cutaneous adverse reaction
SCE	Summary of Clinical Efficacy
SCS	Summary of Clinical Safety
SD	Standard deviation
SE	Standard error
SGLT	Sodium-dependant glucose co-transporter
SGOT	Serum glutamic oxaloacetic transaminase
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA query
SOC	System-organ class
T2DM	Type 2 diabetes mellitus
TS	Treated set
UACR	Urinary-albumin-to-creatinine ratio
UGT	Uridine 5'-diphospho-glucuronosyltransferases
ULN	Upper limit of normal
USPI	United States Product Insert
URTI	Upper Respiratory Tract Infection
UTI	Urinary Tract Infection
UV	Ultra-Violet
vPvB	Very persistent and very bioaccumulative
ZDF	Zucker Diabetic fatty

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Boehringer Ingelheim International GmbH submitted on 8 October 2015 an application for a Marketing Authorisation to the European Medicines Agency (EMA) for Glyxambi, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 25 July 2013.

The applicant applied for the following indication:

Glyxambi is indicated in adults with type 2 diabetes mellitus to improve glycaemic control:

- when diet and exercise, plus metformin and a sodium glucose co-transporter 2 (SGLT2) inhibitor do not provide adequate glycaemic control,
- when diet and exercise, plus metformin and a dipeptidyl peptidase 4 (DPP-4) inhibitor do not provide adequate glycaemic control,
- when already being treated with the free combination of empagliflozin (or another SGLT-2 inhibitor) and linagliptin (or another DPP-4 inhibitor).

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for new fixed combination products.

The application submitted is a new fixed combination medicinal product.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/247/2011 on the granting of a (product-specific) waiver.

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 received Scientific Advice from the CHMP on 20 January 2011. The Scientific Advice pertained to non-clinical and clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Pieter de Graeff Co-Rapporteur: Bart Van der Schueren

- The application was received by the EMA on 8 October 2015.
- The procedure started on 29 October 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 10 January 2016.
- The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 13 January 2016.
- The PRAC Rapporteur's assessment Report was circulated on 29 January 2016.
- During the meeting on 25 February 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 February 2016.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 21 April 2016.
- The following GCP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:
  - A GCP inspection was peformed at 3 sites [2 investigator sites – one in Spain and one in the US) and the sponsor site in the US] between 25 January 2016 – 08 April 2016. The summary report of the inspection carried out was issued on 09 May 2016. The conclusion of the inspection was that data quality is acceptable and the trial has been conducted following GCP and ethical standards. Therefore the inspection team considered that data are trustworthy and can be used in support of the Marketing Authorisation Application for Glyxambi.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 May 2016.
- The PRAC assessment overview was adopted by the PRAC on 9 June 2016.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 17 June 2016.
- During the CHMP meeting on 21 July 2016, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 10 August 2016.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of outstanding issues to all CHMP members on 30 August 2016.
- During the meeting on 15 September 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Glyxambi.

2. Scientific discussion

2.1. Introduction

Problem statement

Diabetes mellitus is an increasingly prevalent disease. Recent estimates suggest that 382 million people worldwide currently have diabetes. This number is expected to increase to 592 million in the next 25 years. The most common form of diabetes, type 2 diabetes mellitus, is characterised by insulin resistance, impaired insulin secretion, and increased hepatic glucose production. In addition, it is associated with microvascular complications and increased cardiovascular risk.

Treatment of type 2 diabetes mellitus usually involves lifestyle interventions such as diet and exercise, as well as the administration of antidiabetic drugs. Although initially effective, currently available oral antidiabetic agents often fail to maintain long-term glycaemic control or are associated with side effects (e.g. weight gain and hypoglycaemia) that may limit their use. Hence, there is an ongoing need for new therapeutic options to provide sustained improvements in glycaemic control and to reduce cardiovascular risk factors in patients with type 2 diabetes mellitus, i.e. overweight and hypertension.

About the product

Based on results of clinical Phase III studies, 2 doses of empagliflozin (25 mg and 10 mg; empa 25 and empa 10) and one dose of linagliptin (5 mg; lina 5) are approved treatments for the treatment of type 2 diabetes. The combinationof empagliflozin and linagliptin may result in improved glycaemic control, since the individual drugs have distinct mode of actions.

Empagliflozin is a potent and selective SGLT-2 inhibitor, 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 insulin pathways, which provides a therapeutic advantage compared with other drugs and has not been associated with an increased risk for hypoglycaemia when administered as monotherapy or other antidiabetic therapies (other than sulphonylurea±insulin). Furthermore, SGLT-2 inhibition is associated with weight loss and a reduction in blood pressure.

Linagliptin is a selective, orally administered, xanthine-based DPP-4 inhibitor. Like other DPP-4 inhibitors, linagliptin lowers blood glucose by extending the half-life of active glucagon-like peptide 1 (GLP-1), which is secreted in response to a meal. Glucagon-like peptide -1 lowers blood glucose by augmenting the glucose-stimulated insulin release and limiting glucagon secretion as well as slowing gastric emptying and inducing satiety. DPP-4 inhibitors have a relatively low risk of hypoglycaemia. The activity of GLP-1 ceases when plasma glucose concentration falls below 55 mg/dL.

Type of application and aspects on development

Boehringer Ingelheim International GmbH submitted a Marketing Authorisation Application for Glyxambi (empagliflozin/linagliptin film-coated tablets with the strengths 10 mg/5 mg and 25 mg/5 mg). Glyxambi is

eligible to the centralised procedure in accordance with article 3(1) – annex (3) New active substance for mandatory indications of regulation EC No 726/2004. The application is submitted in accordance with Article 10b (fixed dose combination).

2.2. Quality aspects

2.2.1. Introduction

Glyxambi finished product is presented as film-coated tablets containing a fixed-dose combination of 10 mg / 5 mg, or 25 mg / 5 mg of empagliflozin and linagliptin, respectively, as the active substances.

Other ingredients of the tablet core are mannitol (E421), pre-gelatinised starch (maize), maize starch, copovidone (K-value nominally 28), crospovidone (Type B), talc and magnesium stearate. The film coating is composed of hypromellose 2910, mannitol (E421), talc, titanium dioxide (E171), macrogol 6000, iron oxide red (E172) (in the 25 mg/ 5 mg film-coated tablets) or iron oxide yellow (E172) (in the 10 mg/ 5 mg film-coated tablets).

The product is available in PVC/PVDC/aluminium perforated unit dose blisters packs.

2.2.2. Active Substances

Empagliflozin

General information

The chemical name of the active substance empagliflozin is (1*S*)-1,5-anhydro-1-(4-chloro-3-{4-[(3*S*)-tetrahydrofuran-3-yloxy]benzyl}phenyl)-D-glucitol, corresponding to the molecular formula $C_{23}H_{27}ClO_7$ and has a relative molecular mass 450.9 g/mol. It has the following structure:

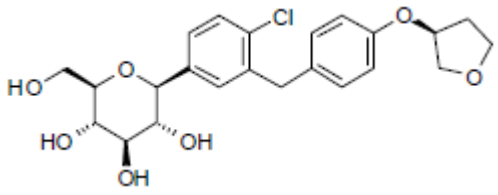

Figure 1. Structure of empagliflozin.

The structure of empagliflozin was unambiguously confirmed by ^{1}H- and ^{13}C-NMR, UV spectroscopy, FT-IR spectroscopy, mass spectrometry and elemental analysis. Empagliflozin appears as a white to yellowish non-hygroscopic crystalline solid, very slightly soluble in water (pH 1-7.4), slightly soluble in acetonitrile and ethanol, sparingly soluble in methanol, and practically insoluble in toluene. The molecule has no ionisable centres. Its partition coefficient has been determined to be 1.7 at pH 7.4.

Empagliflozin is chiral and possesses 6 stereogenic centres. Enantiomeric purity is controlled routinely by chiral HPLC/specific optical rotation. A single polymorphic form has been observed for empagliflozin and is

consistently produced by the proposed manufacturing process. The isolated form is non-solvated and non-hydrated.

Manufacture, characterisation and process controls

Empagliflozin is synthesized by a single manufacturer in 4 steps from well-defined starting materials with acceptable specifications. The active substance is then recrystallized and milled. The process has been described in sufficient detail; amounts, yields and batch size have been stated. Reprocessing has been described and consists of repeating relevant steps. No new solvents are introduced for reprocessing.

Five of the stereocentres originate from the chiral pool whereas the sixth benzylic centre is controlled by a diastereoselective reduction during the process. Potential and actual impurities were well discussed with regards to their origin and fate and characterised. None were deemed to have genotoxic potential.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are considered adequate. The active substance is packaged in a double LDPE bags closed with cable binders, then stored away from light in a fibre drum. The primary packaging material complies with the relevant EC regulations and Ph. Eur. requirements.

Specification

The active substance specification includes tests for appearance, identity (IR, HPLC), impurities (HPLC), diastereomer (chiral HPLC), assay (HPLC), residual solvents (GC), water content (KF), residue on ignition, and particle size (laser diffraction).

Optical purity is controlled by a test for specific optical rotation in the two chiral starting materials.

None of the specified or routinely observed impurities is considered a degradation product of empagliflozin.

The limits of 3 specified impurities are above the qualification threshold according to ICH Q3A and they have been toxicologically qualified (these data were assessed in the MAA procedure for Jardiance (EMEA/H/C/002677)).

Two potential residual solvents are specified in the specification with their respective ICH Q3C limits. Solvents not classified in ICH Q3C are treated as organic impurities according to ICH Q3A (R2).

The omission of testing for benzene and heavy metals has been justified based on batch data. The omission of a microbial limit test from the specification has also been justified based on the fact that water or aqueous solvents are not used in the final step and on batch data.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Sufficient information regarding the reference standards used has been provided.

Batch analysis data on 5 commercial scale batches of the active substance is provided. The results are within the specifications and consistent from batch to batch. Batch analysis data on a further 40 batches (varying from pilot to commercial scale) carried out using previous incarnations of the synthetic process and used for toxicology and clinical studies are also provided, with all batches conforming to specifications in place at the time.

Stability

Stability data on three commercial scale batches of empagliflozin manufactured using the proposed commercial process stored in the intended commercial packaging for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Stability was also tested under stressed conditions in the solid state (one commercial scale batch) and in solution (one development batch). Solid state photostability testing following the ICH guideline Q1B was performed on one commercial scale batch. Solid state material was also exposed to high temperature (80 ºC) and to open storage conditions (40 ºC / 75 % RH). Empagliflozin was tested in solution at low (2.5), intrinsic, and high (13) pH, each under heat stress conditions (80 ºC); in the presence of strong (H2O2), or mild (2,2'-Azobis(2-methylpropionitrile)) oxidants; and under UV irradiation (20 W/m2). The following parameters were tested: appearance, impurities (HPLC), diastereomer (chiral HPLC), assay (HPLC), water content (KF) and particle size (laser diffraction). The analytical methods used were the same as for release and were shown to be stability indicating.

No changes to any test parameters were observed under long term or accelerated conditions. Empagliflozin is neither photosensitive, nor affected by high temperature or humidity in the solid state. In solution, it is prone to degradation at low and high pH and in the presence of a strong oxidant. It is also unstable to a mild oxidant at high pH and slightly sensitive to light. None of the chiral centres showed any propensity to epimerisation during the stability studies. The results demonstrate that the analytical methods are stability indicating. The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container. Primary stability studies on the three commercial batches will continue up until the proposed re-test period.

Based on the presented stability data the proposed retest period of 60 months without specific storage conditions is accepted.

Linagliptin

General information

Linagliptin is chemically designated as 8-[(3R)-3-aminopiperidin-1-yl]-7-(but-2-yn-1-yl)-3-methyl-1- [(4-methylquinazolin-2-yl)methyl]-3,7-dihydro-1H-purine-2,6-dione corresponding to the molecular formula $C_{25}H_{28}N_8O_2$ and has a relative molecular mass 472.5 g/mol and has the following structure:

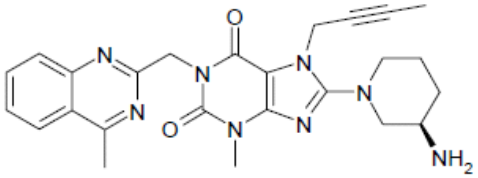

Figure 2. Structure of linagliptin.

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

Linagliptin appears as a white to yellowish slightly hygroscopic crystals with a rod-like habit. It is very soluble in aqueous media (> 1 mg/ml) over the entire physiological pH range. It is soluble in methanol, sparingly soluble in ethanol and very slightly soluble in isopropanol and acetone. Linagliptin is classified as class III compound according to the Biopharmaceutics Classification System (BCS).

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

Linagliptin manufactured according to the proposed manufacturing process exists in two polymorphic modifications ("Form A" and "Form B"), which are enantiotropically related and which reversibly convert into each other approximately at room temperature. Uptake of water does not change the crystal modification. The two polymorphic forms do not differ with regard to biopharmaceutically relevant physicochemical properties and therefore the solid-state differences are unlikely to have any impact on bioavailability.

Manufacture, characterisation and process controls

The synthetic process for linagliptin consists of three steps from three well defined commercially available starting materials. The synthesis is followed by milling process. Reprocessing includes repetition of the crystallisation step, which is acceptable.

The amounts of raw materials, yields, and equipment have been specified, and the in-process controls have been well described. Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are considered adequate.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential impurities were well discussed with regards to their origin and fate.

The active substance is packaged in a double LDPE bags closed with cable binders, then stored in a fibre drum. The primary packaging material complies with the relevant EC regulations and Ph. Eur. requirements.

Specification

The active substance specification includes tests for appearance, identity (IR, chiral HPLC, DSC), impurities (LC), organic volatile impurities (GC), residual solvents (GC), enantiomeric purity (LC), water content (KF), assay (LC), sulphated ash, particle size (laser diffraction).

The proposed regulatory specification was established based on the available developmental, manufacturing, and stability data. Impurities exceeding the qualification threshold of 0.15% were toxicologically qualified. The limit for each individual unspecified impurity as well as the organic volatile impurities is consistent with the identification threshold of ICH guidance Q3A (R2).

The residual solvents are specified in accordance with the ICH Q3C (R4) guidance whereas other class 2 solvents used in earlier synthetic steps remain consistently well below 10% of the respective ICH levels and, are, therefore, not controlled in the active substance specification.

Assay limits were justified taking into account the maximum permitted level of impurities, numerous batch analysis data as well as the analytical error of the assay methods.

The active substance particle size was set based on developmental data on the manufacturability and performance of the finished product (dissolution, content uniformity, stability).

The omission of routine tests for polymorphic form, metal residues, genotoxic substances, and microbiological purity in the active substance specification was sufficiently justified based on relevant ICH guidance and appropriate experimental data.

The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Sufficient information regarding the reference standards used has been provided.

Batch analysis data on 13 commercial scale batches of the active substance was provided. The results are within the specifications and consistent from batch to batch. Batch analysis date on further 23 batches (varying from pilot to commercial scale) carried out in different manufacturing sites and using different suppliers of the starting materials were also provided, with all batches conforming to specifications in place at the time.

Stability

Stability data on three commercial scale batches of linagliptin manufactured using the proposed commercial process stored in the intended commercial packaging for up to 60 months under long term conditions (25 ºC / 60% RH) and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided in accordance with the ICH Q1A(R2) guideline.

Tested parameters were appearance, melting temperature, organic impurities, organic volatile impurities, enantiomeric purity, water content, assay, and particle size. The analytical procedures were shown to be stability indicating.

No significant changes were observed. The only trends were a slight change in appearance from white to slightly yellow at both storage conditions and, a slight increase in the level of an impurity both at long-term and accelerated conditions. This impurity is not a degradation product of the active substance but results from a hydrolytic degradation of another impurity which is the process-related, the level of which slowly decreased during the course of the stability study.

In addition, one of the three stability batches was subjected to stress studies at elevated temperature, humidity, pH, oxidative conditions and light in the solid state and in solution. Photostability testing of the solid drug substance was performed according to ICH guideline Q1B. Tested parameters were appearance, melting temperature, organic impurities, enantiomeric purity, water (only in solid state), and assay.

In solid form, the drug substance is very stable at elevated temperatures, high humidity and the combined effect of both conditions. During photostability testing, only a slight change in colour was observed, but no change in impurity profile.

In solution, no degradation was observed at neutral and intrinsic pH. Degradation is only observed at strongly acidic conditions or at strongly basic conditions at elevated temperature. None of the observed degradation products were found at long term and accelerated conditions.

The drug substance showed a slightly higher sensitivity towards photolysis in solution as compared to the solid state. Strongly oxidative conditions caused no decomposition of the drug substance in solution.

Based on the presented stability data the proposed retest period of 60 months without specific storage conditions is accepted.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Glyxambi is provided as immediate release film-coated tablets intended for oral administration.
10 mg / 5 mg strength tablets are pale yellow, arc triangular, flat-faced, bevel-edged, film-coated tablets, debossed on one side with the Boehringer Ingelheim company symbol and on the other side with "10/5".
25 mg / 5 mg strength tablets are pale pink, arc triangular, flat-faced, bevel-edged, film-coated tablets, debossed on one side with the Boehringer Ingelheim company symbol and on the other side with "25/5". The two strengths can be distinguished by colour and debossing. They have the same form and size and have no score line.

The composition of the two strengths is identical except for the amounts of empagliflozin and mannitol. The amount of mannitol is varied to compensate for the difference in the amount of empagliflozin in the two strengths, in order to yield the same tablet weight for both strengths.

The objective of pharmaceutical development was to develop a fixed dose combination of empagliflozin and linagliptin in an oral tablet formulation, for the once daily long-term treatment of type 2 diabetes mellitus. Formulation development was based on the experience with empagliflozin / linagliptin mono products Jardiance and Trajenta, respectively. Glyxambi was developed using a Quality by Design (QbD) approach. The presented Quality Target Product Profile (QTPP) is considered appropriate for the intended use (table 1). Using the QTPP as a starting point, the Critical Quality Attributes (CQAs) of the product were identified and used to guide formulation and process development.

Table 1. *Quality Target Product Profile (QTPP)*

QTPP Element	**Target**	
Administration	Oral, qd dosing, one dosage unit per dose	
Dosage form	Film-coated tablet, of adequate size to promote patient compliance	
Dosage strengths	10 mg empagliflozin/5 mg linagliptin 25 mg empagliflozin/5 mg linagliptin	
Pharmacokinetic characteristics	Bioequivalent to the free combination of empagliflozin and linagliptin	
Container closure system	The selected container closure system(s) must be compatible with the product and provide suitable protection over the entire shelf life.	
Drug product quality	The drug product must meet the quality targets described below, taking into account safety and efficacy.	
	Physical Attributes	Adequate appearance to ensure patient compliance and drug product differentiation, and adequate mechanical strength for bulk handling, packaging, distribution and administration. Related CQA: “Appearance”, “mechanical strength”
	Drug release	Drug release from the tablet should conform to immediate release characteristics Related CQA: “Drug release”
	Strength	The active ingredient content of the dosage units must be uniform and remain at a suitable level over the entire shelf life. Related CQA: “Identification of API”, “drug content”, “drug content uniformity”
	Purity	Impurities in the drug product must not exceed appropriate limits based on a safety assessment. Related CQA: “Degradation products”, “microbiological purity”
	Stability	The packaged drug product should be physically, chemically, and

		microbiologically stable for at least 24 months, if possible 36 months, in CZ I-IV. Related CQA: “All of the above during the entire shelf life”

The identified CQAs are appearance, identification of API, drug content, content uniformity, drug release, degradation products, microbiological purity and mechanical strength.

In addition to the quality targets defined in the QTPP, the following development goals for the design of empagliflozin / linagliptin film-coated tablets were defined:

- Possibly similar formulation to one of the two mono products
- Similar manufacturing process to one of the two mono products
- Unique shape in order to differentiate tablets from other Boehringer Ingelheim diabetes products
- Film-coating and debossing for differentiation of dosage strengths

Both empagliflozin and linagliptin are classified as a Biopharmaceutical Classification System (BCS) class III compounds (high solubility, low permeability).

The particle size of each substance is controlled in the respective active substance specification. The limits have been established during development of the mono-component products and they were shown to be suitable for Glyxambi film-coated tablets with regard to manufacturability as well as quality attributes such as content uniformity and drug release.

Linagliptin’s two polymorphic forms A and B reversibly convert into each other at room temperature. Active substance batches are either form A, form B or a mix of forms A and B. Studies have demonstrated that both polymorphic forms have the same solubility and intrinsic dissolution properties, are stable and highly soluble so that polymorphism does not affect bioavailability.

The compatibility of the two active substances was investigated using powder triturations at the extremes of a range of possible dose ratios of empagliflozin and linagliptin. There was no indication for chemical degradation of empagliflozin. Some degradation of linagliptin was observed in open containers at 40°C/75% RH. However, no tendency towards degradation of linagliptin was seen at any of the tested conditions in any formulation investigated in the course of the development.

All the excipients used in Glyxambi are of compendial grade, including those used for the film-coat, which are used as proprietary ready-to-use mixtures. They are commonly used in oral commercial pharmaceutical products and have been selected in order to achieve the desired quality attributes of the product, to support a robust manufacturing process and to meet regulatory and pharmacopoeial standards. Excipient selection was further based on the previous experience and knowledge from the development of the single entity tablets (Trajenta and Jardiance).

The compatibility of the two active substances with all excipients was investigated in binary mixtures (1:1). No degradation was observed with the excipients of the tablet core but some degradation was observed in the respective binary mixture with macrogol 6000 and the iron oxides. However these findings are considered non-critical because these excipients are part of the film-coat and are in minimal contact with the active substances. Furthermore potential interactions were not confirmed by the stability data of the finished product and are therefore not considered relevant.

The stages of formulation development were summarised. The linagliptin 5 mg tablet core formulation was used as the starting point. Based on satisfactory stress stability studies of a prototype single layer tablet, it was decided that physical separation of the two active substances was not necessary. Due to the unusual tablet shape, tablet manufacturability was investigated in a set of experiments in order to screen for influencing factors regarding tabletting behaviour and tablet properties. The investigated parameters were

moisture content of the dried granulate, magnesium stearate concentration and mixing time. The major influencing factors were identified. Briefly, ejection force is predominantly influenced by the amount of magnesium stearate; tablet hardness is mainly influenced by the loss on drying (LOD) and also partially influenced by the magnesium stearate mixing time; and disintegration is mainly influenced by the LOD and also influenced by the magnesium stearate amount and mixing time. No interactions of factors were observed. The influence of the moisture content of the granulate was further investigated. In addition, lubricant concentration and lubricant combinations were evaluated in more detail to further improve compression behaviour. The lubricant composition with the best results was selected and then the amount of disintegrant in the formulation was optimised.

To improve differentiation of the two strengths, a pale yellow and a pale pink hypromellose-based non-functional film-coat was added, in the so called *lab-scale formulation*, for the 10/5 mg and 25/5 mg tablets respectively.

At the next stage ready-to-use mixtures of the same composition were introduced instead of individual dispensing of the components, and debossing was introduced. The general manufacturing process remained unchanged. Dissolution profiles remained unchanged. Comparative dissolution profiles between tablet cores and film-coated tablets show a slightly slower dissolution within first 15 minutes for the film-coated tablets but more than 85% of both active substances was dissolved after 15 minutes. All the tablet formulations with 10/5 & 25/5 mg strengths used during different phases of clinical development have been manufactured by wet granulation process. A bioequivalence study (1275.3) was performed with the film coated formulation (*lab scale formulation*) comparing Empagliflozin / Linagliptin 25/5 mg film-coated tablets with the respective empagliflozin and linagliptin mono products. The results showed bioequivalence of the formulations. In addition, a side batch formulation of Empagliflozin / Linagliptin 25/5 mg film-coated tablets with an intended slower dissolution rate also showed bioequivalence to the lab-scale formulation and therefore dissolution was considered not critical for bioavailability. Development studies have shown that tablet hardness across a range of compression forces does not affect dissolution. Holding times for granulation liquid, ready-to-use mix for coating and maximum wet granulation processing time were evaluated. It was demonstrated that the proposed holding time does not impact the microbiological quality of the granulation liquid and coating suspension.

The production scale formulation was further optimised to assure punch/die lubrication during long-term compression at production scale. Comparative dissolution profiles between production and pilot scale batches showed no differences. This so called “production scale formulation” was eventually used in phase III clinical studies.

A dissolution test has been developed to control the CQA ‘drug release’ during development. The dissolution method was based on the solubility of the active substances (ASs), the *in-vitro* dissolution of film-coated tablets within the physiological pH range 1-6.8 (e.g. production batch), and the stability of ASs in dissolution medium. The discriminative power of the dissolution test is limited to particle size of empagliflozin and storage conditions. However, as the pharmacokinetic behaviour is expected to be primarily affected by the low permeability and not by dissolution the disintegration test will be used for routine control (see below in “*Product specification*”). In addition, it was demonstrated that disintegration was more discriminative than dissolution testing.

As described above, the formulation was designed to be similar to the linagliptin single entity product. Accordingly, the same manufacturing process technology is used. The manufacturing process is a robust standard manufacturing process consisting of high shear wet granulation, compression of tablets and film-coating of the tablet cores.

The different steps of the manufacturing process were evaluated through the use of risk assessment (QbD approach). The initial risk assessment to identify potential critical material attributes (CMA) and critical process parameters (CPP) was an informal process based on prior knowledge and the results of formulation development and early process development at lab-scale. The potential CPPs and CMAs identified were then investigated experimentally in detail at pilot scale. The investigated ranges were set to establish appropriate proven acceptable ranges (PARs) and to detect the impact of each potential CPP and CMA on the respective CQA. The ranges were not chosen to establish a design space, but to gain process knowledge for further scale-up. Set points were defined for the process parameters in full production scale to further limit variability within a range. Based on the experiments, a final risk assessment was performed. None of the process parameters was identified as critical. Particle size of both actives, microbiological quality of excipients from natural origin, loss on drying of the granulate, appearance, weight and hardness of tablet cores, appearance and weight/weight gain of film-coated tablets are CMA and controlled by IPCs at relevant points in the manufacturing process or raw material specifications. All CMAs are included in the control strategy. The proposed control strategy is found acceptable.

