CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206073Orig1s000

SUMMARY REVIEW

CLINICAL REVIEW/CROSS-DISCIPLINE TEAM LEADER REVIEW

Application	NDA-206073
Supporting Document Number	SD-1
Submission Receipt Date	January 29, 2014
PDUFA Goal Date	January 30, 2015
Division	Division of Metabolism and Endocrinology Products
Reviewer	William H. Chong
Review Completion Date	January 29, 2015
Generic name	Empagliflozin/Linagliptin
Trade name	GLYXAMBI
Therapeutic class	Fixed dose combination of a sodium dependent glucose cotransporter-2 inhibitor and a dipeptidyl peptidase-4 inhibitor
Applicant	Boehringer Ingelheim
Priority designation	Standard
Formulation	Tablet
Dosing regimen	Empagliflozin 10 mg/Linagliptin 5 mg Empagliflozin 25 mg/Linagliptin 5 mg
Indication	Type 2 diabetes mellitus
Intended population	Adults with type 2 diabetes mellitus
Related INDs/NDAs	IND-108388 (Empagliflozin/Linagliptin); NDA-201280 (Linagliptin); NDA-204629 (Empagliflozin)
Division Director	Jean-Marc Guettier
Statistical Reviewer	Jennifer Clark
Clinical Pharmacology Reviewer	Suryanarayana Sista
Pharmacology/Toxicology Reviewer	David Carlson
Chemistry, Manufacturing and Controls	Joseph Leginus and Kareen Riviere
Project Manager	Callie Cappel-Lynch

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Abbreviations:

AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
CMC	Chemistry, Manufacturing, and Controls
CMQ	Customized MedDRA query
Cr	Creatinine
CT	Computed tomography
DBP	Diastolic blood pressure
DPP4	Dipeptidyl peptidase-4
eGFR	Estimated glomerular filtration rate
Empa	Empagliflozin
FAS	Full analysis set
FDA	Food and Drug Administration
FDC	Fixed dose combination
FPG	Fasting plasma glucose
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c
HDL-C	High density lipoprotein cholesterol
HLT	High level term
HR	Heart rate
ICH	International Conference on Harmonisation
ID	Identification
IND	Investigational new drug
LDL-C	Low density lipoprotein cholesterol
Lina	Linagliptin
LL	Lower limit
LLRR	Lower limit of the reference range
LOAEL	Lowest observed adverse effect level
LOCF	Last observation carried forward
LVOT	Last value on treatment
MACE	Major cardiovascular event
MACE+	Major cardiovascular event plus
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory Activities

MI	Myocardial infarction
mmHg	Millimeters of mercury
MRHD	Maximum recommended human dose
NCF	Noncompleters considered failure
NDA	New drug application
NEC	Not elsewhere classified
NOAEL	No observed adverse effect level
Per 100	Per 100 patient years
PPS	Per protocol set
PSP	Pediatric study plan
PT	Preferred term
Pt-yrs	Patient years
RR	Reference range
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGLT2	Sodium glucose cotransporter 2
SMQ	Standardized MedDRA query
SOC	System organ class
T2DM	Type 2 diabetes mellitus
TEAE	Treatment emergent adverse event
TIA	Transient ischemic attack
TS	Treated set
U.S.	United States
UL	Upper limit
ULRR	Upper limit of the reference range
ZDF	Zucker Diabetic Fatty

1. Recommendations/Risk-Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval for this New Drug Application (NDA).

1.2 Risk-Benefit Assessment

Risk Assessment:

Review of the submitted clinical study of the fixed dose combination (FDC) composed of empagliflozin and linagliptin did not reveal new safety concerns. Patients treated with the combination product had adverse events in-line with what would be expected based on the individual drug safety profiles. Additionally, there did not appear to be any synergistic effect from combining the two drugs.