Glyxambi container closure system consists of push-through blister cards, composed of PVC/PVDC forming foil and aluminum lidding foil. The forming foil is a two-layer laminate with and outer polyvinyl chloride and an inner polyvinylidene chloride film. It was confirmed that the PVC/PVDC/Alu film complies with EU-Regulations No.10/2011 and No.1935/2004/EC. The PVC base film of the blister complies with European Pharmacopoeia chapter 3.1.11. It was further confirmed that the components of the heat seal lacquer for the aluminium lidding foil are listed in EU-Regulation 10/2011. The lidding foil conforms to the requirements of EU-Regulation 1935/2004.

Manufacture of the product and process controls

The manufacturing process is a standard manufacturing process comprising wet granulation of the drug substances with excipients, drying, screening of the dried granulate, pre- and final blending, subsequent compression of the final blend into tablets and finally film-coating of the tablet cores.

The in-process controls (IPCs) have been presented and are justified in relation to how the quality attributes are affected. The control strategy ensures that the manufacturing process consistently delivers a product that meets the defined criteria for all CQAs.
The maximum holding time for each of the intermediates (granulate, final blend and tablet cores) has been specified. Bulk film-coated tablets stability (see ”Stability of the product”) has been studied. It is confirmed that the shelf life of the drug product starts from the date of production and is set according to the relevant CHMP guideline (CPMP/QWP/072/96).

The manufacturing process has been validated on three consecutive production-scale batches of each strength manufactured at the intended manufacturing site. In conclusion it is considered that the manufacturing process is sufficiently robust to provide assurance that it produces finished product film-coated tablets of consistent quality, complying with the designated specification.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for: appearance (visual), identification of empagliflozin (HPLC, UV), identification of linagliptin (HPLC, UV), assay of empagliflozin and linagliptin (HPLC), degradation products of empagliflozin and linagliptin (HPLC), uniformity of dosage units of empagliflozin (Ph. Eur.), uniformity of dosage units of linagliptin (Ph. Eur.) and disintegration (Ph. Eur.).

As mentioned above, disintegration is proposed as a routine test for substitution of dissolution testing to ensure the control of the CQA 'drug release' in line with ICH Q6A, decision tree # 7. The acceptance criterion for disintegration is based on statistical evaluation of release results of clinical and the currently available stability results.

The absence of the test parameter microbial limits in the specification was justified in accordance with ICH Q6A, decision tree # 8. Based on the water activity characteristics and the release and stability data, growth inhibitory properties of the drug product were demonstrated. The omission of this parameter is further justified with upstream microbiological controls such as excipient (prone to microbial growth) controls, environmental monitoring and validated equipment holding times and with data showing that the manufacturing process does not contribute to microbial growth. The duration of wet granulation is limited to the set point and subsequently drying is directly started.

The parameter water content is not included in the specification as appropriate in-process controls are in place for loss on drying of the granulate. Batch release results demonstrate robust results for loss on drying. In addition during stability studies no relevant influence of the increase up to the equilibrium water content on the test parameters degradation and disintegration was observed at long term and open storage conditions at 25°/60% RH.

In accordance with decision tree #5 of ICH Q6A, enantiomeric purity testing is regarded irrelevant as chiral inversion of empagliflozin and linagliptin was not observed during stability testing of the active substances, and no chiral inversion of the active substance was observed in stress stability studies of the finished product.

Residual solvents are not tested because no organic solvents are used during finished product manufacture and each excipient and the active substances meet the limits per option 1 of ICH Q3C (R5).

A correlation between compression force and tablet hardness was seen during development. The IPC specification of tablet core hardness ensures the drug release from the final film-coated tablet.

The limits for the degradations products are in line with ICH Q3B(R2) and are considered justified.

The analytical methods used have been adequately described and non compendial methods have been appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the used reference standards has been presented.

Batch analysis data five commercial scale batches of both strengths and for ten lab or pilot scale development batches were presented. All batches are representative of the commercial formula and process. All batches meet the commercial specification limits.

Stability of the product

Stability data of three commercial scale batches of each strength stored under long term conditions for up to 36 months at 25 ºC / 60% RH and for six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The stability batches are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

One batch of the 10/5 mg strength showed atypical stability behaviour. This was investigated and was found to be due to a contamination with lactose during weighing, which resulted in the formation of the lactose adduct of linagliptin. It was acknowledged that this single event has no consequences for the control

strategy. It has been confirmed that measures were taken to avoid a repetition of this deviation. The stability batch was replaced by another of the same batch size.

Samples were tested according to the specifications, except for the tests of identity and uniformity of dosage units. Dissolution and microbiological quality were monitored with validated methods. The methods are deemed appropriate for their intended purpose and are stability indicating.

For all batches no relevant change was observed under long-term storage conditions at any time point investigated. At accelerated storage conditions minor changes were only observed for the test parameters disintegration, assay of linagliptin as well as degradation of linagliptin and empagliflozin. All results were in compliance with the specification. No significant trends were observed.

Stress stability studies under elevated temperature (50°C), humidity (samples were stored in open HDPE bottles for 6 months at 25°C/60 % RH, 30°C/75 % RH and 40°C/75 % RH) and a photostability study under ICH Q1B conditions were carried out on one production scale primary stability batch of each strength. All samples were subjected to test parameters proposed for routine testing. Additionally, the following test parameters were performed to support omission of these tests for routine testing: loss on drying, dissolution of empagliflozin and linagliptin, resistance to crushing and enantiomeric purity. At humidity stress conditions, water activity was tested in addition as this study is also used to demonstrate in-use stability for multi-use packaging configurations.

Under light stress conditions no change was observed in any of the parameters tested. Under elevated temperature stress a change was only observed for test parameter degradation of linagliptin. The tablets showed good stability properties under humidity stress conditions. Changes were only observed at 30 °C /75 % RH and at 40 °C /75 % RH for test parameters degradation of linagliptin and empagliflozin, assay of linagliptin, dissolution and disintegration. The changes for test parameter disintegration were more pronounced at 40 °C/ 75 % RH for both dosage strengths, albeit minimal for the 25 mg /5 mg dosage strength. The changes for test parameter dissolution were more pronounced at 40 °C/75 % RH and only for the 10 mg /5 mg dosage strength (at 3 and 6 months).

It was concluded that that the finished product is not sensitive to light and has some sensitivity to elevated temperatures and humidity. It is therefore expected that the product will be stable under in-use conditions.

One production scale batch of each strength was put on bulk stability in stainless steel containers and in polyethylene bags in hobbock. Batches were stored under warehouse conditions (15-25 °C /45-65% RH) up to 12 months. Tested parameters were description, disintegration, dissolution, degradation, assay, and microbiological quality. No relevant changes occurred. It was concluded that storage up to 12 months under warehouse conditions has not impact on the quality of the bulk drug product.

Based on the provided stability data, the proposed shelf life of 3 years is acceptable without any special storage conditions, as stated in SmPC (section 6.3).

Adventitious agents

No materials of human or animal origin are used in the manufacture of Glyxambi.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Glyxambi is a fixed dose combination product containing two known active substances which are used in other approved products. The pharmaceutical development was based on prior knowledge with those products and the results of formulation and process development for the combination product. Information on development, manufacture and control of the active substances and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical package of Glyxambi refers to the non-clinical studies conducted with the individual components empagliflozin and linagliptin that have each undergone complete nonclinical development programs.

In support of the application of Glyxambi, bridging studies were performed to support the registration of the empagliflozin/linagliptin fixed-dose combination (FDC):

- Pharmacodynamic effects of the empagliflozin/linagliptin combination were studied in a rat disease model for diabetes.
- The effect of empagliflozin on the in vitro metabolism of linagliptin and vice versa was evaluated in human hepatocytes.
- Combination toxicity studies of up to 13 weeks and combination embryo-fetal development studies were performed in the Wistar rat. In all combination toxicity studies, empagliflozin and linagliptin were tested in

clinically relevant dose ratios of 2:1 and 5:1. These rat studies were also used for pharmacokinetic investigations of the drug combination.

Furthermore, a juvenile toxicity study in rats with empagliflozin has been submitted with this application for the empagliflozin/linagliptin FDC.

2.3.2. Pharmacology

Primary pharmacodynamic studies

Empagliflozin

Empagliflozin is a selective and potent inhibitor of the human, rat and mouse glucose transporter SGLT2. Three glucuronide metabolites of empagliflozin have low affinity for SGLT2, and these therefore do not contribute to the pharmacological effect of empagliflozin. The primary pharmacodynamics effect of empagliflozin on inhibition of glucose re-uptake in the kidneys was demonstrated in mice, rats and dogs. All species showed increased urine glucose concentrations after treatment. Increased urine glucose excretion leads to lowered blood glucose concentration, as shown in diabetic $^{db/db}$mice and ZDF rats. The diabetic ZDF rat has increased glycated hemoglobin (HbA1c), which was reduced by treatment with empagliflozin.

Linagliptin

Linagliptin is a potent, selective, orally active, competitive, reversible and long-acting inhibitor of DPP-4. The main metabolite of linagliptin, CD1790, is pharmacologically inactive. DPP-4 is expressed in many tissues including kidneys, liver, intestine, lymphocytes and vascular endothelial cells. A significant level of DPP-4 activity is also observed in plasma. By inhibiting DPP-4, linagliptin prolongs and enhances activity of the incretins glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), resulting in increased glucose-dependent insulin secretion, suppression of glucagon secretion and delay of gastric emptying and thereby to the maintenance of post-meal glycemic control.

The primary pharmacodynamic effect of linagliptin on inhibition of DPP-4 activity was demonstrated in rhesus monkeys, beagle dogs and in normal and diabetic $^{db/db}$mice and ZDF rats. The results of these studies suggest that a once daily dosing frequency is adequate to maintain an appropriate degree of DPP-4 inhibition that exerts therapeutic effects on glucose. Long-term treatment of diabetic mice reduced fed plasma glucose and HbA1c after 14 and 28 days. This improved hyperglycaemia could not be explained by improved insulin sensitivity by linagliptin.

Empagliflozin plus linagliptin

Empagliflozin (3 mg/kg) in combination with linagliptin (1 mg/kg) has been tested acutely with an oral glucose tolerance test in Zucker fatty diabetes rats. Although glucose excursion, as assessed by AUC, was significantly reduced by each mono-therapy as compared to control, the combination treatment achieved a significant further reduction of glucose AUC versus control. Furthermore, the reduction in glucose AUC mediated by the combination was superior to the effect achieved by each monotherapy.

Overall, the combination of empagliflozin and linagliptin showed a superior effect on glycemic control as compared to the respective monotherapies and the two different mechanisms of action were additive in their efficacy in a rat disease model for diabetes, thus supporting the proposed fixed-dose combination application.

Secondary pharmacodynamic studies

Studies on secondary pharmacology showed that empagliflozin had an effect on body weight loss in obese rats, most likely due to a small decrease in food consumption, together with the pharmacological effect of inhibition of glucose re-uptake in the kidneys. Safety pharmacology studies showed no relevant effect on central nervous system, respiratory system, gastro-intestinal system, and cardiovascular system. Combination treatment with metformin, a sulphonylurea (glipizide), a DPP-4 inhibitor (linagliptin), a GLP-1 analog (exendin-4), an α-glucosidase inhibitor (voglibose), a PPARγ agonist (pioglitazone) and with insulin resulted in greater improvement in glucose tolerance in ZDF rats compared to each individual monotherapy.

Studies on secondary pharmacology showed that linagliptin has no off-target activity at therapeutic concentrations. Although inhibition of DPP-4 may result in decreased gastric emptying, this effect was not observed in the secondary pharmacodynamic study evaluating the effect of linagliptin on gastrointestinal function in rats. Although in-vitro cardiovascular safety studies indicated a low pro-arrhythmic potential for linagliptin, this potential was not confirmed by the results of the in vivo cardiovascular safety studies. Overall, administration of therapeutic dosages linagliptin appears to be safe for patients suffering from diabetes mellitus.

No secondary pharmacodynamic studies were conducted with the empagliflozin/linagliptin FDC. This was considered acceptable, as empagliflozin and linagliptin have different mechanisms of action and no interaction is anticipated with empagliflozin/linagliptin combination as there is sufficient knowledge about potential off-target effects of the individual compounds.

Safety pharmacology programme

There were no adverse effects in empagliflozin or linagliptin safety pharmacology studies indicative of potential human safety concerns. Therefore, evaluation of the combination in a battery of safety pharmacology studies was not conducted. The lack of safety pharmacology studies for empagliflozin/linagliptin combination is acceptable from nonclinical point of view.

Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies were conducted with the combination empagliflozin and linagliptin. The lack of non-clinical studies on the potential of the empagliflozin/linagliptin combination to interact pharmacodynamically with other drugs is acceptable; empagliflozin and linagliptin affect glucose homeostasis by different mechanisms.

2.3.3. Pharmacokinetics

Empagliflozin

Oral bioavailability of empagliflozin was high in mouse (90-97%) and dog (89%) and medium in rat (31%). The steady state volume of distribution was medium (0.6-1.2 L/kg) and binding to plasma proteins was high in all species examined (87-92%). The pharmacokinetics were linear. The elimination half-live was medium in

mouse (0.7-1.3 h), but longer in rat (3.6 h) in rat and dog (6.3 h). Tissue distribution was limited. Highest tissue concentrations were observed at 1 hour and were measured in gastrointestinal tract contents, urine and bile. Some empagliflozin-related material was found after 24 hours in the kidney, suggesting some accumulation may occur when using empagliflozin daily. Toxicokinetics showed no consistent effect of repeated dosing on plasma exposure, indicating that there was little or no accumulation. Faecal and/or biliary excretion are the most important elimination routes.

Empagliflozin crosses the placenta in rats, although at low levels. Empagliflozin may be excreted via milk with milk:plasma ratios up to 5.0 as is observed in rats.

Linagliptin

Oral bioavailability of linagliptin was moderate in mice (18-44%), rats (50%) and monkeys (69%). The steady state volume of distribution was high in all species (>5 L/kg), which suggests extensive tissue distribution. The pharmacokinetics were non-linear be due to saturation of binding to DPP-4 in plasma and tissues. During chronic use of linagliptin, steady state in tissues will be achieved quickly once DPP-4 is saturated. Maximum concentrations were seen 30 minutes post-dose for all tissues, with highest concentrations in liver and kidneys. Measurable concentrations were found 168 hours post-dose in liver, spleen, thymus, Harder´s gland, lung, salivary gland, epididymis, adrenal, skin and bone marrow. In the kidney, a significant retention was observed for the cortex region and especially for the zona intermedia. Toxicokinetic studies showed some plasma accumulation in rat and dog after repeated dosing. Therefore, only limited accumulation in tissue is expected to occur.

The binding of linagliptin to plasma proteins is high at concentrations about 1 nM (>99%). The plasma protein binding is concentration dependent, since the binding is lower (70-85%) when concentrations are about 30 nM or higher. This observed concentration-dependency was due to saturation of binding to DPP-4, which is within the plasma protein fraction. The predominant route of elimination of linagliptin is via faeces, with a minor contribution eliminated in urine (<30%). A considerable fraction of the faecally excreted linagliptin can be assigned to biliary excretion.

Linagliptin crosses the placenta barrier in rats and rabbits. Linagliptin may be excreted via milk with milk:plasma ratios up to 4.0 as is observed in rats.

Empagliflozin plus linagliptin

Single-dose dose pharmacokinetics of empagliflozin/linagliptin combination in rats showed that exposure to empagliflozin increased dose-proportionally and linagliptin more than dose-proportionally at exposures up to 10-times of the therapeutic exposure to the individual compounds when using 25 mg empagliflozin and 5 mg linagliptin as fixed combination.

Repeated-dose toxicokinetic investigations performed as part of the toxicology studies during 2-week and 13-week oral (gavage) combination toxicology studies in rats confirmed these findings. These studies also showed that, at high dose levels, linagliptin increased the exposure to empagliflozin and, vice versa, that empagliflozin decreased the exposure to linagliptin. These exposure changes were noted at high doses in rats (300 mg/60 mg empagliflozin/linagliptin), corresponding with 35- to 40-times of the therapeutic exposure to the individual compounds when using 25 mg empagliflozin and 5 mg linagliptin as fixed combination. Although a mechanistic explanation for this effect has not been provided, it is unlikely that these exposure changes are of relevance at therapeutic exposures.

Pharmacokinetic interactions of empagliflozin/linagliptin combination via plasma protein binding are not expected.

Binding to plasma proteins is high in all species examined for empagliflozin (87-92%). In human plasma, protein binding was 82-84%, and this binding was predominantly to albumin. Protein binding of empagliflozin was independent on the concentration in the range investigated, which indicates no saturation of binding sites. The concentration range (0.01-40 µg/mL) covers the plasma levels of empagliflozin at the therapeutic dose of 25 mg/5 mg of the empagliflozin/linagliptin FDC (Cmax 583 - 862 nM ≈ 0.25 - 0.4 µg/mL, report U11-1690).

The binding of linagliptin to plasma proteins is high at concentrations about 1 nM (>99%). The plasma protein binding is concentration dependent, since the binding is lower (70-85%) when concentrations are about 30 nM or higher. This observed concentration-dependency was shown to be due to saturation of binding to DPP-4, which is within the plasma protein fraction. These data indicate that plasma concentrations of DPP-4 may influence the kinetics of linagliptin. Variation in the fraction unbound of linagliptin in human plasma is expected within the clinically anticipated plasma levels (6.14 - 8.19 nM, report U11-1690). Interactions with other drugs via plasma-protein binding might occur, but are not considered clinically relevant.

Partitioning of empagliflozin into red blood cells was limited and independent of the concentration in any of the species investigated.

The blood-plasma ratio at a plasma concentration of 300 nM [14C]linagliptin was ~1 in rats and ~0.6 in dogs, monkeys and humans. At 1 nM [14C]linagliptin, the blood-plasma ratio was much lower (~0.09 in rats and ~0.05 in monkeys). This concentration dependency is probably due to the binding to plasma DPP-4. Linagliptin is mainly located in plasma, especially at therapeutic plasma levels, giving no cause to expect extensive binding to erythrocytes.

Metabolic interactions between empagliflozin and linagliptin are not expected.

The potential effect of empagliflozin on the in-vitro metabolism of linagliptin and vice versa was evaluated using human hepatocytes. Weak inhibition of total empagliflozin metabolism by human hepatocytes was observed when co-incubated with linagliptin. Calculated Ki values of an inhibition of empagliflozin metabolism by human hepatocytes by linagliptin were in the range of 8.8 to 69 µM. Based on therapeutic plasma concentrations of empagliflozin below 1 µM and of linagliptin in the low nanomolar range, mutual metabolic drug-drug interactions of empagliflozin and linagliptin due to inhibition of hepatic metabolism are unlikely to occur.

CYP enzymes do not contribute significantly to metabolism of empagliflozin. Biotransformation of empagliflozin primarily involved glucuronidation by UGT1A3, UGT1A8, UGT1A9, and UGT2B7, and to a lesser extent oxidation. The enzymes involved in the oxidative metabolism have not been identified. In addition, empagliflozin and the metabolites of empagliflozin did not induce or inhibit the major human hepatic CYP isoforms.

Linagliptin is slowly metabolised by CYP3A4 and there was no indication for a contribution of other CYP enzymes or monoamine oxidases in the metabolism of linagliptin. Linagliptin is not an inducer of CYP enzymes. The metabolism of linagliptin by human liver microsomes and human hepatocytes was very low.

Interactions via efflux transporters are unlikely. Empagliflozin is a substrate for P-gp and BCRP. Empagliflozin is not an inhibitor of P-gp and it weakly inhibits BCRP and MRP2. Linagliptin is a P-gp substrate with low affinity and it inhibited P-gp with low potency with IC50 values > 50 µM. Therefore, the likelihood of

linagliptin to inhibit P-gp at therapeutic plasma levels was considered to be low. Linagliptin is neither a substrate nor an inhibitor for BCRP and MRP2.

Empagliflozin is a substrate of human uptake transporters OAT3, OATP1B1, and OATP1B3, but not OAT1 and OCT2. Empagliflozin also inhibits OATP1B1, OATP1B3, OATP1B1B1, and OAT3; however, IC50 values ranged from 45.2 to >1000 µM, making interactions via these uptake transporters at therapeutic concentrations unlikely. Linagliptin is a substrate for SLC transporters, suggesting that OATP1B3-mediated hepatic uptake, OCT2-mediated renal uptake and OAT4-, OCTN1- and OCTN2-mediated secretion and reabsorption of linagliptin may occur *in vivo*. Linagliptin is an inhibitor of OCT1 and OATP1B1 with low affinity. No pronounced inhibition or only minor inhibition by linagliptin was observed for OATP1B3, OATP2B1, OAT1, OAT3, OAT4, OCT2, OCTN1 and OCTN2.

2.3.4. Toxicology

Empagliflozin

The single-dose toxicity of empagliflozin is low in rodents.

In repeated-dose studies in rodents and dogs, signs of toxicity were observed at exposures greater than or equal to 10-times the therapeutic dose of empagliflozin of 10 mg once daily. Most toxicity findings were considered to be secondary to the pharmacologically mediated urinary glucose loss and electrolyte imbalance. The kidneys and liver were the principal target organs of toxicity. The effects on the kidney included increased organ weight in mice, rats and dogs, histopathology changes of the tubular system in rats (tubular dilation) and dogs (cortical tubular nephropathy) and tubular and pelvic mineralization in rats at approximately 4-times the clinical AUC exposure. of empagliflozin associated with the 25 mg dose. The effects on the liver included increased organ weight (due to hydropic changes possibly due to electrolyte imbalance), accompanied by microvesicular hepatocellular vacuolation (as a result of lipid mobilization) and foci of hepatocellular necrosis at a low incidence. These effects were observed in mice and rats. In dogs, the effects on the liver consisted of centrilobular degeneration characterized by microvesicular vacuolation of centrilobular hepatocytes that may have been associated with loss of hepatocytes. Increases in liver enzymes were small in mice, rats and dogs.

Other target organs of empagliflozin included the pancreas in rats (zymogen depletion), thyroid in rats (minimal follicular cell hypertrophy), and adrenals in rats (increased weight, vacuolation of the zona glomerulosa) and dogs (vacuolation of the zona glomerulosa). The effects are not considered to be adverse. Depletion of zymogen granules in the pancreas is considered secondary to the increased food consumption and decreased body weight. Follicular cell hypertrophy of the thyroid seems not to be relevant for human, since it was minimal in severity and not observed in mice or dogs. Vacuolation of the zona glomerulosa in adrenals. Considering that empagliflozin will reduce sodium reabsorption by SGLT2 (and SGLT1 (in the rat)) inhibition, the observed effects in the zona glomerulosa may reflect an adaptive response to reduced sodium levels triggering increased aldosterone synthesis.

Empagliflozin was not genotoxic.

Empagliflozin did not increase the incidence of tumours in female rats up to the highest dose of 700 mg/kg/day, which corresponds to approximately 72 times the maximal clinical AUC exposure to

empagliflozin. In male rats, treatment-related benign vascular proliferative lesions (haemangiomas) of the mesenteric lymph node were observed at the highest dose, but not at 300 mg/kg/day, which corresponds to approximately 26 times the clinical exposure to empagliflozin. Interstitial cell tumours in the testes were observed with a higher incidence in rats at 300 mg/kg/day and above, but not at 100 mg/kg/day which corresponds to 18 times the maximal clinical exposure to empagliflozin. Both tumours are common in rats and are unlikely to be relevant to humans.

Empagliflozin did not increase the incidence of tumours in female mice at doses up to 1000 mg/kg/day, which corresponds to 62 times the maximal clinical exposure to empagliflozin. Empagliflozin induced renal tumours in male mice at 1000 mg/kg/day, but not at 300 mg/kg/day, which corresponds to approximately 11 times the maximal clinical exposure to empagliflozin. The mode of action for these tumours is dependent on the natural predisposition of the male mouse to renal pathology and a metabolic pathway not reflective of humans. The male mouse renal tumours are considered not relevant to humans.

Empagliflozin crosses the placenta in rats at low levels. At exposures sufficiently in excess of exposure in humans after therapeutic doses, empagliflozin had no adverse effects on fertility or early embryonic development. Empagliflozin administered during the period of organogenesis was not teratogenic. Only at maternally toxic doses, empagliflozin also caused bent limb bones in the rat and increased embryofetal loss in the rabbit.

Empagliflozin may be excreted via milk with milk:plasma ratios up to 5.0 as is observed in rats.

In pre- and postnatal toxicity studies in rats, reduced weight gain of offspring was observed at maternal exposures approximately 4-times the maximal clinical exposure to empagliflozin. No such effect was seen at systemic exposure equal to the maximal clinical exposure to empagliflozin. The relevance of this finding to humans is unclear.

Empagliflozin was assessed in a dermal sensitization test in mice and dermal and ocular irritation tests in rabbits and was found to be negative in all tests.

Linagliptin

The toxicity profile of linagliptin has been established as part of the MAA for Trajenta.

These data showed that the single-dose toxicity of linagliptin is low in rodents.

In repeated-dose studies in mice and rats, the liver, kidneys and gastrointestinal tract are the principal target organs of toxicity at 300 times the human exposure at therapeutic dose of 5 mg once daily.

In rats effects on reproductive organs, thyroid and the lymphoid organs were seen at more than 1500 times human exposure. Strong pseudo-allergic reactions were observed in dogs at medium doses, secondarily causing cardiovascular changes, which were considered dog-specific. Liver, kidneys, stomach, reproductive organs, thymus, spleen, and lymph nodes were target organs of toxicity in Cynomolgus monkeys at more than 450 times human exposure. At more than 100 times human exposure, irritation of the stomach was the major finding in these monkeys.

Linagliptin and its main metabolite were not genotoxic.

Oral 2 year carcinogenicity studies in rats and mice revealed no evidence of carcinogenicity in rats or male mice. A significantly higher incidence of malignant lymphomas only in female mice at the highest dose (> 200 times human exposure) is not considered relevant for humans (explanation: non-treatment related but

due to highly variable background incidence). Based on these studies there is no concern for carcinogenicity in humans.

Linagliptin crosses the placenta in rats and rabbits. In addition, linagliptin may be excreted via milk with milk:plasma ratios up to 4.0 as is observed in rats.

The NOAEL for fertility, early embryonic development and teratogenicity in rats was set at >900 times the human exposure. The NOAEL for maternal-, embryo-fetal-, and offspring toxicity in rats was 49 times human exposure. No teratogenic effects were observed in rabbits at >1000 times human exposure. A NOAEL of 78 times human exposure was derived for embryo-fetal toxicity in rabbits, and for maternal toxicity the NOAEL was 2.1 times human exposure. Therefore, it is considered unlikely that linagliptin affects reproduction at therapeutic exposures in humans.

In-vitro and *in-vivo* studies showed that linagliptin is well tolerated locally.

Empagliflozin plus linagliptin

Single dose toxicity

No single-dose toxicity studies have been performed the empagliflozin/linagliptin FDC. Such studies are not needed since available information in rodents showed that the acute toxicity of empagliflozin and linagliptin is low.

Repeated dose toxicity

The adverse effects of the empagliflozin/linagliptin FDC was studied in a 2-week and 13-week repeated-dose toxicity study in rats were tested in clinical relevant dose ratios of 2:1 and 5:1, respectively.

The target organs of toxicity of empagliflozin and linagliptin are known. New target organs of toxicity were not identified for the empagliflozin/linagliptin FDC. The NOAEL was 100/50 mg/kg/day in the 2-week study and 100/20 mg/kg/day in the 13-week study. These NOAEL values, respectively, correspond with exposures equal to or greater than 10- times of the therapeutic exposure to the individual compounds when using 25 mg empagliflozin and 5 mg linagliptin as FDC.

Most toxicity at higher doses was consistent with secondary pharmacology of empagliflozin, but was enhanced by co-administration of linagliptin. The effects were related to urinary glucose loss and electrolyte imbalances and included decreased body weight and body fat, increased food consumption, diarrhoea, dehydration, decreased serum glucose and increases in other serum parameters reflective of increased protein metabolism and gluconeogenesis, urinary changes such as polyuria and glucosuria, and microscopic changes including mineralisation in kidney and some soft and vascular tissues. Microscopic evidence of the effects of exaggerated pharmacology on the kidney observed in some species included tubular dilatation, and tubular and pelvic mineralisation at approximately 4-times the therapeutic exposure associated with the 25 mg dose empagliflozin.

In the 13 week repeat dose toxicity study conducted in rats with the empagliflozin/linagliptin combination, there was an increase of urine ketone bodies in the combination group as well as in the group given empagliflozin alone as compared to the vehicle control group or the group given linagliptin alone. This

increase of urine ketone bodies after administration of high dosages (≥300 mg/kg/day) of empagliflozin to rats is considered to reflect the metabolic changes due to strong glucose loss and decreased body weight gain. A 13 fold safety margin based on exposure ratio was set at the NOEL of 100 mg/kg.

Test item-related histopathological changes were noted for kidneys, thymus, adrenal glands and pancreas. The changes were considered either secondary (kidneys and pancreas) or related to impaired metabolic homeostasis (thymus and adrenal glands). Based on increases of hepatic enzyme activities noted after repeated administration of 300 mg/kg empagliflozin either alone or in combination with linagliptin, the principal target organ identified was the liver.

Focal areas of hepatocellular necrosis were found in the combination groups at ≥15:30 mg/kg linagliptin: empagliflozin (3.8 times the clinical exposure for linagliptin and 7.8 times the clinical exposure for empagliflozin) as well as in the group treated with empagliflozin alone at high dose.The incidental nature of the focal hepatocellular necrosis observed in the rats given the fixed dose combination could not be ascertained and this non-clinical finding has been described under section 5.3 of the SmPC.

Hyperplasia of ovarian stromal interstitial cells observed in the 13-week fixed-dose combination study in rats given ≥100 mg/kg empagliflozin with or without linagliptin was of low severity. Considering that studies performed with empagliflozin alone at doses up to 700 mg/kg did not reveal ovarian neoplastic change and showed no adverse effect on fertility and reproductive organs, this finding is considered incidental of no clinical relevance.

Genotoxicity

No genotoxicity studies have been conducted with the empagliflozin/linagliptin FDC. Individually, neither linagliptin nor empagliflozin was shown to be genotoxic. Therefore, additional genotoxicity studies are considered unwarranted.

Carcinogenicity

No carcinogenicity studies have been conducted with the empagliflozin/linagliptin FDC. As the carcinogenic potential of each individual compound has been fully characterised and because toxicology combination studies up to 13 weeks did not show evidence for additive toxicity or additional target organs of toxicity, this is considered acceptable.

Reproduction toxicity

Embryofoetal developmental toxicity studies were previously conducted in the rat and in the rabbit with empagliflozin and linagliptin as individual compounds. In the combination embryo-fetal development studies in rats, empagliflozin and linagliptin were tested in clinical relevant dose ratios of 2:1 and 5:1. Embryo-fetal toxicity was only seen in high dose combination Group 4 (700 mg/kg empagliflozin combined with 140 mg/kg linagliptin) as a slightly delayed development secondary to maternal toxicity. Combination effects were restricted to reduced terminal body weight. The safety margins calculated from the derived NOAEL (Group 3: 300 mg/kg empagliflozin combined with 60 mg/kg linagliptin) are 99 times the clinical plasma AUC exposure for empagliflozin and 227 times the clinical plasma AUC exposure for linagliptin.

Juvenile toxicity

The toxicity of the empagliflozin/linagliptin FDC has not been studied in juvenile animals. This is acceptable since the empagliflozin/linagliptin FDC is only indicated for adolescents older than 18 years and adults.

Toxicokinetic data

See section 2.3.3. Pharmacokinetics.

Local tolerance

The empagliflozin/linagliptin FDC has not been tested for local tolerance. This is acceptable, because the FDC is only intended for oral use.

Other toxicity studies

The empagliflozin/linagliptin FDC has not been tested for phototoxicity, since there are no indications that the individual components have phototoxic potential.

The empagliflozin/linagliptin combination is not considered to show an immunotoxic potential based on the information for each compound separately and the absence of an effect on the lymphoid tissues in the 13-week combination study with empagliflozin/linagliptin in the rat.

The combination of empagliflozin and linagliptin into a single tablet has not been associated with new impurities or degradation products. For this reason, no additional studies on impurities are needed.

2.3.5. Ecotoxicity / environmental risk assessment

Empagliflozin

In their environmental risk assessment, the applicant indicates that the environmental risk assessment of the active ingredient empagliflozin is equal for the product Glyxambi to the ERA for Jardiance 25 mg filmomhulde tabletten (registration number: EU/1/14/930).

Since in both procedures the dosage is equal, and the default Fpen is used for PEC calculations, the result of the ERA for Jardiance is equal to that of the current fixed-dose combination product. Thus, the same conclusions apply to the ERA for Glyxambi.

The evaluation of the ERA for empagliflozin was concluded as follows:

- Empagliflozin is considered not to be PBT, nor vPvB.
- No risk is identified for the STP, surface water, groundwater and sediment compartment.

Summary of main study results

Substance (INN / Invented Name): Empagliflozin			
CAS-number (if available): 864070-44-0			
PBT screening		Result	**Conclusion**
Bioaccumulation potential – log K_{ow}	OECD107	Log K_{ow} = 1.73	Potential PBT: No
PBT-assessment			

Parameter	Result relevant for conclusion				Conclusion
Bioaccumulation	log K_{ow}	Log K_{ow} = 1.73			not B
Persistence	ready biodegradability	not readily biodegradable			
	DT50 parent	$DT_{50, water}$ = 2.3/2.1 d (r/p) $DT_{50, sediment}$ = 4.9/3.6 d (r/p) $DT_{50, whole system}$ = 2.5/2.5 d (r/p)			r=river, p=pond, DT50 values corrected to 12°C; Conclusion: not P
	DT50 metabolite M3	$DT_{50, sediment}$ = 169/125 (r/p)			DT50 values corrected to 12°C. Conclusion: P
Toxicity	NOEC	2.4 mg/L			not T
	CMR	not investigated			potentially T
PBT-statement	empagliflozin is considered not PBT, nor vPvB empaglifozin forms a persistent metabolite (M3)				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
PEC $_{surfacewater}$, default F_{pen}	0.125	µg/L			> 0.01 threshold
Other concerns (e.g. chemical class)					No
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	K_{oc} = 51.5 L/kg			Mean of 49 and 54 L/kg for WWTP sludge.
Ready Biodegradability Test	OECD 301B	Not readily biodegradable			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308 parent	$DT_{50, water}$ = 1.2/1.1 d (r/p) $DT_{50, sediment}$ = 2.6/1.9 d (r/p) $DT_{50, whole system}$ = 1.3/1.3 d (r/p) shifting to sediment = 26.4/25.0% (r/p)			r = river, p = pond, DT50 values at 20°C; Significant shifting to sediment observed
	OECD 308 metabolite M3	$DT_{50, sediment}$ = 88.9/66.0 d (r/p)			DT50 values at 20°C
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test / *Pseudokirchneriella subcaptitat*	OECD 201	NOEC	≥ 100	mg/L	
Daphnia sp. Reproduction Test	OECD 211	NOEC	≥ 100	mg/L	
Fish, Early Life Stage Toxicity Test / *Danio rerio*	OECD 210	NOEC	2.4	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	NOEC	≥ 100	mg/L	
Phase IIb Studies					
Sediment dwelling organism / *Chironomus riparius*	OECD 218	NOEC	1011	mg/kg	normalised to 10% o.c.

Linagliptin

In their environmental risk assessment, the applicant indicates that the ERA of the active ingredient linagliptin is equal for the product Glyxambi to the ERA for Trajenta 5 mg filmomhulde tabletten (registration number: EU/1/11/707).

Since in both procedures the dosage is equal, and the default Fpen is used for PEC calculations, the result of the ERA for Trajenta is equal to that of the current fixed-dose combination product. Thus, the same conclusions apply to the ERA for Glyxambi.

The evaluation of the ERA for linagliptin was concluded as follows:

- Linagliptin is considered not to be PBT, nor vPvB.
- No risk is identified for the STP, surface water, groundwater and sediment compartment.

Summary of main study results

Substance (INN/Invented Name): Linagliptin					
CAS-number (if available): 668270-12-0					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD122	log K_{ow} = 1.7 (undissociated compound)			Potential PBT: No
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	log K_{ow} = 1.7 (undissociated compound)			not B
	BCF	-			
Persistence	ready biodegradability	not readily biodegradable			
	DT50	$DT_{50, water}$ = 1.7/2.3d (r/p) $DT_{50, sediment}$ = 234/90d (r/p) $DT_{50, whole system}$ = 11/3.4d (r/p)			r=river, p=pond, DT50 values corrected to 12°C; Conclusion: vP
Toxicity	NOEC	3.2 mg/L			not T
	CMR	not investigated			potentially T
PBT-statement :	The compound is not considered as PBT nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, default	0.025	µg/L			> 0.01 threshold
Other concerns (e.g. chemical class)					N
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	$K_{oc, soil}$ = 19234 L/kg $K_{oc, sludge}$ = 726 L/kg			Mean of 19885, 35627 and 2192 L/kg for soil. Mean of 1211 and 241 L/kg for sludge.
Ready Biodegradability Test	OECD 301A	Not ready biodegradable (0% in 28 days)			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = 0.8/1.1d (r/p) $DT_{50, sediment}$ = 110/42.2d (r/p) $DT_{50, whole system}$ = 5.2/1.6d (r/p) Shifting to sediment = 50.9% (r), 72.4% (p) at day 100			r = river, p = pond, DT50 values at 20°C; Significant shifting to sediment observed
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test (*Pseudokirchneriella subcapitata*)	OECD 201	NOEC EC50 NOEC EC50	4.1 16 4.1 49	mg/L mg/L mg/L mg/L	Based on yield Based on yield Based on growth rate Based on growth rate
Daphnia sp. Reproduction Test	OECD 211	NOEC	3.2	mg/L	
Fish, Early Life Stage Toxicity Test/*Brachydanio rerio*	OECD 210	NOEC	12.0	mg/L	
Activated Sludge, Respiration Inhibition Test	OECD 209	EC50 NOEC	792 210	mg/L mg/L	
Phase IIb Studies					
Bioaccumulation	OECD 305	BCF	-	L/kg	%lipids:

Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$	-		for all 4 soils
Soil Micro organisms: Nitrogen Transformation Test	OECD 216	%effect	-	mg/kg	
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	-	mg/kg	
Earthworm, Acute Toxicity Tests	OECD 207	NOEC	-	mg/kg	
Collembola, Reproduction Test	ISO 11267	NOEC	-	mg/kg	
Sediment dwelling organism (*Chironomus riparius*)	OECD 218	NOEC	125	mg/kg	TOC =2.2%

2.3.6. Discussion on non-clinical aspects

The non-clinical package of Glyxambi refers to the non-clinical studies conducted with the individual components empagliflozin and linagliptin that each has undergone complete nonclinical development programs. These nonclinical studies were performed as part of the marketing authorization application for Jardiance and Trajenta to address the pharmacodynamic, pharmacokinetic and toxicology of these substances.

In support of the application of Glyxambi, bridging studies were performed to support the registration of the empagliflozin/linagliptin FDC:

- Pharmacodynamic effects of the empagliflozin/linagliptin combination were studied in a rat disease model for diabetes.
- The effect of empagliflozin on the in vitro metabolism of linagliptin and vice versa was evaluated in human hepatocytes.
- Combination toxicity studies of up to 13 weeks and combination embryo-fetal development studies were performed in the Wistar rat. In all combination toxicity studies, empagliflozin and linagliptin were tested in clinical relevant dose ratios of 2:1 and 5:1. These rat studies were also used for pharmacokinetic investigations of the drug combination.

New target organs of toxicity were not identified. The NOAEL was 100/50 mg/kg/day in the 2-week study and 100/20 mg/kg/day in the 13-week study. These NOAEL values, respectively, correspond with exposures equal to or greater than 10- times of the therapeutic exposure to the individual compounds when using 25 mg empagliflozin and 5 mg linagliptin as FDC. Most toxicity at higher doses was consistent with secondary pharmacology of empagliflozin, but was enhanced by co-administration of linagliptin. The effects were related to urinary glucose loss and electrolyte imbalances and included decreased body weight and body fat, increased food consumption, diarrhoea, dehydration, decreased serum glucose and increases in other serum parameters reflective of increased protein metabolism and gluconeogenesis, urinary changes such as polyuria and glucosuria, and microscopic changes including mineralisation in kidney and some soft and vascular tissues. Microscopic evidence of the effects of exaggerated pharmacology on the kidney observed in some species included tubular dilatation, and tubular and pelvic mineralisation at approximately 4-times the therapeutic exposure associated with the 25 mg dose empagliflozin.

Additional pharmacodynamic, safety pharmacology or pharmacokinetic studies were not conducted with the FDC combination. This is acceptable and in line with the Guideline on the non-clinical development of fixed combinations of medicinal products (EMEA/CHMP/SWP/258498/2005).

A juvenile toxicity study in rats with empagliflozin has been submitted with this application for the empagliflozin/linagliptin FDC. The results showed a minimal to mild renal tubular and pelvic dilation at 100 mg/kg/day, which approximates 11 times the maximum clinical dose of 25 mg. These findings were absent after a 13 weeks drug-free recovery period. This information has been added to the section 5.3 of the SmPC.

Empagliflozin and linagliptin are already used in existing marketed products Jardiance and Trajenta. The environmental risk assessment of these products does not anticipate a significant increase in environmental exposure.

Since the dosages have not been changed, and the default Fpen is used for PEC calculations, the results of the environmental risk assessments for Jardiance and Trajenta can be used for the current fixed-dose combination product. Thus, the same conclusions apply to the environmental risk assessment for Glyxambi.

The evaluations of the environmental risk assessments for empagliflozin and linagliptin were concluded as follows:

- Empagliflozin and linagliptin is considered not to be PBT, nor vPvB.
- No risk is identified for the STP, surface water, groundwater and sediment compartment.

2.3.7. Conclusion on the non-clinical aspects

From non-clinical data, no safety concerns for the empagliflozin/ linagliptin FDC were identified.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

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

- Tabular overview of clinical studies

The Glyxambi film coated tablet is a fixed dose combination tablet with two orally active glucose lowering agents for the treatment of patients with type 2 diabetes. Two dose strengths have been developed for the empagliflozin/linagliptin FDC: 10 mg/5 mg and 25 mg/5 mg once-daily.

The individual components of the fixed dose combination are already licensed in the EU via a centralised procedure. Empagliflozin is licensed as Jardiance 10 mg and 25 mg tablet (EMEA/H/C/002677/0000) and Linagliptin is licensed as Trajenta 5mg tablet (EMEA/H/C/002110/0000).

During the clinical development programme for the FDC empagliflozin/ linagliptin two phase I studies were conducted analysing the combined administration of empagliflozin and linagliptin: the drug-drug interaction study 1245.30 and the relative bioavailability study 1275.3. These studies have been submitted as part of the application procedure of Jardiance (empagliflozine) EMEA/H/C/002677/0000. Further the following clinical studies were conducted:

Table 2 Overview of the Phase III clinical studies included in the evaluation of efficacy and safety

Study	Short description of study design and analysis strategy	No. of patients [1]
Add-on studies[2]		
1275.9 *(met+lina5)*	16 weeks of open-label treatment with the DPP-4 inhibitor lina 5 on metformin background therapy,	606 (open-label)
	24 weeks of double-blind treatment, empa[3] vs. placebo, add-on therapy to the DPP-4 inhibitor lina 5 and metformin background therapy	332 (double-blind)
1275.10 *(met+empa25)*	16 weeks of open-label treatment with the SGLT-2 inhibitor empa 25 on metformin background therapy,	354 (open-label)
	24 weeks of 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 of open-label treatment with the SGLT-2 inhibitor empa 10 on metformin background therapy,	352 (open-label)
	24 weeks of double-blind treatment, lina[3] vs. placebo, add-on to the SGLT-2 inhibitor empa 10 and metformin background therapy	254 (double-blind)
Factorial design study		
1275.1 *(met)*	52 weeks of double-blind treatment	686
	empa/lina FDCs[3] vs. individual components[4] on metformin background therapy	
	primary analysis at Week 24, exploratory analyses at Week 52	
1275.1 *(naïve)*	52 weeks of double-blind treatment	677
	empa/lina FDCs[3] vs. individual components[4] in drug-naïve patients	
	primary analysis at Week 24, exploratory analyses at Week 52	

[1]Treated patients

[2]Patients who met the HbA_{1c} inclusion criterion (HbA_{1c} values between 7.0 and 10.5%) after 16 weeks of open-label treatment with empagliflozin or linagliptin on a metformin background entered a double-blind treatment period.

[3]Administered as FDC empa 25/lina 5 or FDC empa 10/lina 5

[4]Empa 25, or empa 10, or lina 5; each FDC dose was compared to lina 5 and its corresponding empagliflozin dose

2.4.2. Pharmacokinetics

The pharmacokinetics of empagliflozin and linagliptin have been extensively characterized in healthy subjects and patients with type 2 diabetes in procedures EMEA/H/C/002677/0000 and EMEA/H/C/002110/0000. In this report the results and conclusions of the pharmacokinetic studies submitted in these procedures are shortly summarised. The applicant has submitted two additional pharmacokinetic studies (Study 1245.30 and 1275.3) for the application of the FDC empagliflozin/ linagliptin these are discussed in detail.

Methodology Study 1245.30 and 1275.3

The bioanalytical methods for the analysis of empagliflozin in plasma (method 1217) and (method 1216) linagliptin in plasma (method U07-1535) and urine (method HB-06-038) are suitable and have been validated according to the current standards and according to the EMA guideline on bioanalytical method validation. The main characteristics essential to ensure the acceptability of the performance and the reliability of the analytical methods have been established. The finally accepted methods and the validation procedures were appropriately described with respect to sample collection, storage conditions, preparation of samples, standards, QC samples, ISR data and calculations.

PK parameters of empagliflozin and linagliptin were calculated using non compartmental techniques using WinNonlin software. In the BE study1275.3 C_{max} and AUC_{0-72} were analysed as primary parameters and in the DDI study 1245.30 the steady state pharmacokinetic parameters $C_{max\ ss}$ and $AUC_{\tau,ss}$ were determined as primary parameter. In both pharmacokinetic studies the statistical model was an analysis of variance model (ANOVA) on log-transformed parameters including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. Descriptive statistics were calculated for all other parameters using SASTM (version 9.2, by SAS Institute Inc., Cary, NC, USA).

Absorption and bioavailability

After oral administration empagliflozin and linagliptin are both rapidly absorbed with peak plasma concentrations reached at a median t_{max} of 1.5 hours after dosing. Based on the result of an ADME study with empagliflozin it is assumed that about 60% of the dose is absorbed. Linagliptin had an absolute bioavailability of approximately 30%. Empagliflozin and linagliptin can both be classified as BCS class 3 drugs.

The steady state mean plasma AUC_{tau} and C_{max} were 1870 nmol*h/L and 259 nmol/L with empagliflozin 10 once daily treatment and 4740 nmol*h/L and 687 nmol/L with empagloflozin 25 once daily treatment.

The steady state plasma AUC_{tau} and C_{max} concentrations were 153nmol*hr/L and 12.9 nmol/L for linagliptin 5mg once daily for 7 days.

Although both active substances can be safely administered with food, a small food effect has been reported for empagliflozin and linagliptin. Administration of empagliflozin 25 mg tablet after intake of a high-fat, high-caloric meal resulted in slightly lower exposure than after its administration without food; AUC decreased by about 16% and C_{max} by about 37% compared to the fasted condition. A high fat meal had had no influence on Linagliptin AUC0-72h but prolonged the t_{max} by 2 hours and lowered C_{max} by 15%.

Bioequivalence study 1275.3

In study 1275.3 the relative bioavailability of two different FDC tablets containing empagliflozin 25mg and linagliptin 5 mg (formulation A1 and A3) in comparison with its mono-components was investigated in 42 healthy male and female volunteers. In this study the effect of food on the FDC tablets was characterized as well.

The subjects received the following treatments:

Treatment A	FDC A1 tablet (formulation with normal dissolution)	42 subjects
Treatment B	Empagliflozin and linagliptin individual tablets	40 subjects
Treatment C	FDC A1 tablet, fed conditions (high-fat, high-caloric meal)	18 subjects
Treatment D	FDC A3 tablet(slow dissolving formulation)	24 subjects

The FDC A1 tablet is the formulation that has been used in the clinical trials and is considered representative for the commercial formulation.

The results of the relative bioavailability analyses for the primary parameters of Empagliflozin and linagliptin are presented in the Table 3. Bioequivalence between the FDC empagliflozin /linagliptin tablet 25mg/5mg A1 tablet is bioequivalent and the coadministered individual components has been shown.

Table 3 Comparison FDC A1 tablet (N=42) vs. individual tablets (N=40)

	gMean		Two-sided 90% confidence interval			
	Treatment A FDC A1 tablet fasted	Treatment B Individual tablets fasted	gMean ratio (A/B) [%]	Lower limit [%]	Upper limit [%]	gCV [%]
Empagliflozin						
AUC0-tz (nmol*h/L)	5990	5720	104.9	102.1	107.8	7.2
Cmax (nmol/L)	862	803	107.7	101.7	114.0	15.3
Linagliptin						
AUC0-72 nmol*h/L)	264	250	104.9	100.0	110.1	12.8
Cmax (nmol/L)	8.19	7.49	109.7	99.6	120.8	26.2

The company has analysed the effect of food on the pharmacokinetics of the FDC A1 tablet (Table 4). Food resulted in no change in the overall exposure of empagliflozin or linagliptin and a decrease of the peak exposure by 39.0% and 32.0% for empagliflozin and linagliptin, respectively. These results are in line with the food effect observed for the mono component tablets and therefore the food effect is not considered to be clinically relevant.

Table 4 Effect of food on the FDC A1 tablet fasted (N=42) vs fed (N=18)

	gMean		Two-sided 90% confidence interval			
	Treatment C FDC A1 fed	Treatment A FDC A1 fasted	gMean ratio (A/B) [%]	Lower limit [%]	Upper limit [%]	gCV [%]
Empagliflozin						
AUC0-tz (nmol*h/L)	5400	5990	85.3	80.8	90.1	9.4
Cmax (nmol/L)	583	862	61.4	54.1	69.7	22.0
Linagliptin						
AUC0-72 nmol*h/L)	250	264	91.0	84.2	98.2	13.2
Cmax (nmol/L)	6.14	8.19	68.5	58.6	80.0	27.2

The company also evaluated influence of different dissolution characteristics if the formulations on the bioavailability of both active substances, the results for the primary pharmacokinetic parameters and the median tmax are provided in Table 5. Based on these results it can be concluded that the dissolution rate of the tablet is not relevant for the absorption and bioavailability of both active substances. Therefore dissolution is not considered a rate limiting step for the absorption of the tablet.

Table 5 Comparison formulation normal dissolution (FDC A1(N=42)) vs slow dissolution (FDC A3 (N=24))

	gMean		Two-sided 90% confidence interval			
	Treatment D FDC A3 fasted	Treatment A FDC A1 fasted	gMean ratio (A/B) [%]	Lower limit [%]	Upper limit [%]	gCV [%]
Empagliflozin						
AUC0-tz (nmol*h/L)	5490	5990	95.7	91.2	100.4	9.8
Cmax (nmol/L)	787	862	98.0	92.0	104.5	13.0
Tmax	1.50	1.50				

Linagliptin						
AUC0-72 nmol*h/L)	247	264	96.4	89.8	103.4	14.3
Cmax (nmol/L)	7.93	8.19	103.7	92.9	115.7	22.4
Tmax	1.50	1.50				

Distribution

Empagliflozin has an apparent steady-state volume of distribution of about 73.8 L. Following administration of an oral [14C]-empagliflozin solution, the red blood cell partitioning was about 37.0% and plasma protein binding was 86.0%.

After single oral administration of 5 mg linagliptin the apparent volume of distribution, Vz/F was approximately 12700 L. Plasma protein binding of linagliptin in human plasma is concentration-dependent, decreasing from 98.8% at 2 nM to 75.0-89.0% at concentrations ≥ 30 nmol/L M. This is probably reflecting the saturation of binding to DPP-4 with increasing concentrations of linagliptin. As a result, linagliptin shows non-linear distribution kinetics.

Empagliflozin Linagliptin10/5mg FDC

No Pharmacokinetic studies with the lower empagliflozin/linagliptin dose of 10mg/5mg were performed.

The applicant justified that a bioavailability study 1275.3 with the highest dose strength FDC empagliflozin/linagliptin 25/5 tablet can be regarded as sufficient and can be extrapolated to FDC empagliflozin/linagliptin 10/5 for the following reasons:

- both analytes have been characterised as BCS class 3 drugs. As permeability for those is regarded as the rate limiting step for absorption, differences in formulation are not expected to have a major impact on bioavailability. This was confirmed by the results for the slow dissolution side batch included in study 1275.3, which was bioequivalent to the final formulation FDC;
- empagliflozin shows linear pharmacokinetics, which supports waiving the lower FDC strength and the use of the highest FDC strength in the relative bioavailability study;
- the dissolution profiles of the 2 FDC strengths are similar for both empagliflozin and linagliptin;
- neither of the 2 drugs can be classified as narrow therapeutic index drugs;
- both FDC strengths were used in the Phase III studies and were found to be both efficacious and safe.

The applicant's justification for not performing pharmacokinetic studies with the lower empagliflozin/ linagliptin dose of 10mg/5mg can be accepted, although it should be noted that the conditions for the extrapolation of the conclusions obtained with Study 1275.3 to the 10/5 mg were not strictly fulfilled because the composition of the strengths is not quantitatively proportional and no comparative dissolution profiles between the biobatch and the 10/5mg strength at pH 1.2, 4.5 and 6.8 have been provided. However, as no bridging study was deemed necessary for this application and in view of the reasons listed above, the extrapolation to the 10/5 mg strength is not considered to be an issue.

Elimination

In humans, unchanged empagliflozin is the most abundant drug-related component in plasma (75.5 - 77.4% of total radioactivity). Metabolism thus represents a minor elimination pathway for empagliflozin. Empagliflozin biotransformation primarily involved glucuronidation via UGT2B7, UGT1A3, UGT1A8, and UGT1A9. Following administration of an oral [14C]-empagliflozin solution to healthy volunteers, the drug-related radioactivity was eliminated in faeces (41.0%) or urine (54.0%). The majority of drug-related radioactivity recovered in faeces was unchanged parent drug. Empagliflozin has an apparent terminal elimination half-life of 12.4 hours and apparent oral clearance was 10.6 L/hour.

After an oral dose of 5 mg linagliptin, plasma concentrations decline in at least a bi-phasic manner with a long terminal half-life (up to 200 hours). This is assumed to be related to the tight binding of linagliptin to DPP-4 and the slow dissociation of the linagliptin-DPP-4 complex. The accumulation half-life of linagliptin, as determined from accumulation after oral administration of multiple doses of 5 mg linagliptin, is 11.4 hours. Linagliptin shows a dose–dependent apparent total clearance at steady-state. After repeated oral administration of a 5 mg dose CL/F,ss is 1120 mL/min and renal clearance was
70 mL/min. Metabolism represents a minor elimination pathway for linagliptin. In the ADME trial with oral [14C]-linagliptin all metabolites contributed to less than 10% of the excreted radioactivity. In plasma, CD 1790 was identified as major metabolite with 16.9% of sample radioactivity in pooled samples after oral administration. Other metabolites found in humans showed exposure levels well below 10% of linagliptin plasma exposure. Linagliptin is metabolised mainly by CYP3A4. The parent compound was mainly excreted unchanged in urine and faeces.

No additional studies with the FDC were conducted.

Dose proportionality and time dependencies

Empagliflozin demonstrates approximately linear pharmacokinetics and no unexpected accumulation occurs after multiple dosing of empagliflozin. Linagliptin AUCss and Cmax,ss increased less than proportionally with dose after multiple dose administration of single tablets with dose strengths of 1 mg, 2.5 mg, and 5 mg. This is of minor importance as only the 5 mg tablet is marketed.

Special populations

Empagliflozin and linagliptin both display similar pharmacokinetics between T2DM patients and healthy subjects. This is probably also applicable for the FDC tablet.

No dose adjustment for empagliflozin or linagliptin is required on the basis of renal or hepatic impairment, BMI, gender, race, or age.

In patients with mild, moderate, severe renal impairment, and with kidney failure/end-stage renal disease (ESRD), the AUC of empagliflozin was higher by 18.0%, 20.0%, 66.0%, and 48.0% than the corresponding AUC value in subjects with normal renal function. Also, population pharmacokinetic analysis showed that the apparent oral clearance of empagliflozin decreased with a decrease in eGFR, leading to an increase in drug exposure.

In subjects with mild, moderate, and severe hepatic impairment according to the Child-Pugh classification, the AUC of empagliflozin increased by 23.0%, 47.0%, and 75.0%, while Cmax increased by 4.0%, 23.0%, and 48.0%, compared with the corresponding AUC and Cmax values in subjects with normal hepatic function.

Body mass index, gender, age had no clinically relevant effect on the pharmacokinetics of empagliflozin based on a population pharmacokinetic analysis. In this population pharmacokinetic analysis, the AUC value for empagliflozin was estimated to be 13.5% higher in Asian patients with a BMI of 25 kg/m2 compared to the corresponding AUC value in non-Asian patients with the same BMI.

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

The pharmacokinetics of linagliptin was only slightly influenced by reduction of the hepatic functions. Only exposure to the main metabolite was significantly reduced, however, as the elimination of linagliptin by metabolism is small (less than 13%), this reduction in exposure is of no clinical relevance.

In the population pharmacokinetic analysis for linagliptin, the influence of gender, weight, age (up to 80 years) and race was considered of no clinical relevance.

Studies characterising the pharmacokinetics of empagliflozin and linagliptin in paediatric patients have not been performed.

No additional information on the special populations is required for the FDC tablet, as empagliflozin and linagliptin are both well known and approved medications, and the drug-drug interaction study between empagliflozin and linagliptin showed no clinically meaningful effect of empagliflozin and linagliptin PK parameters and vice versa.

Pharmacokinetic interaction studies

Drug-drug interaction study 1245.30

This study 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. This study was an open-label, randomised, multiple dose, crossover study. The cross-over design of the DDI study is the recommended design in the guideline on the Investigation of drug Interactions and the more usual for an in vivo interaction study. The open-labelling of the study is satisfactory. The choice of a partly fixed sequence design is not fully understood by the assessor (probably linked to the very long half-life of linagliptin and the objective of reducing inter-subject variability) but does not question the conclusions on the absence of interactions.

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: Linagiptin once daily for 7 days	8 subjects
Treatment C_AB	C: Linagiptin 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 AUCτ,ss of empagliflozin was similar when the drug was given alone and in combination with linagliptin but the Cmax,ss of empafgliflozin was reduced by approximately 12% when the drug was given with linagliptin. Median tmax,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 6 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			

Even if small, the number of subjects enrolled in the study (n=16) is higher than 12 and it is the applicant's responsibility to correctly determine the sample size with the aim to have a sufficient power, reducing its own producer's risk and allowing for drop-outs. The chosen sample size seems finally sufficient to conclude.

A 35-day washout period between doses is judged sufficient for both drugs as this represents more than 5 times the respective half-lives: the effective half-life for accumulation of linagliptin is 12 hours with a long terminal half-life of more than 100 hours. The terminal half-life of empagliflozin was estimated to be 12.4 hours. Eight subjects had quantifiable linagliptin pre-dose concentrations after multiple oral administration of empagliflozin and linagliptin but these concentrations were <5% of the Cmax and were therefore all included in the analysis.

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 7).

Table 7 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. However the decrease of the urinary glucose does not appear to be related to the slightly decreased Empagliflozin Cmax, as around tmax,ss of Empagliflozin (1.5 hours) the decrease of the urinary glucose excretion rate was similar to other time-intervals.

The combination of 50 mg Empagliflozin and 5 mg linagliptin q.d. was safe and well tolerated in all patients.

Therefore it can be concluded that no significant interaction between empagliflozin and linagliptin was observed and that the drugs can be coadministered without dose adjustment and there are no additional safety concerns expected due to the combination of both drugs.

Interactions with other drugs

The potential for interactions with other drugs has been extensively evaluated in the original applications for Jardiance and Trajenta. The overall potential for either empagliflozin or linagliptin to be involved in meaningful DDIs is assessed to be low, and is not expected to be increased due to combined use of both drugs. No additional information is required.

The interaction studies in healthy volunteers suggest that the pharmacokinetics of empagliflozin were not influenced by its coadministration with metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, verapamil, ramipril, simvastatin, torasemide, hydrochlorothiazide, or oral contraceptives.

Overall exposure (AUC) of empagliflozin increased 1.6-fold following co-administration with gemfibrozil, 1.35-fold with rifampicin, and 1.5-fold with probenecid. The observed increases in the overall exposure of empagliflozin were not considered to be clinically significant. No dosage adjustment of empagliflozin is recommended when it is administered concomitantly with gemfibrozil, rifampicin, or probenecid. Therefore interaction on the level of the transporters OATP1B1, OATP1B3, OATP2B1 and OAT3 are considered not clinical relevant.

Coadministration of empagliflozin with diuretics may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension. Coadministration of empagliflozin with insulin secretagogues (SU) may increase the risk for hypoglycaemia. Therefore, a lower dose of SU may be required to reduce the risk of hypoglycaemia when used in combination with empagliflozin. Further details can be found in the SmPC of empagliflozin for further details.

Empagliflozin had no clinically meaningful effect on the pharmacokinetics of metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, warfarin, digoxin, ramipril, simvastatin, hydrochlorothiazide, torasemide, and oral contraceptives when co-administered with any of these drugs.

Interaction studies in healthy volunteers suggest that the pharmacokinetics of linagliptin were not influenced by the coadministration of metformin, glibenclamide, simvastatin, warfarin, digoxin, or oral contraceptives. Coadministration of a single dose of linagliptin with multiple doses of ritonavir resulted in a 2- to 3-fold increase in linagliptin AUC and C_{max}. Simulations of steady-state plasma concentrations of linagliptin with and without ritonavir indicated that the increase in exposure is not associated with an increased accumulation. These changes were not considered clinically meaningful.

Rifampicin was shown to decrease linagliptin exposure. Multiple coadministration of linagliptin with rifampicin resulted in 39.6% and 43.8% decreased linagliptin steady-state AUC and Cmax values and about 30% decreased DPP-4 inhibition at trough. Thus, full efficacy of linagliptin in combination with strong P-gp (permeability glycoprotein) inducers might not be achieved, particularly if these are administered long-term. See the SmPC for linagliptin for further details.

Linagliptin had no clinically relevant effect on the pharmacokinetics of metformin, glyburide, pioglitazone, warfarin, simvastatin, digoxin or oral contraceptives.

Pharmacokinetics using human biomaterials

none

2.4.3. Pharmacodynamics

No new data were submitted on pharmacodynamics. The clinical pharmacology programme that supported the original empagliflozin and linagliptin clinical development programmes provides sufficient information to support the empagliflozin/linagliptin FDC programme. Key clinical pharmacology information about empagliflozin and linagliptin, with and without combination with metformin, are available in the respective product labels.

Mechanism of action

Empagliflozin is a potent and selective SGLT-2 inhibitor, 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 insulin pathways, which provides a therapeutic advantage compared with other drugs and has not been associated with an increased risk for hypoglycaemia when administered as monotherapy or other antidiabetic therapies (other than sulphonylurea±insulin). Further benefits of SGLT-2 inhibition include weight loss and a reduction in blood pressure.

Linagliptin is a selective, orally administered, xanthine-based DPP-4 inhibitor. Like other DPP-4 inhibitors, linagliptin lowers blood glucose by extending the half-life of active glucagon-like peptide 1 (GLP-1), which is secreted in response to a meal. Glucagon-like peptide-1 lowers blood glucose by augmenting the glucose-stimulated insulin release and limiting glucagon secretion as well as slowing gastric emptying and inducing satiety. The advantages of DPP-4 inhibitors over other established antidiabetic medications include the low risk of hypoglycaemia. The activity of GLP-1 ceases when plasma glucose concentration falls below 3.1 mmol/l (55 mg/d).

Primary and Secondary pharmacology

In patients with type 2 diabetes, urinary glucose excretion increased immediately and in a dose-dependent manner following administration of multiple **empagliflozin** doses over the 24-h dosing interval. It was maintained at the end of a 4-week treatment period; it was about 64.0 grams/day with empa 10 treatment and 78.0 grams/day with empa 25 treatment. Increased urinary glucose excretion resulted in an immediate reduction in plasma glucose levels in patients with type 2 diabetes.

Linagliptin binds to DPP-4 in a reversible manner and thus leads to a sustained increase and prolongation of active incretin hormone levels. Linagliptin increases insulin secretion and lowers glucagon secretion in a glucose-dependent manner, thus resulting in a better regulation of the glucose homeostasis. It binds selectively to DPP-4 and selectively inhibits DPP-4 and exhibits a >10000-fold selectivity vs. DPP-8 or DPP-9 activity in vitro at concentrations close to therapeutic exposures.

The mechanism of action of empagliflozin is independent of the insulin pathway and β-cell function. Therefore, it is different from and complementary to the mechanisms of other currently available type 2 diabetes medications. In the Phase I study 1245.30, an increased urinary glucose excretion was observed both after the administration of empagliflozin alone and in combination with linagliptin, consistent with the mode of action of empagliflozin. Trough DPP-4 inhibition was similar when linagliptin was administered alone or with empagliflozin. Administration of empagliflozin alone had no effect on DPP-4 activity. Following the administration of multiple oral doses of empa 50, the urinary glucose excretion of empagliflozin at steady-state (reached by Day 5) was not affected by the coadministration of linagliptin. The mean fraction of the excreted empagliflozin dose was similar when given alone and when coadministered (~21.0%). Following the administration of multiple oral doses of linagliptin, the urinary glucose excretion of linagliptin at steady-state (reached by Day 7) was not affected by the coadministration of empagliflozin. The mean fraction of the excreted dose was similar when linagliptin was given alone and when it was coadministered (~5.0%).

2.4.4. Discussion on clinical pharmacology

The applicant conducted two pharmacokinetic studies to bridge the pharmacokinetic data of the monocomponents to the FDC tablets. These studies were properly designed and appropriate bioanalytical and statistical methods have been used.

Study 1275.3 shows bioequivalence between the fixed dose combination Empagliflozin/linagliptin tablet (25mg/5mg FDC tablets) and the individual components. The effect of food on the FDC tablets was characterized as well; the food effect on Empagliflozin /linagliptin 25mg/5mg FDC tablets was similar to that for the monotherapy products. The applicant adequately justified that the results of the bioavailability study 1275.3 with the highest dose strength FDC empagliflozin/linagliptin 25/5 tablet can be extrapolated to FDC empagliflozin/linagliptin 10/5.

In study 1245.30 no significant pharmacokinetic or pharmacodynamic interaction between empagliflozin and linagliptin was observed and the combination of the medicinal products was well tolerated. Furthermore, based on the pharmacokinetic properties of empagliflozin and linagliptin and the results of previously conducted drug interaction studies the overall interaction potential of the fixed dose combination is assessed to be low. Based on this interaction study can be concluded that empagliflozin and linagliptin can be coadministered without dose adjustment and there are no additional safety concerns expected due to the combination of both drugs.

No new studies were performed on pharmacodynamics. Key clinical pharmacology information about empagliflozin and linagliptin, with and without combination with metformin, are available in the respective product labels.

For the empagliflozin/linagliptin FDC, effects on HbA1c and weight were shown in the clinical phase 3 trials (see Clinical Efficacy).

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetics of empagliflozin/linagliptin FDC is sufficiently characterised. No additional studies of pharmacokinetic studies are considered necessary for this application.

No new studies were performed on pharmacodynamics. Key clinical pharmacology information about empagliflozin and linagliptin, with and without combination with metformin, are available in the respective product labels.

2.5. Clinical efficacy

2.5.1. Dose response study

Not applicable

2.5.2. Main study(ies)

The clinical development programme for the FDC empa/lina comprised 2 Phase I studies in healthy volunteers (1275.3 and 1245.30) and 3 Phase III pivotal studies in patients with type 2 diabetes mellitus: 1 factorial design study (1275.1) and 2 add-on studies (1275.9 and 1275.10).

Phase I studies

Two phase I studies were conducted analysing the combined administration of empagliflozin and linagliptin: the drug-drug interaction study 1245.30 and the relative bioavailability study 1275.3. Study 1245.30 investigated the effect of combined administration of empagliflozin and linagliptin; it showed no clinically relevant effect on the pharmacokinetics of either drug and concluded that empagliflozin and linagliptn can be coadministered without any dose adjustment. Study 1275.3 established the bioequivalence of the FDC and the individual components. Studies 1245.30 and 1275.3 were previously included in the dossier of the empagliflozin development programme.

Phase III studies

Study 1275.9 was an add-on study that investigated the efficacy, safety, and tolerability of empagliflozin as add-on therapy to the DPP-4 inhibitor linagliptin and metformin. Patients with type 2 diabetes and inadequate glycaemic control despite metformin background therapy underwent an initial 16-week period of open-label treatment with linagliptin 5 mg. Patients who met the inclusion criterion of HbA1c values between 7.0 and 10.5% after 16 weeks of open-label linagliptin therapy on a metformin background were eligible for randomisation into the 24-week double-blind period into 3 groups, following an additional 1-week open-label

placebo run-in period: empa 25 (given as FDC empa 25/lina 5), empa 10 (given as FDC empa 10/lina 5), and placebo (given in addition to lina 5). All patients continued treatment with metformin throughout the double-blind treatment period.

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. 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 or empagliflozin 10 mg. 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). All patients continued treatment with metformin throughout the double-blind period.

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. 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.

Methods

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 1275.9, 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 (studies 1275.9 and 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 (studies 1275.9 and 1275.10) or randomisation (1275.1(met)). Study 1275.1(naïve) included patients without prior antidiabetic treatment for 12 weeks prior to randomisation.

Treatments

See description under Summary of main efficacy studies below.

Objectives

Study 1275.9

The objective of this trial was to investigate the efficacy, safety, and tolerability of empagliflozin 25 mg (empa 25) and empagliflozin 10 mg (empa 10) compared with placebo, each administered as add-on therapy to linagliptin 5 mg (lina 5) and metformin, over 24 weeks in patients with type 2 diabetes (T2DM).

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).

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.

Outcomes/endpoints

The primary efficacy endpoint in all studies was the change from baseline in glycated haemoglobin (HbA1c) after 24 weeks of double-blind treatment.

Secondary end points after 24 weeks of double-blind treatment were the change from baseline in fasting plasma glucose (FPG), body weight and blood pressure, and the proportion of patients with HbA1c<7.0%.

Sample size, Randomisation and Blinding (masking)

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

Statistical methods

The primary analysis in studies 1275.9 and 1275.10 was performed on the full analysis set (FAS), consisting 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. An observed case (OC) approach was used for the main analyses of the primary, key secondary, and most of the further efficacy endpoints. Missing data were not directly imputed prior to analysis and were handled implicitly by the statistical model used. The primary analysis used 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. The superiority of empagliflozin as add-on to linagliptin and metformin (study 1275.9) or 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).

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. For handling missing data, 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. 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 α = 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).

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.

Results

Participant flow

In the Phase III studies, 733 patients received combined therapy on a metformin background and most of them (>90.0% in each study) completed 24 weeks of double-blind treatment. In the factorial design study 1275.1, at the time of the primary endpoint analysis of 24 weeks, over 90.0% of the patients continued in the study and over 84.0% of the patients completed the 52-week treatment period. In general there were no relevant differences in the proportions of patients with premature discontinuation across treatment groups. The most common reasons for premature discontinuations were patients being lost to follow-up and the occurrence of adverse events (each ≤3.5% in each study).

Recruitment

Dates of recruitment and follow-up for the respective trials were as follows :

Study 1275.1: 31 August 2011 - 10 September 2013

Study 1275.9: 01 Mar 2013 - 23 Mar 2015

Study 1275.10: 13 Feb 2013 - 30 Mar 2015

Conduct of the study

A routine GCP inspection was performed for the clinical study: 1275.1. Three sites [2 investigator sites – one in Spain and one in the US) and the sponsor site in the US] between 25 January 2016 – 08 April 2016. The summary report of the inspection carried out was issued on 09 May 2016. The conclusion of the inspection was that data quality is acceptable and the trial has been conducted following GCP and ethical standards. Data quality was found to be acceptable and the trial has been conducted following GCP and ethical standards.

Baseline data

Except for race and region, the overall demographic characteristics were generally similar across trials and treatment groups. Study 1275.9 included patients from all races across most regions (except Africa), with almost two thirds of patients being White and a quarter Asian. In study 1275.10, more than 95.0% of the patients were White and from Europe; there were no patients from Asia or Africa. In study1275.1, almost three quarters of patients were White and mainly from North America, but there were also some patients from all other races and regions.

About half of the patients in each study were male. The mean age in each study was about 55 years. About 80.0% of the patients were younger than 65 years at baseline, and only about 2.0% were 75 years of age or older. Most patients were obese based on their BMI (body mass index) value. Based on eGFR (estimated glomerular filtration rate) values at baseline, calculated using the MDRD formula, most of the patients (about 97.0%) had either normal renal function (more than 40.0% of patients) or mild renal impairment (about half of patients) at baseline. Moderate or severe renal impairment (eGFR<60 mL/min/1.73m^2) was an exclusion criterion in all Phase III studies because of the metformin add-on therapy. About one third (in each of the 2 given categories) of the patients in each study had been diagnosed with type 2 diabetes mellitus for either >1 to 5 years or >5 to 10 years, one quarter of patients had had type 2 diabetes mellitus for >10 years, and less than 10.0% of patients had been diagnosed for 1 year or less.

Mean baseline HbA_{1c} and fasting plasma glucose (FPG) values were generally similar across treatments and trials. The overall mean baseline value for HbA1c was 8.0%, with three quarters of patients having an HbA1c of below 8.5% at baseline. A summary of the main baseline characteristics is presented in Table 8.

Table 8 Key baseline1 efficacy characteristics in Phase III trials – FAS

Study	N	HbA_{1c}, mean (SD) [%]	FPG, mean (SD) [mmol/L]	Body weight, mean (SD) [kg]	BP, mean (SD) [mmHg]	
					SBP	DBP
Add-on studies						
1275.9 *(met+lina5)*	327	7.97 (0.84)	9.27 (2.12)	85.05 (20.03)	130.5 (15.1)	79.2 (8.6)
1275.10 *(met+empa25)*	220	7.85 (0.81)	8.54 (1.85)	87.79 (16.53)	129.0 (13.3)	77.7 (7.7)
1275.10 *(met+empa10)*	247	8.03 (0.91)	8.78 (2.08)	86.99 (17.47)	127.9 (12.7)	77.3 (8.3)
Factorial design studies						
1275.1 *(met)*	674	7.98 (0.85)	8.76 (1.91)	86.20 (18.69)	130.1 (14.3)	79.1 (8.9)
1275.1 *(naïve)*	667	8.02 (0.96)	8.68 (2.09)	87.85 (20.13)	128.3 (14.7)	78.5 (8.8)

Numbers analysed

Please refer to the tables summarizing the efficacy results in the following section.

Outcomes and estimation

The endpoints are presented in the tables summarizing the efficacy results in the following section.

Summary of main studies

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

Tabulated summaries of the studies included in the evaluation of efficacy

Title: A phase III, randomised, double-blind, parallel group, 24 week study to evaluate efficacy and safety of once daily empagliflozin 10 mg and 25 mg compared to placebo, all administered as oral fixed dose combinations with linagliptin 5 mg, in patients with type 2 diabetes mellitus and insufficient glycaemic control after 16 weeks treatment with linagliptin 5 mg once daily on metformin background therapy.

Study identifier	1275.9, EudraCT No.: 2012-002270-31, CTR c02820144		
Design	This was a randomised, double-blind, parallel group comparison study. Patients were recruited and randomised at a 1:1:1 ratio to treatment with empagliflozin 25 mg, empagliflozin 10 mg, or placebo, each as add-on therapy to linagliptin 5 mg and metformin. 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 empagliflozin 25 mg and empagliflozin 10 mg compared with placebo, as add-on to linagliptin 5 mg 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 linagliptin 5 mg and metformin.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		16 weeks open-label active treatment, 24 weeks double-blind randomised treatment, 1 week follow-up period 1 week open-label placebo, before double-blind period not applicable
Hypothesis	Superiority of empagliflozin (25 mg and 10 mg) vs. placebo, add-on therapy to linagliptin 5 mg and metformin		
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 lina 5 and 1 week with placebo) on a metformin background, denoted empa 25 in Results, 24 weeks, 111 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 lina 5 and 1 week with placebo) on a metformin background, denoted empa 10 in Results, 24 weeks, 112 patients randomised
	Placebo+lina 5		Placebo and lina 5 after 17 weeks of open-label treatment (16 weeks with lina 5 and 1 week with placebo) on a metformin background, denoted placebo in Results, 24 weeks, 110 patients randomised
Endpoints and definitions	Primary endpoint	Glycaeted haemo-globin (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
Database lock	16 April 2015		
Results and Analysis			
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 empagliflozin add-on to linagliptin 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 first tested for significance of the higher empagliflozin dose; it was to proceed to the lower empagliflozin dose only if statistical significance had been proven for the higher dose. The 2 key secondary endpoints were to be subsequently tested in a pre-defined order (see results below). 24 weeks			
Descriptive statistics and estimate variability	Treatment group	Met + lina 5 **Empa 25**	Met + lina 5 **Empa 10**	Met + lina 5 **Placebo**
	Number of subjects	110	109	108
	Mean HbA_{1c} [%] Baseline (SE)	7.97 (0.08)	7.97 (0.08)	7.96 (0.08)
	Week 24 (SE)	7.35 (0.09)	7.27 (0.09)	7.95 (0.12)
	Mean FPG [mmol/L] Baseline (SE)	9.44 (0.23)	9.32 (0.21)	9.04 (0.17)
	Week 24 (SE)	7.47 (0.17)	7.72 (0.18)	9.19 (0.27)
	Mean body weight [kg] Baseline (SE)	84.38 (1.83)	88.41 (1.99)	82.26 (1.94)
	Week 24 (SE)	81.58 (1.94)	85.49 (2.08)	82.24 (2.07)
Effect estimate per comparison	**Primary endpoint** Change from baseline in HbA_{1c} [%] after 24 weeks – MMRM FAS (OC)	Comparison vs. placebo	**Empa 25**	**Empa 10**
		Adjusted mean change in HbA_{1c} [%] (SE)	-0.70 (0.12)	-0.79 (0.12)
		95% CI	(-0.93, -0.46)	(-1.02, -0.55)
		P-value	<0.0001	<0.0001
	First key secondary endpoint Change from baseline in FPG [mmol/L] after 24 weeks – MMRM FAS (OC)	Comparison vs. placebo	**Empa 25**	**Empa 10**
		Adjusted mean change in FPG [mmol/L] (SE)	-2.09 (0.26)	-1.80 (0.26)
		95% CI	(-2.61, -1.57)	(-2.31, -1.28)
		P-value	<0.0001	<0.0001
	Second key secondary	Comparison vs. placebo	**Empa 25**	**Empa 10**

	endpoint Change from baseline in body weight [kg] after 24 weeks – MMRM FAS (OC)	Adjusted mean change in body weight [kg] (SE)	-2.22 (0.36)	-2.77 (0.36)
		95% CI	(-2.92,-1.52)	(-3.47,-2.07)
		P-value	<0.0001	<0.0001
Notes	Treatment with empagliflozin 25 mg or empagliflozin 10 mg resulted in statistically significant and clinically meaningful improvements in HbA_{1c}, FPG, and body weight compared with placebo as add-on treatment to linagliptin 5 mg and metformin after 24 weeks of treatment in patients with type 2 diabetes mellitus having met the HbA_{1c} criterion (HbA_{1c} ≥7.0% and ≤10.5%) after 16 weeks of open-label treatment with linagliptin 5 mg and metformin. 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 empagliflozin (25 mg and 10 mg) treatment than after placebo treatment. For the further endpoints systolic and diastolic blood pressure, clinically relevant reductions were seen in both empagliflozin dose groups from baseline to Week 24.			

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	Glycaeted 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	Comparison vs. placebo	**Lina 5**
		Adjusted mean change in HbA_{1c} [%] (SE)	-0.32 (0.10)

	24 weeks – MMRM FAS (OC)	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	Glycaeted 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 24 weeks – ANCOVA FAS (LOCF)	**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)
		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 efficacyresponse (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.

Effects on HbA_{1c}

In the Phase III trials, the primary endpoint was the change from baseline in HbA_{1c} after 24 weeks of double-blind treatment.

Empagliflozin add-on to linagliptin (study 1275.9)

The confirmatory analyses conducted on trial level showed statistically significant and clinically meaningful reductions in HbA_{1c} compared with placebo after 24 weeks of double-blind treatment for each dose of empagliflozin add-on to linagliptin and metformin (Table 9).

Table 9 Change from baseline in HbA_{1c} [%] after 24 weeks of double-blind treatment in study 1275.9 – MMRM FAS (OC)

			Change from baseline		Difference to placebo		
Treatment group[1]	N[2]	Baseline HbA_{1c}, mean (SE)	Mean (SE)	Adjusted mean (SE)	Adjusted mean (SE)	95% CI	p-value
Empa 25	110	7.97 (0.08)	-0.62 (0.09)	-0.56 (0.08)	-0.70 (0.12)	(-0.93,-0.46)	<0.0001
Empa 10	109	7.97 (0.08)	-0.67 (0.10)	-0.65 (0.08)	-0.79 (0.12)	(-1.02,-0.55)	<0.0001
Placebo	106	7.96 (0.08)	0.07 (0.10)	0.14 (0.09)			

[1]Add-on therapy to lina 5+metformin
[2] Number of analysed patients with value at baseline

Figura 1 shows the mean change from baseline in HbA1c over the 24 weeks of double-blind treatment. Treatment effects were seen in both empagliflozin groups starting at Week 6; at Week 12, near-maximum treatment effects of empagliflozin were achieved and sustained through Week 24.

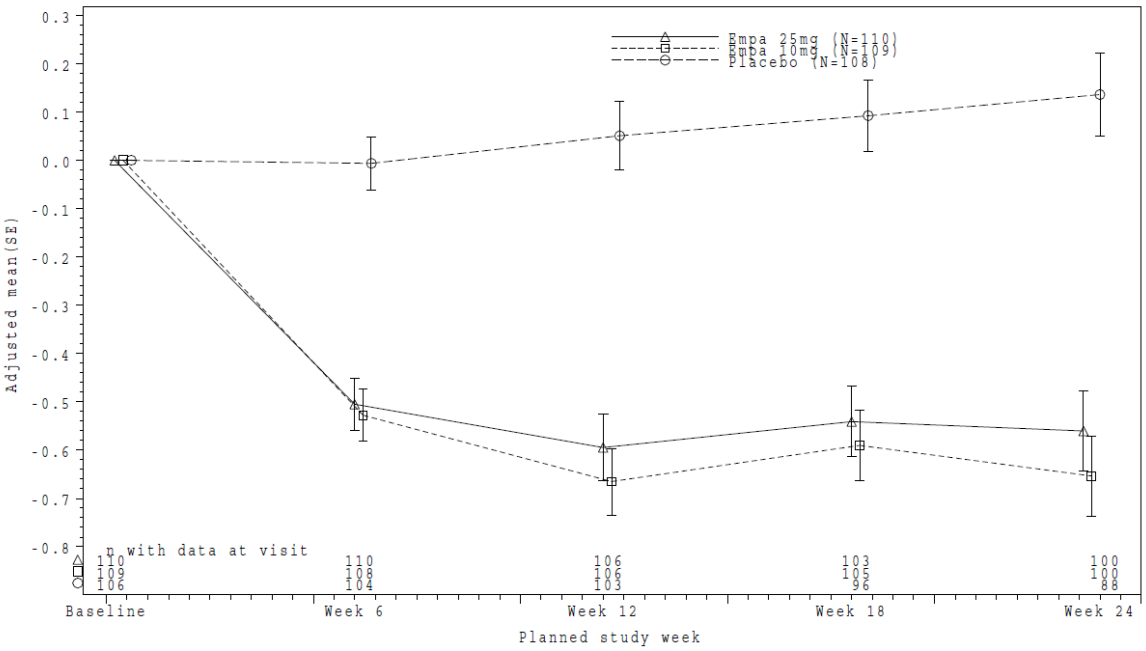

Figure 1 HbA1c [%] change from baseline over time in study 1275.9 - MMRM FAS

Linagliptin add-on to empagliflozin (study 1275.10)

The confirmatory analyses conducted on trial level showed statistically significant reductions in HbA_{1c} compared with placebo after 24 weeks of double-blind treatment with linagliptin add-on to either empa 25 or empa 10 and metformin (Table 10).

Table 10 Change from baseline in HbA_{1c} [%] after 24 weeks of double-blind treatment in study 1275.10 – MMRM FAS (OC)

			Change from baseline		Difference to placebo[1]		
Treatment group[1]	N[2]	Baseline HbA_{1c}, mean (SE)	Mean (SE)	Adjusted mean (SE)	Adjusted mean (SE)	95% CI	p-value
1275.10 ***(met+empa25)***							
Lina 5	109	7.82 (0.07)	-0.60 (0.07)	-0.58 (0.07)	-0.47 (0.10)	(-0.66,-0.28)	<0.0001
Placebo	108	7.88 (0.09)	-0.13 (0.07)	-0.10 (0.07)			
1275.10 ***(met+empa10)***							
Lina 5	122	8.04 (0.09)	-0.55 (0.08)	-0.53 (0.07)	-0.32 (0.10)	(-0.52,-0.13)	0.0013
Placebo	125	8.03 (0.08)	-0.21 (0.07)	-0.21 (0.07)			
1275.10 ***(pooled)*** [3]							
Lina 5	231	7.94 (0.06)	-0.57 (0.06)	-0.55 (0.05)	-0.40 (0.07)	(-0.53,-0.27)	<0.0001
Placebo	233	7.96 (0.06)	-0.17 (0.05)	-0.16 (0.05)			

[1]Add-on therapy to empagliflozin and metformin

[2]Number of analysed patients with value at baseline
[3]Not done as confirmatory analyses

Figura 2 shows the change from baseline in HbA_{1c} over 24 weeks of double-blind treatment. Treatment effects were seen in both empagliflozin patient populations starting at Week 6, with a maximum effect achieved at Week 18 and sustained through Week 24.

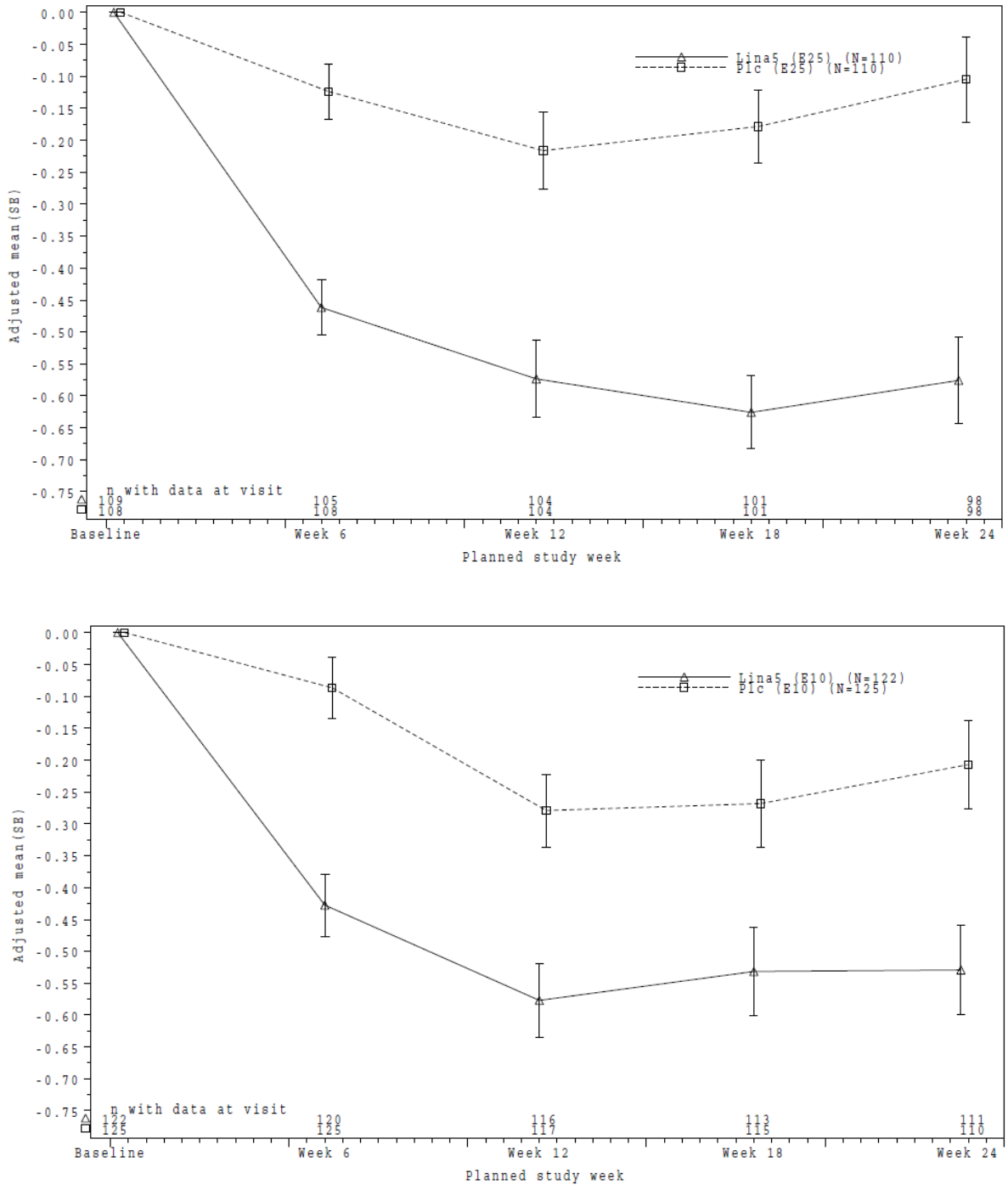

Figure 2 HbA1c [%] change from baseline over time in study 1275.10(met+empa 25) (upper panel) and 1275.10(met+empa 10) (lower panel) – MMRM FAS (OC)

Fixed dose combination of empagliflozin/linagliptin compared with empagliflozin or linagliptin (study 1275.1)

Treatment with the 2 dose combinations of empagliflozin and linagliptin on a metformin background in the factorial design study 1275.1*(met)* led to reductions in HbA_{1c} after 24 weeks of double-blind treatment. The primary analysis using an ANCOVA model on the FAS (LOCF) confirmed that each FDC was superior to empagliflozin (corresponding dose) and linagliptin in terms of change from baseline in HbA_{1c} after 24 weeks.

Treatment with the 2 dose combinations of empagliflozin and linagliptin in drug-naïve patients in the factorial design study 1275.1*(naïve)* also resulted in clinically relevant reductions in HbA_{1c} after 24 weeks of double-blind treatment, of about -1.1%. The FDC empa 25/lina 5 was statistically superior to lina 5 treatment, but not to empa 25 treatment (Table 11).

Table 11 Change from baseline in HbA_{1c} [%] after 24 weeks of double-blind treatment in the factorial design 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]		

[1]With value at baseline

[2]The FDC empa 25/lina 5 was statistically superior to lina 5 treatment, but not to empa 25 treatment; subsequently, the confirmatory testing hierarchy was stopped and therefore the p-values for these comparisons are not displayed here.

Categorical efficacy responses: proportions of patients achieving HbA_{1c} values below 7.0%

In study 1275.9, the proportion of patients who achieved HbA_{1c} <7% was about 2-fold higher with empagliflozin treatment (25 mg: 32.7% and 10 mg: 37.0%) than with placebo (17.0%) add-on to linagliptin and metformin.

In study 1275.10, the proportion of patients who achieved HbA_{1c} <7% was more than 2-fold higher with linagliptin treatment than with placebo: 36.0% for lina 5 add-on to empa 25 and metformin and 15.0% for placebo; 25.9% for lina 5 add-on to empa 10 and metformin and 10.9% for placebo.

The proportion of patients achieving HbA_{1c} values of less than 7% after 24 weeks was a key secondary endpoint in study 1275.1*(met)*. It was tested in the last step of the hierarchical confirmatory testing sequence. The proportion of patients who achieved the HbA_{1c} goal was higher with FDC treatment (high dose: 61.8%, low dose: 57.8%) than with the corresponding individual components (empa 25: 32.6%, empa 10: 28.0%, lina 5: 36.1%). Treat-to target response analyses after 52 weeks of treatment were consistent with those of Week 24.

Effects on fasting plasma glucose

The change from baseline in FPG was a key secondary endpoint in all Phase III trials. In general, the results for changes in FPG were consistent with the results for the changes in HbA_{1c}.

In study 1275.9, treatment with empagliflozin (25 mg and 10 mg) add-on to linagliptin and metformin resulted in statistically significant reductions in FPG after 24 weeks of treatment compared with placebo, with placebo-adjusted mean treatment differences of -2.09 (SE 0.26) mmol/L for empa 25 and -1.80 (SE 0.26) mmol/L for empa 10.

In study 1275.10, treatment with linagliptin add-on to empagliflozin (25 mg or 10 mg) and metformin resulted in statistically significant reductions in FPG after 24 weeks of treatment compared with placebo, with placebo-adjusted mean treatment differences of -0.44 (SE 0.22) mmol/L for lina 5 add-on to empa 25 and -0.65 (SE 0.25) mmol/L for lina 5 add-on to empa 10.

In study 1275.1*(met)*, both FDCs provided statistically significant and clinically meaningful reductions in FPG compared with their individual components. 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.

Effects on body weight

In study 1275.9, treatment with empagliflozin add-on to linagliptin and metformin resulted in statistically significant body weight reductions vs. placebo, with placebo-adjusted mean treatment differences of -2.2 (SE 0.4) kg for empa 25 and -2.8 (SE 0.4) kg for empa 10.

In study 1275.10, treatment with linagliptin add-on to empagliflozin and metformin did not result in clinically relevant changes in body weight after 24 weeks of treatment compared with placebo. Based on the mode of action of linagliptin, a body weight change was not expected.

In study 1275.1*(met)*, the change from baseline in body weight after 24 weeks of treatment was a key secondary endpoint. Overall, there was a mean body weight change from baseline of -3.0 (SE 0.3) kg for FDC empa 25/lina 5 and of -2.6 (SE 0.3) kg for FDC empa 10/lina 5. The analyses showed statistically significant differences for each FDC empa/lina compared with lina 5 treatment, of -2.3 (SE 0.4) kg for the higher dose and -1.9 (SE 0.4) kg for the lower dose. There was no treatment difference between the FDCs and empagliflozin treatment.

Effects on blood pressure

In study 1275.9, empagliflozin add-on to linagliptin and metformin provided clinically meaningful reductions in systolic blood pressure after 24 weeks of treatment compared with placebo, with placebo-adjusted mean changes of -2.6 (SE 1.5) mmHg for empa 25 treatment and -1.3 (SE 1.5) mmHg for empa 10 treatment. A clinically relevant reduction in diastolic blood pressure was also observed for patients treated with empa 25, with a placebo-adjusted mean change of -1.1 (SE 1.1) mmHg; however, there was no reduction in diastolic blood pressure for patients treated with empa 10; the placebo-adjusted mean change for this group of patients was -0.1 (SE 1.1) mmHg.

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. Based on the mechanism of action of linagliptin, a reduction in blood pressure during the double-blind treatment period was not expected with linagliptin treatment.

In study 1275.1$_{(met)}$, there were similar, clinically meaningful reductions in both systolic and diastolic blood pressure in the FDC and empagliflozin groups, ranging from -5.9 (SE 1.0) mmHg to -4.2 (SE 1.0) mmHg for systolic blood pressure and from -3.4 (0.6) mmHg to -2.5 (0.7) mmHg for diastolic blood pressure. Blood pressure reduction was minimal with linagliptin treatment.

Use of rescue therapy

In study 1275.9, the proportions of patients needing rescue therapy during the 24 weeks of double-blind treatment with empagliflozin (25 mg or 10 mg) add-on to linagliptin and metformin was 3 times lower in the empagliflozin treatment groups (around 5.0% of patients requiring rescue medication) than in the placebo group (around 15.0% of patients). In study 1275.10, a lower proportion of patients needed rescue therapy when treated with linagliptin add-on to empagliflozin (25 mg or 10 mg) and metformin (0% and 1.6%) than when treated with placebo (2.7% and 4.0%). In study 1275.1$_{(met)}$, 1 (0.7%) to 6 (4.3%) patients per treatment group required rescue therapy after 24 weeks of treatment, without a clear trend in differences between groups. In study 1275.1(naive), 1 (0.7%) to 11 (8.3%) patients per treatment group required the use of rescue therapy. The linagliptin monotherapy group had the highest number of patients requiring rescue therapy (8.3%).

Efficacy in subpopulations

Subgroup analyses were done to investigate the consistency of the treatment effect on HbA_{1c} across subpopulations. Subgroup analyses for efficacy were conducted at study level on data from the 24-week double-blind period of the Phase III trials. An interaction p-value of <0.1 was considered to indicate a potential treatment-by-subgroup interaction.

Reductions from baseline in HbA_{1c} were observed throughout Phase III studies for all subgroup analyses, with a trend towards larger treatment effects in patients with higher baseline HbA_{1c} values. For most investigated subgroups (gender, ethnicity, race, age, geographical region, time since diagnosis of type 2 diabetes, body weight, and renal function), the treatment effect with regard to the HbA_{1c} change from baseline was generally consistent, with no meaningful trends observed across subcategories and no apparent treatment-by-subgroup interaction.

A potential interaction for the treatment-by-time since diagnosis of type 2 diabetes was observed in study 1275.9 (p-value 0.0213). The strongest treatment effects were seen for the group of recently diagnosed patients; the strength of the treatment effect generally decreased for longer time periods since diagnosis.

The group of patients diagnosed for a year or less before study start was small (22 patients), thus its results should be interpreted with caution.

Subgroup analyses results are discussed in detail below for the following subgroups of particular interest in the treatment of type 2 diabetes: baseline HbA_{1c}, age, and renal function.

Efficacy in subpopulations in the add-on study 1275.9

Although the treatment effects were clinically meaningful in all tested HbA_{1c} subcategories (<8.5, ≥8.5%; <8%, 8% to <9%, ≥9%), higher baseline HbA_{1c} levels were associated with greater HbA_{1c} reductions. There was a clear effect (treatment-by-baseline HbA_{1c} interaction p-value: 0.0156) of baseline HbA_{1c} on the treatment effect of empagliflozin add-on therapy to linagliptin and metformin, for both empagliflozin doses.

With regard to age, there were clinically meaningful reductions of HbA_{1c} for empagliflozin (both doses) add-on therapy to linagliptin and metformin for all the analysed categories of patients younger than 75 years (treatment-by-baseline age interaction p-value was 0.1617). The group of patients aged 75 years or older was not analysed due to the low number of patients (5 patients) in this category.

Due to their mechanism of action, the efficacy of SGLT-2 inhibitors is generally lower in patients with renal impairment than in patients with normal renal function (eGFR ≥90 mL/min/1.73 m^2). However, in this study, the efficacy was maintained in patients with mild renal impairment (baseline eGFR of 60 to <90 mL/min/1.73 m^2) for both empagliflozin doses. Patients with a baseline eGFR ≤60 mL/min/1.73 m^2 were not analysed separately due to the low number of patients with eGFR 45 to <60 mL/min/1.73 m^2 (5 patients) and with eGFR <45 mL/min/1.73 m^2 (no patient). There was no evidence of an interaction-by-baseline renal function (p-value 0.6992).

Efficacy in subpopulations in the add-on study 1275.10

Efficacy in subpopulations in study 1275.10$_{(met+empa25)}$

Reductions in HbA_{1c} levels were observed with lina 5 add-on to empa 25 and metformin in all tested HbA_{1c} subcategories. There were similar treatment effects in patients with a baseline HbA_{1c} value ≥8.5% and in patients with a baseline HbA_{1c} value <8.5%. The p-value for the treatment-by-subgroup interaction for HbA_{1c} categories was 0.4115 and thus it did not suggest an interaction.

With regard to age, larger reductions in HbA_{1c} for linagliptin add-on therapy to empagliflozin and metformin were observed in older patients (65 to<75 years) than in younger patients (<65 years), with a p-value for the treatment-by-age interaction of 0.0699. The group of patients aged 75 years or more was not analysed due to the low number of patients (4 patients) in this category.

The reductions in HbA_{1c} for linagliptin add-on therapy to empagliflozin and metformin were numerically larger in patients with normal renal function than in patients with mild renal impairment. The p-value for the treatment-by-baseline renal function interaction was 0.1416. Patients with a baseline eGFR <60 mL/min/1.73 m^2 were not analysed separately given the low number of patients with eGFR 45 to <65 mL/min/1.73 m^2 (5 patients) and with eGFR <45 mL/min/1.73 m^2 (1 patient).

Efficacy in subpopulations in study 1275.10$_{(met+empa10)}$

Reductions in HbA_{1c} levels were observed with lina 5 add-on to empa 10 and metformin in all tested HbA_{1c} subcategories. The subgroup analysis showed comparable treatment effects in the baseline HbA_{1c} categories ≥8.5% and <8.5%; there was no indication of a treatment-by-baseline HbA_{1c} interaction (p-value 0.9869).

With regard to age, clinically meaningful reductions in HbA_{1c} after 24 weeks of treatment with lina 5 add-on to empa 10 and metformin were in the same range for patients aged <65 years and patients aged 65 to <75 years. There was no indication of a treatment-by-age interaction (p-value 0.8851). The group of patients aged 75 years or older was not analysed due to the low number of patients (4 patients) in this category.

The reduction in HbA_{1c} for lina 5 add-on therapy to empa 10 and metformin was numerically larger in patients with normal renal function at baseline than in patients with mild renal impairment. The p-value for the treatment-by-baseline renal function interaction was 0.1962. Patients with a baseline eGFR <60 mL/min/1.73 m^2 were not analysed as separate categories due to the low number of patients with eGFR 45 to <65 mL/min/1.73 m^2 (5 patients) and with eGFR <45 mL/min/1.73 m^2 (1 patient).

Efficacy in subpopulations in the factorial design study 1275.1*(met)*

In all subgroup analyses by baseline HbA_{1c}, there was a clear trend towards larger mean changes from baseline to Week 24 in patients with higher baseline HbA_{1c}. For the subgroup analyses in patients with baseline HbA_{1c} <8.5% and in those with baseline HbA_{1c} ≥8.5%, the p-value for the treatment-by-baseline HbA_{1c} interaction was 0.1142.

There were changes in HbA_{1c} across all age categories and treatment groups. The p-value for the treatment-by-age group interaction (4 pre-defined age categories: <50 years, 50 to <65 years, 65 to <75 years, ≥75 years) was 0.0058, suggesting that the treatment effect differed across the analysed subgroups. Generally, the magnitude of the treatment difference between the FDCs and the individual components decreased with increasing age. The subcategory of patients aged 75 years or older was not analysed due to the low number of patients (fewer than 35 patients) in this category.

The adjusted mean changes from baseline in HbA_{1c} were generally 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).

Long term effects and persistance of efficacy

The Phase III trial 1275.1(met) compared the FDC empa 25/lina 5 and FDC empa 10/lina 5 with the corresponding doses of the individual components on a background of metformin and provides the main evidence of the efficacy of the FDCs over 52 weeks of treatment.

Reductions from baseline in HbA1c were observed over the entire 52-week treatment period for patients treated with the empa/lina FDCs. The HbA1c reductions after 52 weeks of treatment were higher with the FDCs than with the monotherapies. All Week 52 sensitivity analyses in study 1275.1(met) provided further evidence for the sustained reductions in HbA1c with FDC therapy over time for both doses.

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 in Figure 8 below. The maximal treatment effect in all groups was reached at Week 12 and sustained through Week 52. The MMRM analysis of changes over time in HbA1c provided similar, consistent results.

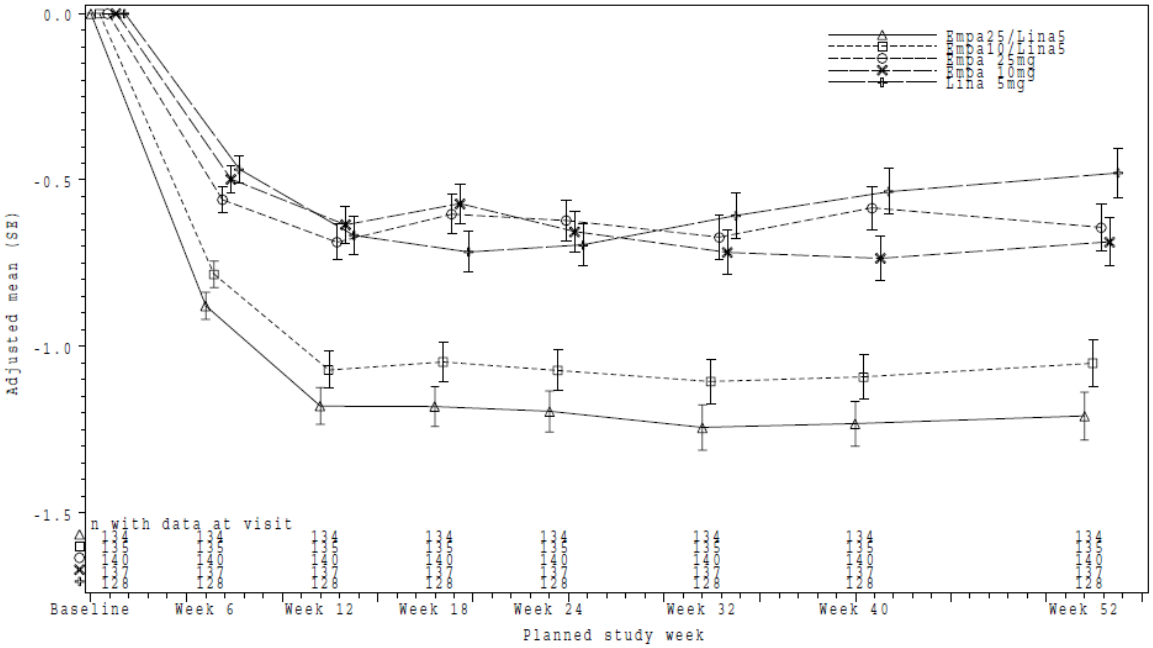

Figure 8 Change from baseline in HbA1c (%) over 52 weeks in study 1275.1(met) – ANCOVA FAS (LOCF)

In study 1275.1(met), results for the percentage of patients who reached HbA1c <7.0% after 52 weeks of double-blind treatment were similar to the results of the 24-week analysis (Section 4.1.3). In both FDC groups, about half of the patients had a sustained response to treatment at Week 52, of 48.0 for the high dose and 51.6% for the low dose, compared with 32.6% for empa 25, 32.0% for empa 10, and 28.6% for lina 5.

Other efficacy endpoints (FPG, body weight, and blood pressure) were also evaluated in study 1275.1(met) as part of the long-term analyses described above. In general, the reductions in FPG in the FDC groups were consistent with the reductions in HbA1c and were sustained over time; they indicated a larger treatment effect than in the individual treatment groups. The reductions in body weight and in blood pressure observed on combined therapy vs. treatment with lina 5 were sustained up to 52 weeks of treatment.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

Complete development programs including several Phase III studies were conducted for empagliflozin and linagliptin and supported the approval of both drugs for the treatment of type 2 diabetes. The clinical development programme for the FDC empa/lina consists of three pivotal studies in patients with type 2 diabetes mellitus: two add-on studies (1275.9 and 1275.10) and one factorial design study (1275.1).

The two Phase III add-on studies investigated the efficacy, safety, and tolerability of empagliflozin as add-on therapy to the DPP-4 inhibitor linagliptin (study 1275.9) and 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.

According to the Applicant, the FDC is indicated in adults with type 2 diabetes mellitus to improve glycaemic control:

- when diet and exercise, plus metformin and a sodium glucose co-transporter 2 (SGLT2) inhibitor do not provide adequate glycaemic control,
- when diet and exercise, plus metformin and a dipeptidyl peptidase 4 (DPP-4) inhibitor do not provide adequate glycaemic control,
- when already being treated with the free combination of empagliflozin (or another SGLT-2 inhibitor) and linagliptin (or another DPP-4 inhibitor).

In general, the development program for the fixed dose combination, including two add-on studies and a study with a factorial design, is acceptable. The three studies will be able to investigate the efficacy of the FDC and the monocomponents, and whether both components contribute to the effect of the FDC. More specifically, in patients with inadequate glycaemic control during treatment with metformin and one of the monocomponents (i.e. either linagliptin or empagliflozin), the two add-on studies will be able to investigate the effects of replacing monocomponent treatment with the fixed dose combination (linagliptin and empagliflozin). The factorial design study will investigate the effects of starting the fixed dose combination at once in comparison to starting treatment with one of the monocomponents.

The concomitant use of empagliflozin and linagliptin with sulphonylurea derivatives and insulin has not been studied. Both empagliflozin and linagliptin as monotherapy have shown to have a higher rate of hypoglycemia when combined with these agents. For the combination of empagliflozin and linagliptin, hypoglycaemia can therefore also be expected to occur when combined with these agents. For this reason, hypoglycaemia (with insulin and/or SU) is considered an important identified risk in the RMP. However, the combination with insulin is not sought and is not in the indication. Concomitant use of empagliflozin and linagliptin with glucagon like peptide 1 (GLP 1) analogues and thiazidediones has not been studied, but is also not sought.

The benefits of concomitant add-on treatment vs sequential add-on treatment in terms of glucose lowering effect have not been investigated. Sequential treatment allows the physician to evaluate the value of each added drug individually and thus avoids over-treating patients. In addition, efficacy is modest and may be variable between patients. As it is not known which patient will benefit most, treatment effects should be monitored in individual patients. This also argues in favour of sequential add-on treatment.

The initially proposed wording of the indication by the Applicant was not acceptable. Switching from other DPP4-inhibitors and SGLT2-inhibitors to empagliflozin/linagliptin combination therapy has not been studied. The Applicant therefore proposed a new wording for the indication taking into account the CHMP comments in the responses to the D 120 LOQ.

In addition, there was a contradiction between part of the indication (the substitution therapy) and section 4.2 where a starting dose of empa 10/lina 5 was recommended for all patients. The Applicant added more guidance to address all the patients cases as targeted in the agreed indication.

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

The randomisation and blinding procedures were adequate. The analysis populations, analysis of the primary and secondary endpoints and the hierarchical testing procedure to ensure control of the overall type I error rate are acceptable.

Efficacy data and additional analyses

A total of 1468 patients contributed to the analyses of efficacy (number of patients in the full analysis set). Of these, 1005 patients were treated with the actual fixed dose combination of empagliflozin (25 mg or 10 mg) and linagliptin (5 mg). The baseline characteristics were well balanced across the treatment groups.

Primary endpoint: HbA1c

Combined empagliflozin and linagliptin therapy with metformin background was associated with improvements in HbA1c in all Phase III studies. The contribution of empagliflozin to the effect of the FDC is relevant. However, the contribution of linagliptin to the effect of the FDC is borderline clinical relevance.

Empagliflozin as add-on therapy to linagliptin (study 1275.9):

The treatment effect of empagliflozin in patients that are treated with linagliptin was modest, but clinically relevant. The treatment effect of empagliflozin on top of linagliptin was -0.70% (95% CI: -0.93, -0.46) for empa 25 and -0.79% (95% CI: -1.02, -0.55) for empa 10.

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). 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%.

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

The difference between the FDC and monotherapy with linagliptin was of modest clinical relevance. In naïve patients, the treatment difference for the FDC empa 10/lina 5 was -0.57% (95% CI: -0.76, -0.37) versus lina 5. The treatment difference for the FDC empa 25 /lina 5 was -0.41% (95% CI: -0.61, -0.22; p<0.0001) versus lina 5. In metformin treated patients, the treatment difference for the FDC empa 10/lina 5 was -0.39% (95% CI: -0.56, -0.21) versus lina 5. The treatment difference for the FDC empa 25 /lina 5 was -0.50% (95% CI: -0.67, -0.32) versus lina 5.

The difference between the FDC and monotherapy with empagliflozin is of borderline clinical relevance. This is especially true for the naïve patients. In naïve patients, the treatment difference for the FDC empa 25/lina 5 group was only -0.14% (95% CI: -0.33, 0.06; p = 0.1785) vs. empagliflozin 25 mg monotherapy. The

treatment difference for the FDC empa10/lina 5 was only -0.41% (95% CI: -0.61, -0.21) versus empa 10 monotherapy. However, Glyxambi is only indicated in combination with metformin. 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. In metformin treated patients, the proportions of patients who achieved an HbA1c value of 7% were 64.9% and 60.0% for linagliptin in combination with empagliflozin 25 mg and 10 mg respectively and 35.7% and 34.3% for empagliflozin 25 mg and 10 mg respectively.

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 empagliflozin on top of linagliptin on fasting plasma glucose in study 1275.09 were modest. The placebo-adjusted mean change in FPG was -2.09 mmol/L (95% CI: -2.61, -1.57) for empa 25 and -1.80 mmol/L (95% CI: -2.31, -1.28) for empa 10.

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 and monotherapy with linagliptin in study 1275.1 was modest, but the differences between the FDC 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. In naïve patients, there was no relevant difference in the adjusted mean changes in FPG at Week 24 between the FDCs and the respective empagliflozin groups.

Other endpoints: body weight

Empagliflozin was associated with modest reductions in body weight. In study 1275.9, the placebo-adjusted mean change from baseline to Week 24 in body weight was -2.22 kg (95% CI: -2.92, -1.52) for empa 25 and -2.77 kg (95% CI: -3.47, -2.07) for empa 10.

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), empagliflozin and not linagliptin was associated with weight loss. 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. In study 1275.01 (naive): the difference was -1.22 kg (95.0% CI: -2.23,-0.21) for the FDC empagliflozin 25 mg/linagliptin 5 mg group and -1.96 kg (95.0% CI: -2.97,-0.95) for the FDC empagliflozin 10 mg/linagliptin 5 mg group.

Other endpoints: blood pressure

In study 1275.9, empagliflozin add-on to linagliptin and metformin provided reductions in systolic blood pressure after 24 weeks of treatment compared with placebo, with placebo-adjusted mean changes of -2.6 (SE 1.5) mmHg for empa 25 treatment and -1.3 (SE 1.5) mmHg for empa 10 treatment. A clinically relevant reduction in diastolic blood pressure was also observed for patients treated with empa 25, with a placebo-adjusted mean change of -1.1 (SE 1.1) mmHg; however, there was no reduction in diastolic blood pressure for patients treated with empa 10 (-0.1 (SE 1.1 mmHg).

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 similar reductions in both systolic and diastolic blood pressure in the FDC and empagliflozin groups. There were 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.

2.5.4. Conclusions on the clinical efficacy

The contribution of empagliflozin to the FDC empa/lina is relevant. When added to linagliptin, empagliflozin was associated with clinically relevant reductions in HbA1c. Moreover, addition of empagliflozin was associated with reductions in fasting glucose, body weight and blood pressure. Effects of linagliptin on HbA1c, when added to empagliflozin, were of modest clinical relevance. Addition of linagliptin was not associated with relevant reductions in fasting glucose nor with effects on body weight and blood pressure. In the fixed combination guideline (EMA/CHMP/689925/2014), it is stated that each component should contribute to the efficacy. Data from the factorial design study 1275.1(met) suggest that the treatment difference between the combination of empagliflozin/linagliptin and empagliflozin monotherapy was acceptable. Proportions of patients who achieved an HbA1c value of 7% due to linagliptin were also acceptable in study 1275.1 and 1275.10.

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 limits the external validity of the trial to the total population.

2.6. Clinical safety

Patient exposure

Overall, 2173 patients were treated in the Phase III studies 1275.9, 1275.10, and 1275.1. Of these, 1496 patients (68.8%) received metformin background medication and 1005 patients received combined empagliflozin and linagliptin treatment: 733 patients (72.9%) with pre-existing metformin background therapy (in studies 1275.9, 1275.10, and 1275.1(met)) and 272 (27.1%) without (in study 1275.1(naïve)). There were no safety issues in the 2 Phase I trials, which included a total of 58 healthy subjects.

Adverse events

Overview of adverse events in study 1275.9

In study 1275.9, the numbers of patients reported with at least 1 adverse event on-treatment were similar between both empagliflozin (add-on to linagliptin 5 mg and metformin) groups; a higher proportion of patients was reported for the placebo group (Table 12).

The proportion of patients reported with adverse events leading to treatment discontinuation was overall low (<2%). No patient died during the study. The numbers of patients reported with serious adverse events were similar between both empagliflozin (add-on to linagliptin 5 mg and metformin) groups; a higher proportion of patients was reported for the placebo group. For a detailed description of the different types of adverse events, see the sections below.

Table 12 Overview of patients with adverse events in study 1275.9 – TS

	Add-on to linagliptin 5 mg and metformin		
	Empa 25	**Empa 10**	**Placebo**
	N (%)	**N (%)**	**N (%)**
Number of patients	110 (100.0)	112 (100.0)	110 (100.0)
Patients with any adverse event	57 (51.8)	62 (55.4)	75 (68.2)
Adverse events leading to premature discontinuation of study medication	0	2 (1.8)	2 (1.8)
Serious adverse events	4 (3.6)	5 (4.5)	10 (9.1)
Fatal adverse event	0	0	0
Patients with AESIs			
Decreased renal function[1]	0	0	1 (0.9)
Hepatic injury[1]	0	0	2 (1.8)
Pancreatitis[1]	0	0	0
Urinary tract infection[2]	4 (3.6)	8 (7.1)	8 (7.3)
Genital infection[2]	5 (4.5)	2 (1.8)	2 (1.8)
Confirmed hypoglycaemic adverse events[3]	3 (2.7)	0	1 (0.9)
Bone fracture[2]	0	0	1 (0.9)
Volume depletion[2]	1 (0.9)	0	0
Malignancy[2]	0	1 (0.9)	1 (0.9)
Hypersensitivity reactions[1]	5 (4.5)	3 (2.7)	2 (1.8)

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 13). 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 13 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 14). 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 14 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)

Overview of adverse events in study 1275.1(naïve)

In study 1275.1(naïve), the numbers of patients reported with at least 1 adverse event on treatment were overall similar between treatment groups, with more patients reported with adverse events in the empagliflozin 10 mg group (Table 15). Adverse events leading to treatment discontinuation were reported for more patients in the empagliflozin/linagliptin and empagliflozin groups than in the linagliptin group. The proportion of patients reported with serious adverse events was overall low, but higher in the empagliflozin/linagliptin and empagliflozin groups than in the linagliptin group. Four cases of deaths were reported on-treatment: 2 patients died in the empagliflozin 25 mg treatment group, 1 patient in the empagliflozin 10 mg/linagliptin 5 mg treatment group, and 1 patient in the empagliflozin 10 mg treatment group. For a detailed description of the different types of adverse events, see the sections below.

Table 15 Overview of patients with adverse events in study 1275.1(naïve) – TS

	Empa 25/ lina 5	Empa 25	Empa 10/ lina 5	Empa 10	Lina 5
	N (%)	N (%)	N (%)	N (%)	N (%)
Number of patients	136 (100.0)	135 (100.0)	136 (100.0)	135 (100.0)	135 (100.0)
Patients with any adverse event	103 (75.7)	93 (68.9)	99 (72.8)	110 (81.5)	97 (71.9)
Adverse events leading to premature discontinuation of study medication	9 (6.6)	5 (3.7)	8 (5.9)	7 (5.2)	2 (1.5)
Serious adverse events	6 (4.4)	9 (6.7)	7 (5.1)	10 (7.4)	2 (1.5)
Fatal adverse event	0 (0.0)	2 (1.5)	1 (0.7)	1 (0.7)	0 (0.0)
Patients with AESIs					
Decreased renal function[1]	0	0	0	0	0
Hepatic injury[1]	2 (1.5)	4 (3.0)	3 (2.2)	0	4 (3.0)
Pancreatitis[1]	1 (0.7)	0	0	0	0
Urinary tract infection[2]	17 (12.5)	14 (10.4)	21 (15.4)	22 (16.3)	14 (10.4)
Genital infection[2]	8 (5.9)	6 (4.4)	4 (2.9)	7 (5.2)	4 (3.0)
Confirmed hypoglycaemic adverse events[3]	0	1 (0.7)	0	4 (3.0)	1 (0.7)
Bone fracture[2]	3 (2.2)	2 (1.5)	0	0	0
Volume depletion[2]	1 (0.7)	0	3 (2.2)	0	0
Malignancy[2]	2 (1.5)	1 (0.7)	1 (0.7)	0	0
Hypersensitivity reactions[1]	9 (6.6)	5 (3.7)	7 (5.1)	5 (3.7)	3 (2.2)

Serious adverse event / deaths / other significant events

Serious adverse events

Most frequently reported serious adverse events

The frequency of patients with serious adverse events in each add-on study was generally low (less than 9.5%) and overall lower in the add-on therapy groups than in the respective placebo groups in patients who had already received treatment with either linagliptin or empagliflozin and metformin. Each serious adverse event PT was reported for only 1 patient (0.9%) per treatment group. In the factorial design study 1275.1, the frequencies of patients with serious adverse events were generally similar across treatment groups (less than 8.0%).

Overall, treatment with empagliflozin added to linagliptin and metformin, with linagliptin added to empagliflozin and metformin, or combined FDC therapy in patients with or without metformin background did not indicate an increased risk of serious adverse events compared with treatment with either individual component in the presence or absence of metformin.

Deaths

No patients were reported with fatal adverse events in the open-label or double-blind treatment periods of studies 1275.9 and 1275.10. Six patients in study 1275.1 had fatal adverse events with an on-treatment onset, 2 of whom had received combined therapy with empa 10/lina 5 and metformin (fatal PTs: haemorrhagic stroke and hypertensive heart disease). Each fatal PT was reported in 1 patient only.

Adverse events of special interest

Based on the modes of action, known safety profiles, or safety topics of interest for currently available SGLT-2 and DPP-4 inhibitors, safety data were searched for AESIs.

Decreased renal function

As the mode of action of SGLT-2 inhibitors depends on renal function, decreased renal function was a prespecified event in the Phase III clinical trial protocols. Investigators were to report increased serum creatinine values (≥ 2x baseline and above the upper limit of normal [ULN]) as in an expedited manner to the sponsor. In all studies, the frequency of patients with decreased renal function adverse events or significant laboratory values was low (0 to 0.9%). Patients were reported with adverse events belonging to the SMQ 'acute renal failure' at low frequencies in Phase III studies (1 patient per treatment group, 0.4 to 0.9%). In an analysis based on the criterion for serum creatinine values defined above, only 2 patients were identified, both in study 1275.1(met): 1 patient in the low dose FDC group and 1 patient in the high dose FDC group.

Small comparable fluctuations in mean eGFR and eCCr values over time were observed in all treatment groups in each study. There were no differences across groups with regard to the proportions of patients who shifted into worse or better renal function categories based on eGFR values. In line with the study inclusion criteria, the majority of the patients had baseline values in the normal or microalbuminuria ranges. The proportions of patients with shifts from one urine-albumine-to-creatinine ratio (UACR) category to another were overall low and comparable across studies and treatment groups.

Hepatic injury

Expedited reporting by the investigators was required for patients with laboratory values consistent with a biochemical Hy's law constellation, defined as ALT and/or AST ≥ 3x ULN with concomitant or subsequent total bilirubin ≥ 2x ULN within 30 days after ALT/AST elevation; information on whether alkaline phosphatase levels (the maximum value in the 30-day period mentioned above) reached 2x ULN or more was to be provided. In addition, increased ALT/AST levels were to also be reported (ALT or AST ≥ 3x, ≥ 5x, ≥ 10x, ≥ 20x ULN). Patients with ALT and/or AST ≥ 5xULN met the criteria for adjudication by an independent committee.

Overall, there was no evidence of an increased risk of patients developing increased liver enzyme values or drug-induced liver injury when empagliflozin was added to linagliptin treatment on a metformin background, when linagliptin was added to empagliflozin on a metformin background, or when the FDC was compared to the individual components in the presence or absence of metformin.

The frequency of patients reported with hepatic adverse events was low (<3.0%) and comparable across treatment groups in each study. Liver enzyme (ALT/AST) elevations in the range ≥ 3x ULN and <5x ULN were rare in each study (reported for ≤ 2 patients per treatment group). The most common PTs were hepatic steatosis and several PTs indicating increased liver enzymes. Hepatic events with an onset within 30 days after the last dose of double-blind treatment medication were rare (≤ 1 patients per study).

All treatment-emergent cases suspected of drug-induced liver injury were adjudicated in a blinded fashion by an independent committee of external hepatic experts. A total of 5 patients in combined therapy groups, all on metformin background therapy, had hepatic cases sent for adjudication that were confirmed: 2 with a possible causal relationship to study drug and 3 with a probable relationship to study drug.

Pancreatitis

Overall in the Phase III studies, only 3 patients were reported with pancreatitis: 1 patient (0.8%) with a serious acute pancreatitis in the lina 5 group (add-on to empa 10 and metformin) in study 1275.10; 1 patient (0.8%) with a serious chronic pancreatitis in the lina 5 group in study 1275.1(met); 1 patient (0.7%) with a non-serious acute pancreatitis in the FDC empa 25/lina 5 group in study 1275.1(naïve).

Urinary tract infection

Despite urinary tract infection being a labelled side-effect for empagliflozin, there was no evidence of an increased risk of urinary tract infection for combined empagliflozin and linagliptin treatment with or without metformin background, compared with either empagliflozin or linagliptin treatment, in the presence or absence of metformin.

Overall, less than 16.5% of patients across studies and treatment groups were reported with (BIcMQ: Boehringer Ingelheim customized MEdDRA Query) urinary tract infection events. Most patients were assigned therapy as consequence of their infection, and most patients only had 1 episode of urinary tract infection. The frequency of patients with urinary tract infection (BIcMQ) was higher in women than in men, but there was no treatment difference in either women or men. There was no clear effect of age, baseline HbA1c, or history of urinary tract infections on the occurrence of urinary tract infections. Discontinuation of trial medication due to a urinary tract infection was rare (≤ 3 patients per study.)

In study 1275.9 (empagliflozin add-on to linagliptin and metformin), 3.6% of the patients in the empa 25 group and 7.1% of the patients in the empa 10 of patients had urinary tract infections (BIcMQ), compared with 7.3% of the patients treated with placebo. In study 1275.10(met+empa 25) (lina 5 add-on to empa 25 and metformin), a higher proportion of patients had urinary tract infections when treated with lina 5 (13.4% of patients) than when treated with placebo (8.0%). In study 1275.10(met+empa 10) (lina 5 add-on to empa 25 and metformin), similar proportions of patients had urinary tract infections (BIcMQ) when treated with lina 5 (9.5%) and with placebo (7.8%). In the add-on studies, only 1 severe event was reported, for 1 patient in study 1275.10(met+empa10), which led to hospitalisation of the patient.

There were no clinically relevant differences in the frequencies of patients reported with urinary tract infections across treatment groups in the factorial design study 1275.1. In study 1275.1(met), the frequency of patients with urinary tract infections ranged from 9.6 to 15.2%. In study 1275.1(naïve), the proportion of patients with urinary tract infections ranged from 10.4 to 16.3% across treatment groups.

Genital infections

In the empagliflozin/linagliptin clinical development programme, combined treatment with empagliflozin and linagliptin did not increase the risk of genital infection compared with empagliflozin treatment, in the presence or absence of metformin.

Overall, less than 9.0% of patients at treatment group level in each study had (BIcMQ) genital infections. Overall, the numerical differences between treatment groups in Phase III studies were not considered clinically relevant, given the low number of patients reported with such events. Most events were of mild or moderate intensity. Most patients were assigned therapy as a consequence of their infection, and most patients had only 1 episode of genital infection (BIcMQ). Overall, the frequency of patients with genital infection (BIcMQ) was higher in women than in men; an exception to this was the group FDC empa 25/lina 5, where frequencies of genital infection (BIcMQ) were comparable between genders. There was no clear treatment difference in either women or men; no clear effect of age, baseline HbA1c, or history of genital

infections was observed. Severe or serious genital infections and premature discontinuations of study medication due to genital infection were very infrequent (2 patients, both in study 1275.1(met)).

In study 1275.9 (empagliflozin add-on to linagliptin and metformin), a higher proportion of patients had genital infection (BIcMQ) in the empa 25 group (4.5%) than in the empa 10 and placebo groups (1.8% each). In study 1275.10(met+empa25) (linagliptin add-on to empa 25 and metformin), the frequency of patients with genital infections was lower with linagliptin treatment (2.7%) than with placebo treatment (8.0%). In study 1275.10(met+empa10) (linagliptin add-on to empa 10 and metformin), the frequency of patients with genital infections was similar across groups: 2.4% in the lina 5 group and 3.1% in the placebo group. Premature discontinuation due to a genital infection was not reported in studies 1275.9 and 1275.10. One patient in study 1275.10 required hospitalisation. In the factorial design study 1275.1, the frequencies of patients with genital infections ranged from 2.2 to 8.5% for metformin-treated patients and 2.9 to 5.9% for drug-naïve patients.

Hypoglycaemic adverse events

Hypoglycaemia is a labelled side effect of both empagliflozin and linagliptin (when taken together with insulin or sulphonylurea). In the Phase III studies, investigators were asked to provide additional information on the case report forms (CRFs) for hypoglycaemic events, such as whether they were symptomatic or not, as well as the corresponding plasma glucose value. In the safety analyses, 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. Events that required the assistance of another person were categorised as major hypoglycaemia.

The frequency of patients with confirmed hypoglycaemic adverse events was low (0 to 2.7% per treatment group in each Phase III study). Overall, 2 events required external assistance: 1 event in the empa 25 group (add-on to lina 5+metformin in study 1275.9) and 1 event in the lina 5 group (add-on to empa 25+metformin in study 1275.10). No clear effect of sex or time to onset of confirmed hypoglycaemic events was observed.

In conclusion, combined treatment with empagliflozin and linagliptin on a metformin background did not increase the risk of (major) hypoglycaemia compared with empagliflozin or linagliptin, regardless of which of the sequence of adding the individual components.

Bone fracture

Bone fracture (BIcMQ) was not identified as a potential risk in the Phase III clinical study protocols. The BI-customised MedDRA search included about 60 PTs of fractures. The overall frequencies of patients with bone fracture (BIcMQ) were low and similar across treatment groups (≤ 4 patients [<3.0%] per treatment group in each study). At PT level, there were no notable imbalances across treatment groups [Module 2.7.4, Section 2.1.6.7]. Combined treatment with empagliflozin and linagliptin with or without metformin background was not associated with an increased risk of bone fracture compared with treatment with empagliflozin, with or without metformin.

Volume depletion

Volume depletion is a labelled side effect of empagliflozin and was summarised based on a MedDRA search of reported adverse events (BIcMQ). Based on the mode of action of empagliflozin, treatment with empagliflozin lowers blood pressure, possibly because of osmotic diuresis and fluid loss. Volume depletion could also be a result of increased urination (such as pollakiuria and polyuria). There was no specific exclusion criterion for patients at risk for volume depletion in the trial protocols. The overall frequencies of patients with volume

depletion (BIcMQ) were low for all studies and treatment groups (<3.0%). The most frequently reported adverse event was hypotension. Combined treatment with empagliflozin and linagliptin with or without metformin background therapy did not increase the risk of volume depletion compared with empagliflozin treatment, with or without metformin.

Malignancy

Malignancy was not identified as a possible risk in the study protocols. Fifteen patients were reported with malignancies during the double-blind treatment period of the Phase III studies (not more than 3 patients per treatment group, 0 to 2.2%). Two patients were reported with malignancies in the post-treatment period. The reported malignancies were of several different tumour types and locations at PT level, without a clear trend for a certain tumour type or location. About half of the malignancies had an onset date after 6 months of treatment. No cases of thyroid neoplasms were reported in any Phase III study.

Most of the reported malignancies were in the 52-week study 1275.1 (13 patients, 0.4% to 1.8% per treatment group, of which 7 patients [1.3%] were on FDC treatment). Two patients were reported with malignancies in the empagliflozin add-on to linagliptin study 1275.9: 1 patient in the empa 10 (add-on to lina 5 and metformin) group had breast cancer and 1 patient in the placebo (add-on to lina 5 and metformin) group had a bladder neoplasm. One malignancy was reported in the post-treatment period of the linagliptin add-on to empagliflozin study 1275.10 (in the lina 5 add-on to empa10 and metformin group, PT: pancreatic carcinoma).

Hypersensitivity reactions

The frequency of patients with hypersensitivity reactions (SMQ) was less than 7.0% per treatment group at study level and generally similar across treatment groups in each trial.

At PT level, patients were most frequently reported with dermatitis in study 1275.9 (empagliflozin add-on to linagliptin and metformin): 1 patient in the empa 25 group and 2 patients in the empa 10 group. In study 1275.10 (linagliptin add-on to empagliflozin and metformin), each hypersensitivity event was reported in 1 patient only at PT level.

In study 1275.1(met), patients were most frequently reported with eczema: 2 patients in each of the empa 25 and lina 5 groups and 1 patient in each of the FDC empa 25/lina5 and empa 10 groups. In study 1275.1(naïve), patients were most frequently reported with rash and allergic rhinitis (4 patients for each PT, 1 in each treatment group except for empa 25). Urticaria was the only PT reported in 2 patients per treatment group, both in the empa 25 group. All other reported hypersensitivity reactions PTs were in 1 patient each at treatment group level.

Thus, combined treatment with empagliflozin and linagliptin did not increase the risk of hypersensitivity reactions compared with the individual components when administered in patients, with or without metformin background therapy.

Laboratory findings

This section summarises parameters with results of particular interest (haematocrit, uric acid, lipase, and serum lipids).

Haematocrit

Treatment with empagliflozin (25 or 10 mg) add-on therapy to linagliptin and metformin in study 1275.9 resulted in small increases in haematocrit levels (of about 4.0%) from baseline to the last value on-

treatment; there was no change in haematocrit in the placebo group. There were no notable changes in haematocrit levels in the linagliptin add-on to empagliflozin and metformin study 1275.10. In the factorial study 1275.1, treatment with either dose of the FDC empa/lina or empagliflozin monotherapy resulted in increased haematocrit levels from baseline to last value on-treatment (of up to 4.5%), compared with a smaller increase from baseline with lina 5 treatment (1.3%).

In line with these results, higher proportions of patients had shifts from the normal range at baseline to higher than ULN values at the end-of-treatment when treated with empagliflozin add-on to linagliptin and metformin than with placebo in study 1275.9. In contrast, treatment with linagliptin as add-on therapy to empagliflozin and background metformin in study 1275.10 was not associated with shifts from normal baseline values to higher than ULN values at the end-of-treatment. In the factorial design study 1275.1, higher proportions of patients had shifts from normal values to higher than ULN values with FDC or empagliflozin treatment (4.3 to 8.9% in study 1275.1(met) and 9.7 to 15.1% in study 1275.1(naïve)) than with linagliptin treatment (1.7% in study 1275.1(met) and 0.8% in study 1275.1(naïve)). Possibly clinically significant abnormal haematocrit values in the high range were reported for <3.5% of patients per treatment group at study level in all Phase III studies.

In conclusion, treatment with empagliflozin as add-on to linagliptin on a metformin background or with the FDC empagliflozin/linagliptin in patients with or without metformin background were associated with small increases in haematocrit; however, these changes were not associated with thromboembolic complications.

Uric acid

Treatment with empagliflozin 25 or 10 mg as add-on therapy to linagliptin and metformin background in study 1275.9 resulted in decreased uric acid values from baseline to last value on-treatment, whereas there was a small increase in the placebo group. In contrast, treatment with linagliptin as add-on therapy to empagliflozin and metformin background in study 1275.10 was not associated with decreased uric acid levels. Treatment with either FDC dose or (with or without metformin) in study 1275.1 resulted in decreased uric acid levels from baseline to last value on-treatment. There was a slight increase from baseline with linagliptin.

In the empagliflozin add-on to linagliptin and metformin study 1275.9, higher proportions of patients had shifts from higher than ULN values at baseline to normal values at end-of-treatment, or from normal values at baseline to lower than LLN at the end-of-treatment when treated with empagliflozin than when treated with placebo. In the linagliptin add-on to empagliflozin and metformin study 1275.10, shifts in uric acid from one range at baseline to another range after 24 weeks of treatment were rare and similar across treatment groups. In the factorial design study 1275.1, higher proportions of patients had shifts from the normal range to less than LLN values or from higher than ULN values at baseline to the normal range at the end-of treatment when treated with FDC or empagliflozin than with linagliptin. The proportion of patients with possibly clinically significant abnormal uric acid values was low in all studies.

Uric acid increased with empagliflozin add-on therapy to linagliptin, but decreased during treatment with the FDC. The clinical relevance of changes in uric acid values is unclear. In some epidemiological studies, uric acid has been reported as a marker of cardiovascular risk, with lower uric acid levels associated with lower cardiovascular morbidity and mortality.

Lipase

Normalised mean baseline lipase values were generally similar in all treatment groups in the Phase III studies. In the empagliflozin add-on to linagliptin and metformin study 1275.9, a mean decrease in lipase

values was observed in the empagliflozin groups; there was no change in the placebo group. In the linagliptin add-on to empagliflozin and metformin study 1275.10, a mean increase in lipase values was observed in all groups. In the factorial design study 1275.1(met), there was a mean increase in lipase from baseline to Week 52 in the lina 5 and FDC groups and no change in the empagliflozin groups. In the factorial design study 1275.1(naïve), a similar pattern for lipase changes was observed.

The proportions of patients with shifts from normal values at baseline to >ULN at last value on-treatment or with possibly clinically significant abnormal high values were generally higher in the treatment groups including linagliptin than in treatment groups including empagliflozin alone. Frequencies of shifts were similar across treatment groups in study 1275.9. In study 1275.1(naïve), the proportions of patients with possibly clinically significant abnormal high values ranged from 2.3 to 10.6% across treatment groups.

As expected, linagliptin was associated with higher lipase levels.

Serum lipids

Changes from baseline to the last value on-treatment

In studies 1275.9 and 1275.1, small mean increases from baseline to end-of-treatment were observed for total cholesterol, HDL-cholesterol, and LDL-cholesterol in the empagliflozin and combined therapy groups, but not for lina 5 treatment. There was no notable trend in the change from baseline in cholesterol levels in study 1275.10. In study 1275.9, mean decreases in triglyceride levels were noticed across; there were generally mean increases in triglycerides in study 1275.10. In study 1275.1, mean increases were observed for triglyceride levels in the linagliptin or combined therapy groups, compared with decreases in the empagliflozin groups. The HDL-cholesterol/LDL-cholesterol ratio did not change. The causes for the increases in serum lipids are unknown but haemoconcentration might have contributed to this effect, given the mode of action of empagliflozin.

Shifts from baseline to end-of-treatment

In the add-on study 1275.9, the proportions of patients with shifts from normal values at baseline to higher than ULN levels at last value on-treatment were slightly higher in the empagliflozin groups than in the placebo group for total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglycerides. Additionally, for triglycerides, the proportions of patients with shifts from higher than ULN values at baseline to the normal range at last value on-treatment were also higher in the empagliflozin groups than in the placebo group.

In the add-on study 1275.10, the proportions of patients with shifts from normal cholesterol values at baseline to higher than ULN at last value on-treatment ranged from 20% to 22.6% and were comparable between treatment groups. The proportions of patients with shifts from normal triglycerides values at baseline to higher than ULN levels at last value on-treatment, or from higher than ULN values at baseline to the normal range at last value on-treatment were higher in the empagliflozin groups than in the placebo group.

In the factorial design study 1275.1(met), higher proportions of patients had shifts from normal cholesterol values to higher than ULN values at Week 52 with FDC or empagliflozin treatment than with linagliptin treatment. There were no notable differences across treatment groups in the proportions of patients with shifts from normal values at baseline to higher than ULN or to lower than LLN values at end of treatment for triglycerides.

In the factorial design study 1275.1(naïve), there were frequent transitions from baseline values to higher than ULN for total cholesterol, LDL-cholesterol, and triglycerides. Higher proportions of patients had shifts in

LDL-cholesterol from normal values at baseline to higher than ULN values at Week 52 in the FDC empa 10/lina 5 and empa 10 groups than in the other groups. Lower proportions of patients had shifts in total cholesterol values from the normal range at baseline to higher than ULN values at Week 52 in the lina 5 group than in other groups. Apart from that, there were no notable differences between groups with regard to shifts from the normal range at baseline to higher than ULN or lower than LLN values at Week 52.

Possibly clinically significant abnormalities

Overall in Phase III studies, the proportions of patients with possibly clinically significant abnormalities for lipid parameters ranged from 1.9 to 12.9% per treatment group across studies. In the add-on study 1275.9, the proportions of patients with possibly clinically abnormal values in the high range were higher in the empagliflozin groups than in the placebo group for total cholesterol; comparable proportions of patients had possibly clinically abnormal triglyceride values across treatment groups. In the add-on study 1275.10, similar proportions of patients had possibly clinically abnormal total cholesterol and triglyceride values across treatment groups. In the factorial design study 1275.1, in both patient populations, the proportions of patients with possibly clinically significant abnormal values of cholesterol and triglycerides were comparable across treatment groups.

Vital signs

The frequency of patients with hypotension or orthostatic hypotension was low and comparable between treatment groups in all studies, despite the reduction in blood pressure with empagliflozin add-on to linagliptin and metformin compared with placebo in study 1275.9, and after treatment with the FDCs compared with linagliptin in study 1275.1(met). Therefore, in the empagliflozin/linagliptin clinical development programme, combined treatment with empagliflozin and linagliptin with or without metformin did not lead to a higher frequency of risk for hypotensive adverse events compared with treatment with the individual components, in the presence or absence of metformin. For all treatment groups in all studies, there were almost no changes in pulse rate from baseline to end-of-treatment.

Safety in special populations

For the integrated analyses, subgroup analyses were generally only performed for individual Phase III studies and not for study groupings. This summary focuses on subgroups analyses in the pivotal Phase III studies 1275.9 and 1275.10.

Age

Only subjects at least 18 years of age were included in the studies described in this document. In the add-on studies 1275.9 and 1275.10, about 90% of the patients were younger than 65 years at baseline. Only around 15% were between 65 and 75 years, 2% were older than 75 years, and 1 patient was older than 85 years. Therefore results of subgroup analyses of patients older than 65 years are mostly inconclusive.

The number of patients by age category is shown in Table 16,17 and 18.

Table 16 Number of patients by age category (FDC empa/lina) – Treated Set

eCTD Module	Age 65-74 number / total number (all ages)	Age 75-84 number / total number (all ages)	Age 85+ number / total number (all ages)

Efficacy and safety Studies	167/1005	19/1005	0/1005
Human PK Studies 1275.3 healthy volunteers, crossover design (all patients received different free or fixed combinations) 1245.30 healthy volunteers, crossover design (all patients received mono and free combination)	0/42 0/16	0/42 0/16	0/42 0/16
Human PD Studies	NA	NA	NA
Biopharmaceutical Studies	NA	NA	NA

Table 17 Number of patients by age category (empagliflozin) – Treated Set

eCTD Module	**Age 65-74** number / total number (all ages)	**Age 75-84** number / total number (all ages)	**Age 85+** number / total number (all ages)
Efficacy and safety Studies	113/791	21/791	2/791
Human PK Studies 1275.3 healthy volunteers, crossover design (all patients received different free or fixed combinations)	0/16	0/16	0/16
Human PD Studies	NA	NA	NA
Biopharmaceutical Studies	NA	NA	NA

Table 18 Number of patients by age category (linagliptin) – Treated Set

eCTD Module	**Age 65-74** number / total number (all ages)	**Age 75-84** number / total number (all ages)	**Age 85+** number / total number (all ages)
Efficacy and safety Studies	64/377	7/377	0/377

Human PK Studies 1245.30 healthy volunteers, crossover design (all patients received mono and free combination)	0/16	0/16	0/16
Human PD Studies	NA	NA	NA
Biopharmaceutical Studies	NA	NA	NA

The frequency of patients with adverse events by the age category are shown in, Table 19, Table 20 and 21

Table 19 Frequency of patients with adverse events by age in study 1275.9$_{(met+lina5)}$ – Treated Set

MedDRA Terms	**Age <65 number (%[1])**	**Age 65-74 number (%[1])**	**Age 75-84 number (%[1])**	**Age 85+ number (%[1])**
Total AEs	164 (58.2)	26 (57.8)	4 (80.0)	0
Serious AEs – Total	16 (5.7)	3 (6.7)	0	0
- Fatal	0	0	0	0
- Hospitalization/prolong existing hospitalization				
- Requiring hospitalization	12 (4.3)	3 (6.7)	0	0
- Prolonging hospitalization	0	0	0	0
- Life-threatening	0	0	0	0
- Disability/incapacity	0	0	0	0
- Other (medically significant)	5 (1.8)	0	0	0
AE leading to drop-out	4 (1.4)	0	0	0
Psychiatric disorders[2]	12 (4.3)	2 (4.4)	0	0
Nervous system disorders[2]	26 (9.2)	4 (8.9)	0	0
Accidents and injuries[3]	15 (5.3)	1 (2.2)	0	0
Cardiac disorders[2]	3 (1.1)	0	0	0
Vascular disorders[2]	7 (2.5)	1 (2.2)	0	0
Cerebrovascular disorders[3]	0	0	0	0
Infections and infestations[2]	72 (25.5)	14 (31.1)	2 (40.0)	0

Anticholinergic syndrome[3]	11 (3.9)	1 (2.2)	0	0
Quality of life decreased[2]	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[4]	10 (3.5)	1 (2.2)	0	0
Other AE appearing more frequently in older patients[5]				
- Nasopharyngitis	12 (4.3)	5 (11.1)	0	0

Table 20 Frequency of patients with adverse events by age in study 1275.10*(met+empa25)* – Treated Set

MedDRA Terms	**Age <65 number (%[1])**	**Age 65-74 number (%[1])**	**Age 75-84 number (%[1])**	**Age 85+ number (%[1])**
Total AEs	98 (53.8)	22 (59.5)	4 (100.0)	1 (100.0)
Serious AEs – Total	5 (2.7)	1 (2.7)	1 (25.0)	0
- Fatal	0	0	0	0
- Hospitalization/prolong existing hospitalization				
- Requiring hospitalization	4 (2.2)	1 (2.7)	1 (25.0)	0
- Prolonging hospitalization	0	0	0	0
- Life-threatening	0	0	0	0
- Disability/incapacity	0	0	0	0
- Other (medically significant)	1 (0.5)	0	0	0
AE leading to drop-out	3 (1.6)	2 (5.4)	1 (25.0)	0
Psychiatric disorders[2]	7 (3.8)	1 (2.7)	0	0
Nervous system disorders[2]	4 (2.2)	1 (2.7)	0	0
Accidents and injuries[3]	9 (4.9)	1 (2.7)	0	0
Cardiac disorders[2]	4 (2.2)	0	0	0
Vascular disorders[2]	5 (2.7)	2 (5.4)	1 (25.0)	0
Cerebrovascular disorders[3]	0	0	0	0
Infections and infestations[2]	45 (24.7)	9 (24.3)	3 (75.0)	0
Anticholinergic syndrome[3]	1 (0.5)	0	0	0

Quality of life decreased[2]	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[4]	4 (2.2)	0	0	0
Other AE appearing more frequently in older patients				
- Urinary tract infection[5]	12 (6.6)	6 (16.2)	0	0

[1] Within each age category
[2] By system-organ class, exposure-adjusted safety data
[3] Based on an SMQ (Standard MedDRA query) search, exposure-adjusted safety data; 387 PTs were included in the search for the SMQ category 'Accidents and injuries', 49 PTs for 'Anticholinergic syndrome', and 197 for 'Cerebrovascular disorders'
[4] The total number of selected PTs was 3778.
[5] Patients ≥65 years of age were reported more frequently with this preferred term than patients <65 years of age

Table 21 Frequency of patients with adverse events by age in study 1275.10*(met+empa10)* – Treated Set

MedDRA Terms	Age <65 number (%[1])	Age 65-74 number (%[1])	Age 75-84 number (%[1])	Age 85+ number (%[1])
Total AEs	103 (50.5)	24 (57.1)	5 (62.5)	0
Serious AEs – Total	8 (3.9)	1 (2.4)	0	0
- Fatal	0	0	0	0
- Hospitalization/prolong existing hospitalization				
- Requiring hospitalization	7 (3.4)	1 (2.4)	0	0
- Prolonging hospitalization	0	0	0	0
- Life-threatening	0	0	0	0
- Disability/incapacity	0	0	0	0
- Other (medically significant)	1 (0.5)	0	0	0
AE leading to drop-out	7 (3.4)	0	0	0
Psychiatric disorders[2]	6 (2.9)	2 (4.8)	0	0
Nervous system disorders[2]	13 (6.4)	1 (2.4)	1 (12.5)	0
Accidents and injuries[3]	3 (1.5)	1 (2.4)	0	0
Cardiac disorders[2]	3 (1.5)	4 (9.5)	0	0
Vascular disorders[2]	5 (2.5)	1 (2.4)	1 (12.5)	0
Cerebrovascular disorders[3]	1 (0.5)	0	0	0
Infections and infestations[2]	50 (24.5)	11 (26.2)	3 (37.5)	0
Anticholinergic syndrome[3]	8 (3.9)	2 (4.8)	0	0
Quality of life decreased[2]	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[4]	4 (2.0)	1 (2.4)	1 (12.5)	0

Other AE appearing more frequently in older patients				
- Back pain[5]	5 (2.5)	2 (4.8)	3 (37.5)	0
- Arthralgia[5]	2 (1.0)	1 (2.4)	2 (25.0)	0

[1] Within each age category
[2] By system-organ class, exposure-adjusted safety data
[3] Based on an SMQ (Standard MedDRA query) search, exposure-adjusted safety data; 387 PTs were included in the search for the SMQ category 'Accidents and injuries', 49 PTs for 'Anticholinergic syndrome', and 197 for 'Cerebrovascular disorders'
[4] The total number of selected PTs was 3778.
[5] Patients ≥65 years of age were reported more frequently with this preferred term than patients <65 years of age

Table 22 Frequency of patients with adverse events by age in study 1275.1$_{(met)}$ – Treated Set

MedDRA Terms	**Age <65 number (%[1])**	**Age 65-74 number (%[1])**	**Age 75-84 number (%[1])**	**Age 85+ number (%[1])**
Total AEs	382 (69.6)	82 (71.3)	18 (85.7)	0
Serious AEs – Total	27 (4.9)	8 (7.0)	4 (19.0)	0
- Fatal	2 (0.4)	0	0	0
- Hospitalization/prolong existing hospitalization				
- Requiring hospitalization	22 (4.0)	4 (3.5)	3 (14.3)	0
- Prolonging hospitalization	2 (0.4)	0	0	0
- Life-threatening	1 (0.2)	0	0	0
- Disability/incapacity	0	0	1 (4.8)	0
- Other (medically significant)	4 (0.7)	4 (3.5)	1 (4.8)	0
AE leading to drop-out	13 (2.4)	7 (6.1)	2 (9.5)	0
Psychiatric disorders[2]	25 (4.6)	1 (0.9)	1 (4.8)	0
Nervous system disorders[2]	78 (14.2)	13 (11.3)	5 (23.8)	0
Accidents and injuries[3]	35 (6.4)	14 (12.2)	3 (14.3)	0
Cardiac disorders[2]	17 (3.1)	4 (3.5)	0	0
Vascular disorders[2]	23 (4.2)	7 (6.1)	3 (14.3)	0
Cerebrovascular disorders[3]	4 (0.7)	0	0	0
Infections and infestations[2]	212 (38.6)	46 (40.0)	9 (42.9)	0
Anticholinergic syndrome[3]	22 (4.0)	4 (3.5)	3 (14.3)	0

Quality of life decreased[2]	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[4]	35 (6.4)	9 (7.8)	3 (14.3)	0
Other AE appearing more frequently in older patients				
- Bronchitis[5]	12 (2.2)	9 (7.8)	1 (4.8)	0
- Constipation[5]	14 (2.6)	10 (8.7)	1 (4.8)	0

[1] Within each age category

[2] By system-organ class, exposure-adjusted safety data

[3] Based on an SMQ (Standard MedDRA query) search, exposure-adjusted safety data; 387 PTs were included in the search for the SMQ category 'Accidents and injuries', 49 PTs for 'Anticholinergic syndrome', and 197 for 'Cerebrovascular disorders'

[4] The total number of selected PTs was 3778.

[5] Patients ≥65 years of age were reported more frequently with this preferred term than patients <65 years of age

Table 23 Frequency of patients with adverse events by age in study 1275.1*(drug-naïve)* – Treated Set

MedDRA Terms	**Age <65 number (%[1])**	**Age 65-74 number (%[1])**	**Age 75-84 number (%[1])**	**Age 85+ number (%[1])**
Total AEs	416 (73.9)	79 (75.2)	7 (77.8)	0
Serious AEs – Total	24 (4.3)	8 (7.6)	2 (22.2)	0
- Fatal	2 (0.4)	1 (1.0)	1 (11.1)	0
- Hospitalization/prolong existing hospitalization				
- Requiring hospitalization	20 (3.6)	6 (5.7)	2 (22.2)	0
- Prolonging hospitalization	1 (0.2)	1 (1.0)	0	0
- Life-threatening	4 (0.7)	0	0	0
- Disability/incapacity	3 (0.5)	0	0	0
- Other (medically significant)	3 (0.5)	1 (1.0)	0	0
AE leading to drop-out	25 (4.4)	5 (4.8)	1 (11.1)	0
Psychiatric disorders[2]	22 (3.9)	5 (4.8)	0	0
Nervous system disorders[2]	80 (14.2)	20 (19.0)	1 (11.1)	0
Accidents and injuries[3]	30 (5.3)	4 (3.8)	1 (11.1)	0
Cardiac disorders[2]	15 (2.7)	5 (4.8)	1 (11.1)	0

Vascular disorders[2]	25 (4.4)	10 (9.5)	0	0
Cerebrovascular disorders[3]	2 (0.4)	1 (1.0)	0	0
Infections and infestations[2]	222 (39.4)	40 (38.1)	4 (44.4)	0
Anticholinergic syndrome[3]	37 (6.6)	8 (7.6)	1 (11.1)	0
Quality of life decreased[2]	0	0	0	0
Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures[4]	29 (5.2)	6 (5.7)	1 (11.1)	0
Other AE appearing more frequently in older patients				
- Urinary tract infection[5]	52 (9.2)	15 (14.3)	2 (22.2)	0

[1] Within each age category

[2] By system-organ class, exposure-adjusted safety data

[3] Based on an SMQ (Standard MedDRA query) search, exposure-adjusted safety data; 387 PTs were included in the search for the SMQ category 'Accidents and injuries', 49 PTs for 'Anticholinergic syndrome', and 197 for 'Cerebrovascular disorders'

[4] The total number of selected PTs was 3778.

[5] Patients ≥65 years of age were reported more frequently with this preferred term than patients <65 years of age

In studies 1275.9 and 1275.10, the frequency of patients with adverse events was not obviously affected by the age category. Within each age category, the trends in the frequency of all types of adverse events were consistent with those for the overall population.

In the factorial design study 1275.1*(pooled)*, 81.6% of the patients were younger than 65 years at baseline. Only 16.1% were between 65 and 75 years, 2.2% were between 75 and 85 years and only 1 patient (0.1%) was older than 85 years. Therefore results of subgroup analyses of patients older than 75 years are mostly inconclusive.

The frequency of patients with adverse events was not obviously affected by the age category. Within each age category, the trends in the frequency of all types of adverse events were consistent with those for the overall population.

Gender

In study 1275.9, two-thirds of patients were men, and in study 1275.10, about half of the patients were men. Demographic data were largely similar for men and women and among the treatment groups in both studies.

In the Phase III studies 1275.9 and 1275.10, the frequency of patients with any adverse event, with urinary tract infection (BIcMQ), or with genital infection (BIcMQ) was higher for women than for men for all treatment groups. For either gender, the trends in the frequency of the other types of adverse events were consistent with those for the overall population of the trials.

In study 1275.1*(pooled)*, about half of the patients were men. Demographic data were largely similar for men and women and among the treatment groups.

The frequency of patients with any adverse event or with genital infection (BIcMQ) was higher for women than for men for all treatment groups except the empagliflozin 25/linagliptin 5 mg group. The frequency of patients with urinary tract infection (BIcMQ) was higher for women than for men for all treatment groups. For either gender, the trends in the frequency of the other types of adverse events were consistent with those for the overall population.

Race

Study 1275.9 included patients from all races, with 58% White patients, 27% Asian patients and 9% Black patients. Urinary tract infection (BIcMQ) was more frequently reported for White than for Black or Asian patients. For all other types of events, there was no clear trend for differences between races.

Study 1275.10 included 97% White patients, therefore results of subgroups analyses of race are inconclusive and are not presented.

Study 1275.1 included patients from all races, with 74% White patients, 13% Asian patients and 7% Black patients. For all types of adverse events, there was no clear trend for differences between races.

Renal function

Based on 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), and moderate or severe renal impairment (<60 mL/min/1.73m^2). Moderate or severe renal impairment was an exclusion criterion in all Phase III studies because of the metformin background therapy. Very few patients are included in these subgroups, mostly because study inclusion was based on local calculation of renal function with the Cockcroft-Gault formula.

In the add-on studies 1275.9 and 1275.10, about half of the patients had normal renal function and the other half had mild renal impairment at baseline. Demographic data were overall similar between subgroups. The frequency of patients with all types of adverse events was not obviously affected by the renal function category.

In the factorial design study 1275.1$_{(pooled)}$, about half of the patients had normal renal function and the other half had mild renal impairment at baseline. Demographic data were overall similar between subgroups. The frequency of patients with all types of adverse events was not obviously affected by the renal function category.

Geographical region

Subgroup analyses were performed for the following regions: Africa/Middle East, Asia, Europe, Latin America, and North America.

Study 1275.9 included patients from all regions except Africa. Study 1275.10 included only patients from Europe and North and Latin America. Patients from Europe and Latin America had overall a higher frequency of adverse events than patients from Asia and North America in Study 1275.9, whereas there was no difference in the frequency of adverse events in study 1275.10. For the other types of adverse events, there was no clear trend towards a difference between regions in either study.

Study 1275.1($_{pooled}$) included patients from all regions (North America: 43.3%, Europe: 26.6%, Latin America: 17.9%, Asia: 8.7%, and Africa/Middle East: 3.5%). For all types of adverse events, there was no clear trend towards a difference between regions.

Safety related to drug-drug interactions and other interactions

Empagliflozin and linagliptin drug-drug interaction (study 1245.30) and FDC empa/lina food interaction (study 1275.3) are described in detail in the clinical pharmacology section.

There was no clinically relevant pharmacokinetic interaction between empagliflozin and linagliptin, and there was no clinically relevant effect of a high-fat, high-caloric meal on the pharmacokinetics of the FDC empa/lina.

Discontinuation due to adverse events

Adverse events leading to premature discontinuation of study medication

The frequency of patients with adverse events leading to premature discontinuation of study medication was <7% and similar across treatment groups in all studies.

Adverse events leading to premature discontinuation of study medication in the Phase III studies

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 studies 1275.9 and 1275.10.

In study 1275.9, none of the patients in the empagliflozin 25 mg (add-on to linagliptin 5 mg and metformin) group, 2 patients (1.8%) in the empagliflozin 10 mg (add-on to linagliptin 5 mg and metformin) group and 2 patients (1.8%) in the placebo (add-on to linagliptin 5 mg and metformin) group were reported with adverse events leading to premature discontinuation of study medication.

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).

In study 1275.1(naïve), 9 patients (6.6%) in the empagliflozin 25 mg/linagliptin 5 mg, 5 patients (3.7%) in the empagliflozin 25 mg, 8 patients (5.9%) in the empagliflozin 10 mg/linagliptin 5 mg, 7 patients (5.2%) in the empagliflozin 10 mg, and 2 patients (1.5%) in the linagliptin 5 mg group 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 0.7%) per treatment group, except for pollakiuria (2 patients [1.5%] in the empagliflozin 10 mg/linagliptin 5 mg group), lipase increased (2 patients [1.5%] in the empagliflozin 10 mg/linagliptin 5 mg group), weight decreased (2 patients [1.5%] in the empagliflozin 25 mg group), and depression (2 patients [1.5%] in the empagliflozin 10 mg group).

Adverse events leading to premature discontinuation of study medication in the Phase I studies

In study 1275.3, 1 subject discontinued the study after the second treatment period due to severe nausea and moderate vomiting in 2 treatment periods (treatment with the normal dissolution and slow dissolution tablets). The adverse events were not considered as leading to treatment discontinuation by the investigator, as the treatment in a single-dose administration study could not be discontinued or reduced in dose.

No subject discontinued the study medication in study 1245.30.

Post marketing experience

No post-marketing data are available for the empagliflozin/linagliptin FDC.

2.6.1. Discussion on clinical safety

The safety assessment of empagliflozin combined with linagliptin was based on data from the 3 Phase III clinical studies, of whom 1496 patients had ongoing metformin therapy and 677 were treatment-naïve. Overall, 810 patients were treated for up to 24 weeks in the add-on studies and 1363 patients were treated for up to 52 weeks in the factorial design study. The number of treated patients is acceptable. The number of patients >65 years was relatively low. Almost no patients >75 years and no patients > 85 years were included in the FDC empa/lina groups. This is now reflected in the SmPC.

On average, 11% of the empa/lina treated patients prematurely discontinued from study medication in the 3 Phase III studies which is considered acceptable for 24-week and 52-week studies in a chronic indication. No clear differences in reasons for discontinuation were observed between the different treatments; the most common reasons were adverse events and patients being lost to follow-up.

For most PTs, overall, the frequencies of AEs were quite balanced between treatment groups, and the common AEs were generally consistent with the known safety profiles of empa and lina. When the 3 Phase III studies are pooled, the 3 most frequently reported AEs for empa/lina were UTIs (8.8%), nasopharyngitis (5.3%) and URTIs (4.4%).

In patients with normal renal function or mild renal impairment, both empagliflozin as add-on to linagliptin and metformin background therapy and linagliptin as add-on to empagliflozin and metformin background therapy were well tolerated. The frequencies of patients with treatment-emergent adverse events were generally similar across treatment groups in all studies. In the add-on studies 1275.9 and 1275.10, an overall lower proportion of patients was reported with adverse events in the empagliflozin (add-on to linagliptin and metformin) and linagliptin (add-on to empagliflozin and metformin) groups than in the corresponding placebo groups. 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 empagliflozin or linagliptin treatment groups than in the corresponding placebo groups in the add-on studies 1275.9 and 1275.10, and similar across treatment groups in the factorial design study 1275.1

In the present Phase III studies, the frequency of patients with confirmed hypoglycaemic events was low. However, when taken together with sulphonylurea, both empagliflozin and linagliptin are associated with hypoglycaemia. In the present studies, empagliflozin and linagliptin were not investigated in combination with sulphonylurea. It is not likely 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 MOA and the data provided, no added safety concerns of hypoglycaemia are to be expected when linagliptin and empagliflozin are used together.

Despite the overall higher frequency of patients with genital infections for empagliflozin treatment, severe, serious genital infection events, or discontinuations of study medication were rare. Only 3 patients were reported with pancreatitis, but these three patients were all treated with linagliptin (or a combination of linagliptin with empagliflozin). Treatment with linagliptin was associated with small increases in lipase, which is now reflected in the SmPC. Pancreatitis is identified as a possible risk with DPP-4 inhibitors.

Treatment with empagliflozin as add-on to linagliptin on a metformin background or with the FDC empagliflozin/linagliptin in patients with or without metformin background were associated with small increases in haematocrit. This also is now reflected in the SmPC.

There were small increases in serum lipids with empagliflozin, which is now reflected in the SmPC. Importantly, in the empa-reg cardiovascular outcome trial, there was a decreased cardiovascular risk with empagliflozin, but the cardiovascular effects of linagliptin are unknown.

The frequencies of patients with decreased renal function adverse events were small and similar for all groups. The frequency of patients reported with hepatic adverse events or relevant laboratory findings was generally low and comparable across all treatment groups in each study, except for lipase, haematocrit and serum lipids. Although the overall number of patients with hepatic injury in the empa/lina treatment groups was low (5 empa/lina patients, all on metformin background treatment), it is retained as an important potential risk for the FDC empa/lina in the RMP as it was for the monocomponent empa. 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, volume depletion or bone fracture. The incidences of venous embolic and thrombotic events, cardiac failure, increased urination and skin reaction were low, with no relevant differences between groups.

There were no cases of diabetic ketoacidosis in the phase 3 program. However, following the review of the risk of diabetic ketoacidosis with SGLT-2 inhibitors in a referral under Article 20 of regulation EU nr 726/2006, the final outcome of this referral (i.e. inclusion of DKA as an adverse event in SmPC section 4.8 with cross-reference to a warning in section 4.4 to inform physicians and patients of the possible occurrence of atypical DKA together with the symptoms and risk factors to consider and corresponding recommended actions) was implemented in the product information of Glyxambi.

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

Safety issues in the context of post-marketing surveillance should be taken into account.

2.6.2. Conclusions on the clinical safety

In patients with type 2 diabetes mellitus and metformin background therapy, treatment with the add-on therapy of empagliflozin to the DPP-4 inhibitor linagliptin or linagliptin to the SGLT-2 inhibitor empagliflozin was well tolerated and the safety profiles were generally consistent with the known safety profiles of the

individual components. In patients uncontrolled on metformin monotherapy the addition of the FDC was well tolerated, with similar safety profiles to the individual components.

In general, the FDC empa/lina is tolerated reasonably well and the 3 most frequently reported AEs for empa/lina were UTIs, nasopharyngitis and URTIs.

The safety profile of the FDC empa/lina is overall similar to the ones of the monocomponents.

Some adverse effects emerged from assessment of the analysis of the 3 Phase III studies: the common AE and laboratory value increased lipase, as well as the increases in haematocrit and serum lipids. These adverse effects are now adequately reflected in the SmPC.

Furthermore, the product information of GLYXAMBI reflects the final conclusions of the Article 20 referral for the risk of diabetic ketoacidosis with the SGLT2-inhibitors.

2.7. Risk Management Plan

Safety concerns

Summary of safety concerns	
Important identified risks	Urinary tract infection Genital infection Volume depletion Hypoglycaemia (with insulin and/or SU) Pancreatitis Hypersensitivity reactions, including Angioedema/urticaria Diabetic ketoacidosis with atypical presentation
Important potential risks	Urinary tract carcinogenicity Renal impairment Liver injury Bone fracture Skin lesions Infections Pancreatic cancer Arthralgia Off-label use Cardiac failure
Missing information	Paediatric patients Elderly patients Pregnancy/breast-feeding Clinical impact of dyslipidaemia Long-term safety (particularly cardiovascular) Use in combinations not studied or approved Concomitant therapy with P-gp and CYP 3A4 inhibitors Use in patients with severe hepatic impairment Malignancies (including long-term safety information on melanoma) Idiosyncratic reactions Immunological adverse reactions

Pharmacovigilance plan

Study/activity[1]	Objectives	Safety concerns addressed	Status[2]	Date for submission of interim or final reports[3]
Empagliflozin/linagliptin				
Enhanced pharmacovigilance study of ketoacidosis (1245.146); category 3	To evaluate the risk of diabetic ketoacidosis in patients treated with empagliflozin	Diabetic ketoacidosis with atypical presentation	Started	Q4 2021
Empagliflozin				
Long-term CV safety study 1245.25; category 3	To evaluate long-term CV safety of empagliflozin in patients with T2DM and increased CV risk	Long-term safety (particularly CV), dyslipidaemia, concomitant use of GLP-1 analogues, urinary tract carcinogenicity, bone fracture, missing long-term safety information on melanoma	Started	Event driven, final CTR, 2015
PASS (1245.96) to assess the risk of renal and liver injury, urinary tract and genital infection; category 3	To evaluate the risk of urinary tract and genital infection, acute renal and hepatic injury, resulting in hospitalisations, in empagliflozin-treated patients, compared to users of other antidiabetic treatment.	Urinary tract infection, genital infection, renal impairment, liver injury	Started	Final report, July 2020
Study/activity[1]	**Objectives**	**Safety concerns addressed**	**Status[2]**	**Date for submission of interim or final reports[3]**
PASS (1245.97) to assess the risk of urinary tract malignancies,	To evaluate the risk of renal and bladder cancer in empagliflozin-	Urinary tract carcinogenicity	Planned	Study protocol currently under review

preceded by feasibility assessment; category 3	treated patients, compared to users of other antidiabetic treatment.			
DUS (1245.122) to assess characteristics of patients initiating empagliflozin, including potential off-label use; category 3	To evaluate the characteristics of patients initiating empagliflozin treatment, including potential off-label use	Off-label use	Started	Q4 2016
Non-clinical experiments; category 3	To investigate the proketogenic mechanism of SGLT-2 inhibition	Diabetic ketoacidosis with atypical presentation	Started	Q4 2016
Linagliptin				
1218.74 (CAROLINA) 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 (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	Started	Interim analysis is planned for September 2016. Final CTR estimated 2020.

Study/activity[1]	Objectives	Safety concerns addressed	Status[2]	Date for submission of interim or final reports[3]
CV safety study 1218.22 (CARMELINA) 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 (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	Started	Final CTR estimated 2018

[1] Type, title, and category (1-3).
[2] Planned or started.
[3] Planned or actual.

Risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Important identified risks		
Urinary tract infection	Labelling in SmPC sections 4.4 and 4.8. Prescription only medicine	None
Genital infection	Labelling in SmPC section 4.8. Prescription only medicine	None
Volume depletion	Labelling in SmPC sections 4.4 and 4.8. Prescription only medicine	None
Hypoglycaemia (with insulin and/or SU)	Labelling in SmPC sections 4.4 and 4.8. Prescription only medicine	None
Pancreatitis	Labelling in SmPC sections 4.4 and 4.8. Prescription only medicine	None
Hypersensitivity reactions, including angioedema/urticaria	Labelling in SmPC sections 4.3 and 4.8. Prescription only medicine	None
Diabetic ketoacidosis with atypical presentation	Labelling in SmPC sections 4.4 and 4.8. Prescription only medicine	None
Important potential risks		None
Urinary tract carcinogenicity	Prescription only medicine	None
Renal impairment	Labelling in SmPC sections 4.2 and 4.4. Prescription only medicine	None
Liver injury	Labelling in SmPC sections 4.2 and 4.4. Prescription only medicine	None
Bone fracture	Prescription only medicine	None
Skin lesions	Prescription only medicine	None
Infections	Prescription only medicine	None
Pancreatic cancer	Prescription only medicine	None
Arthralgia	Prescription only medicine	None
Off-label use	Prescription only medicine	None
Cardiac failure	Prescription only medicine	None

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Missing information		None
Paediatric patients	Labelling in SmPC section 4.2. Prescription only medicine	None
Elderly patients	Labelling in SmPC sections 4.2 and 4.4. Prescription only medicine	None
Pregnancy/breast-feeding	Labelling in SmPC section 4.6; prescription only medicine	None
Clinical impact of dyslipidaemia	Prescription only medicine	None
Long-term safety (particularly cardiovascular)	Prescription only medicine	None
Use in combinations not studied or approved	Prescription only medicine	None
Concomitant therapy with p-gp and CYP 3A4 inhibitors	Prescription only medicine	None
Use in patients with severe hepatic impairment	Labelling in SmPC section 4.2. Prescription only medicine	None
Malignancies (including long-term safety information on melanoma)	Prescription only medicine	None
Idiosyncratic reactions	Prescription only medicine	None
Immunological adverse reactions	Prescription only medicine	None

Conclusion

The CHMP and PRAC considered that the **risk management plan version 1.3** is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.9. Product information

2.9.1. User consultation

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

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Glyxambi (empagliflozin / linagliptin) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The Applicant is applying for a marketing authorisation for the fixed dose combination (FDC) of empagliflozin (a sodium-dependent glucose cotransporter-2 [SGLT-2] inhibitor) and linagliptin (a dipeptidylpeptidase [DPP-4] inhibitor) for the treatment of adults with type 2 diabetes mellitus.

The wording of the indication initially proposed by the Applicant was that the FDC is indicated in adults with type 2 diabetes mellitus to improve glycaemic control:

- when diet and exercise, plus metformin and a sodium glucose co-transporter 2 (SGLT2) inhibitor do not provide adequate glycaemic control,
- when diet and exercise, plus metformin and a dipeptidyl peptidase 4 (DPP-4) inhibitor do not provide adequate glycaemic control,
- when already being treated with the free combination of empagliflozin (or another SGLT-2 inhibitor) and linagliptin (or another DPP-4 inhibitor).

Two dose strengths have been developed for the FDC empagliflozin/linagliptin: FDC empagliflozin 25 mg/linagliptin 5 mg (FDC empa 25/lina 5) and FDC empagliflozin 10 mg/linagliptin 5 mg (FDC empa 10/lina 5). Pharmacokinetic studies demonstrated that empagliflozin and linagliptin can be coadministered without any dose adjustment. In addition, bioequivalence of the FDC and the individual components was established.

The clinical development programme for the FDC empa/lina consists of three pivotal studies in patients with type 2 diabetes mellitus: two add-on studies (1275.9 and 1275.10) and one factorial design study (1275.1). Previously, complete development programs including several Phase III studies were conducted for empagliflozin and linagliptin as monocomponents and supported the approval of both drugs for the treatment of type 2 diabetes.

The two Phase III add-on studies investigated the efficacy, safety, and tolerability of empagliflozin as add-on therapy to the DPP-4 inhibitor linagliptin (study 1275.9) and 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.

A total of 1468 patients contributed to the analyses of efficacy (number of patients in the full analysis set). Of these, 1005 patients were treated with the actual fixed dose combination of empagliflozin (25 mg or 10 mg) and linagliptin (5 mg).

Combined empagliflozin and linagliptin therapy with metformin background was associated with improvements in HbA1c that were statistically larger than therapy with one of the monocomponents. The treatment effect of empagliflozin on top of linagliptin was -0.70% for empa 25 and -0.79% for empa 10 (study 1275.9). The treatment effects of linagliptin on top of empagliflozin were -0.47% on top of empa 25 mg and -0.32% on top of empa 10 mg (1275.10). In the factorial design study with FDC and individual components (study 1275.1), the difference between the FDC and monotherapy with linagliptin ranged from -0.39% to -0.57%. The difference between the FDC and monotherapy with empagliflozin ranged from -0.14% to -0.58%.

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

Empagliflozin was associated with reductions in body weight. In study 1275.9, the placebo-adjusted mean change in body weight was -2.22 kg for empa 25 and -2.77 kg for empa 10. 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 factorial design study 1275.01, empagliflozin was associated with weight loss (ranging from -1.22 to -2.30 kg), but linagliptin was not associated with weight loss.

In study 1275.9, empagliflozin 25 mg and 10 mg add-on to linagliptin and metformin provided small reductions in blood pressure after 24 weeks of treatment compared with placebo, (SBP: -2.6 and -1.3 mmHg; DBP -1.1 and -0.1 respectively). 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 the factorial design study 1275.1, there were similar reductions in both systolic and diastolic blood pressure in the FDC and empagliflozin groups. There were 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 effect of empagliflozin on top of linagliptin was clinically relevant. However, treatment effects of linagliptin on top of empagliflozin were smaller (1275.10; (-0.47% on top of empa 25 mg and -0.32% on top of empa 10 mg).

In patients that are treated with metformin, the benefits of concomitant add-on treatment with linagliptin and empagliflozin vs sequential add-on treatment in terms of glucose lowering effect have not been investigated.

Switching from other DPP4-inhibitors and SGLT2-inhibitors to empagliflozin/linagliptin combination therapy has not been studied. The MAH agreed with the CHMP that it is premature to conclude that it is appropriate to extrapolate between members of the classes. The Applicant therefore changed the wording for the indication. During the further assessment the CHMP proposed to shorten the wording of the indication for more clarity; the Applicant adapted the indication as requested.

The treatment effect of empagliflozin on top of linagliptin was -0.70% (95% CI: -0.93, -0.46) for empa 25 and -0.79% (95% CI: -1.02, -0.55) for empa 10.

The study populations can be considered relatively representative of the target population. However, 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.

Risks

Unfavourable effects

The safety assessment of empagliflozin combined with linagliptin was based on data from the 3 Phase III clinical studies, of whom 1496 patients had ongoing metformin therapy and 677 were treatment-naïve. Overall, 810 patients were treated for up to 24 weeks in the add-on studies and 1363 patients were treated for up to 52 weeks in the factorial design study.

In patients with normal renal function or mild renal impairment, both empagliflozin as add-on to linagliptin and metformin background therapy and linagliptin as add-on to empagliflozin and metformin background therapy were well tolerated. The frequencies of patients with treatment-emergent adverse events were generally similar across treatment groups in all studies. In the add-on studies 1275.9 and 1275.10, an overall lower proportion of patients was reported with adverse events in the empagliflozin (add-on to linagliptin and metformin) and linagliptin (add-on to empagliflozin and metformin) groups than in the corresponding placebo groups. 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 empagliflozin or linagliptin treatment groups than in the corresponding placebo groups in the add-on studies 1275.9 and 1275.10, and similar across treatment groups in the factorial design study 1275.1.

The frequencies of patients with decreased renal function adverse events were small and similar for all groups. The frequency of patients reported with hepatic adverse events or relevant laboratory findings was low and generally comparable across all treatment groups in each study, except for lipase, haematocrit and serum lipids, which is now reflected in the SmPC. There was no clinically relevant difference in the frequencies of patients reported with urinary tract infection across treatment groups in each study. Despite the overall higher frequency of patients with genital infections for empagliflozin treatment, severe, serious genital infection events, or discontinuations of study medication were rare. There were no new signals with respect to hypersensitivity reactions, malignancy, volume depletion or bone fracture. The incidences of venous embolic and thrombotic events, cardiac failure, increased urination and skin reaction were low, with no relevant differences between groups.

Three patients were reported with pancreatitis during treatment with linagliptin (or a combination of linagliptin with empagliflozin). No patients were reported with pancreatitis in the other groups. Treatment with linagliptin was associated with small increases in lipase.

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. It is not likely that combination of empagliflozin and linagliptin with sulfonylurea 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 MOA and the data provided, no added safety concerns of hypoglycaemia are to be expected when linagliptin and empagliflozin are used together.

Treatment with empagliflozin as add-on to linagliptin on a metformin background or with the FDC empagliflozin/linagliptin in patients with or without metformin background were associated with small increases in haematocrit.

There were small increases in serum lipids with empagliflozin. In the empa-reg cardiovascular outcome trial, a decreased cardiovascular risk with empagliflozin was observed, but the cardiovascular effects of linagliptin are unknown.

There were no cases of diabetic ketoacidosis in the phase 3 program. However, a causal association between empagliflozin treatment and the development of DKA in T2DM patients cannot be ruled out.

Balance

Importance of favourable and unfavourable effects

Bioequivalence of the FDC with the monocomponents and the individual components was established. No drug-drug-interactions between the monocomponents were observed. In the current application, the proposed FDCs have been used in the clinical studies, and thus efficacy and safety can be assessed for the FDCs themselves. In addition, bioequivalence allows for bridging data from the phase 3 studies of the individual components.

Combined empagliflozin and linagliptin therapy with metformin background was associated with relevant improvements in HbA1c in all Phase III studies. HbA1c is considered an important endpoint. Combination therapy was also associated with reductions in several important secondary endpoints (fasting glucose, body weight, blood pressure).

With FDC's, it is required that all active ingredients contribute to the product's therapeutic effect. In combination with linagliptin, empagliflozin was associated with modest, but clinically relevant reductions in HbA1c. In addition, empagliflozin was associated with reductions in fasting glucose, body weight and blood pressure. The contribution of linagliptin to the FDC empa/lina was smaller. In combination with empagliflozin, effects of linagliptin on HbA1c varying between - 0.32% and -0.47% in the clinical add-on study when added to 10 and 25 of empagliflozin, respectively. In addition, linagliptin was associated with small or absent reductions in fasting glucose, and not associated with reductions in body weight and blood pressure. However, the proportions of patients who achieved an HbA1c value of 7% or lower were clearly higher due to linagliptin. In addition, in the factorial design study 1275.1(met), the treatment differences between the combination of empagliflozin/linagliptin and empagliflozin monotherapy were acceptable.

In general, it is important that treatment with the add-on therapy of empagliflozin to linagliptin or linagliptin to empagliflozin was well tolerated and the safety profiles were generally consistent with the known safety profiles of the individual components. In patients uncontrolled on metformin monotherapy, the addition of the FDC was well tolerated, with similar safety profiles to the individual components.

Cardiovascular risk is important in the evaluation of glucose lowering medication. The long term effects of the FDC on cardiovascular risk are unknown.

There were no cases of diabetic ketoacidosis in the phase 3 program.

Benefit-risk balance

Combined empagliflozin and linagliptin therapy with metformin background was associated with reductions in HbA1c in all Phase III studies. Treatment was well tolerated and the safety profiles were generally consistent with the known safety profiles of the individual components. The contribution of linagliptin to the FDC empa/lina was less than that of empagliflozin but acceptable. The B/R of of the fixed dose combination of linagliptin and empagliflozin is positive as sequential add-on treatment, or substitution in patients already being treated with the free combination of empagliflozin and linagliptin. Combination with SU is acceptable.

Discussion on the benefit-risk assessment

Only few patients ≥ 75 years old were included in the trial. The limited experience in elderly is mentioned in the SmPC. Empagliflozin should not be initiated in subjects ⩾75 years.

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 patients tolerating empagliflozin whose eGFR falls persistently below 60 ml/min, the dose of empagliflozin should be adjusted to or maintained at 10 mg once daily. Although formally the FDC empagliflozin/linagliptin has not been investigated in patients with a GFR<60 ml/min it is obvious to keep the restriction of use of Glyxambi in patients with renal impairment in line with the most restrictive SmPC of the mono components – empagliflozin. The long term effects of the FDC on cardiovascular risk are unknown. In the EMPA-REG cardiovascular outcome trial with empagliflozin, there was a decreased cardiovascular risk with empagliflozin, but this is under assessment by the CHMP in a separate variation. The cardiovascular effects of linagliptin are unknown, but a cardiovascular outcome trial with linagliptin is ongoing.

There were no cases of diabetic ketoacidosis in the phase 3 program. However, a causal association between empagliflozin treatment and the development of DKA in T2DM patients cannot be ruled out. The conclusions of a recent referral procedure under Article 20 of Regulation EU no 726/2004 related to the risk of keto-acidosis for SGLT-2 inhibitors have been adequately reflected in the SmPC.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Glyxambi in the indication:

Glyxambi, fixed dose combination of empagliflozin and linagliptin, is indicated in adults aged 18 years and older with type 2 diabetes mellitus:

- to improve glycaemic control when metformin and/or sulphonylurea (SU) and one of the monocomponents of Glyxambi do not provide adequate glycaemic control
- when already being treated with the free combination of empagliflozin and linagliptin

(See sections 4.2, 4.4, 4.5 and 5.1 for available data on combinations studied)

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

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information

being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

Not applicable.