Benefit Assessment:

The evidence for glucose lowering benefit is more complex. In the study evaluating use of the FDC in two distinct clinical use settings (i.e., treatment naïve and add-on to metformin), only one clinical use setting demonstrated improvement in glycemic control of the combination for all doses over the individual products. In patients already treated with metformin, there was a statistically significant greater decrease in hemoglobin A1c (HbA1c) from baseline with the combination product compared to empagliflozin alone and linagliptin alone (for all doses studied). In the treatment naïve population, however, the higher dose of the FDC (i.e. empagliflozin 25 mg plus linagliptin 5 mg) was not statistically significantly better than empagliflozin 25 mg alone for improving glycemic control as measured by HbA1c. Though the lower dose (i.e. empagliflozin 10 mg plus linagliptin 5 mg) showed a statistically significantly greater reduction in HbA1c than the individual components, the pre-specified statistical testing hierarchy prevented this hypothesis from being formally tested before reaching this point.

Despite this finding, I feel that there is adequate evidence to conclude that use of the FDC product has an added benefit over the individual components. Though there is a question regarding the efficacy of the FDC 25/5 dose in the treatment naïve population, the nominally statistically significant difference for the FDC 10/5 compared to empagliflozin 10 and linagliptin 5 are convincing that this dose is more efficacious than the individual components. Though exploratory, the FDC 10/5 dose also appears more efficacious than empagliflozin 25 alone. If one accepts all of the comparisons for the primary endpoint as valid comparisons, there is failure to demonstrate superiority in only one of eight comparisons. Failure to show superiority of the FDC 25/5 over empagliflozin 25 may be a chance observation. Additionally, given that the

proposed recommended starting dose is FDC 10/5, I am less concerned with the puzzling observation that the FDC 25/5 dose was not more efficacious than empagliflozin 25 in the treatment naïve population. Finally, in the care setting this FDC is likely to be used as add-on to metformin and in this clinical scenario the FDC at both doses provided slightly superior glycemic control.

Overall Assessment:

It is unclear why the 25/5 dose of the FDC failed to demonstrate statistically significant superiority over the individual components in the treatment-naïve population. Additionally, that dose appears to offer only minimal additional benefit in terms of the secondary endpoints. Despite this, I recommend approval of the FDC product. Both of the individual components are available and nothing prevents the combination of the two drugs from being used in practice. The study submitted with this application provide efficacy and safety data for combination use. These data are not otherwise available from sequential, add-on, co-administration studies at this time. If all of the primary efficacy comparisons are considered, only one of eight comparisons failed to demonstrate an added glycemic benefit of the FDC over the individual components. Thus, I believe there is adequate data to support a conclusion that the glucose lowering efficacy of the FDC product is greater than the glucose lowering efficacy afforded by each of the individual components administered alone. Further, there are no apparent safety concerns beyond what would be expected for the individual components. I believe that despite an unresolved question concerning the efficacy of the 25/5 FDC dose in the treatment-naïve setting, the overall risk-benefit supports an approval action. (b) (4) Metformin is the recognized first line agent and the data on the effect of the FDC in the add-on to metformin setting is the most clinically informative and relevant use scenario. The FDC product will most likely be used as a sequential add-on to metformin and a second line agent as it represents a benefit in terms of convenience. There are two additional ongoing studies which will inform sequential add-on use of empagliflozin to maximally effective doses of metformin and linagliptin and sequential add-on use of linagliptin to maximally effective doses of metformin and empaliflozin. These will provide additional efficacy and safety data for combined sequential use. Although some in the diabetes field, advocate initiating two or more, rather than one, anti-diabetic agents[1] in drug naïve patients, these recommendations are largely based on informed personal opinions and not on robust clinical data demonstrating this approach is better from a clinical outcomes perspective than an approach relying on a sequential add-on strategy. The data in this supplement shows that initiation of two agents simultaneously only provides marginally better HbA1c control (i.e., an additional reduction of 0.2-0.6%) at the end of six month. Given the unresolved efficacy findings in the drug naïve population, I would consider the drug-naïve trial a supportive study only (b) (4) These concerns are not substantial enough for me to recommend a limitation of use. Current practice

[1] Diabetes Care Volume 36, Supplement 2, August 2013

guidelines [2, 3] (b) (4) should dissuade use of the FDC product as initial therapy.

1.3 Recommendations for Post market Risk Evaluation and Mitigation Strategies

No risk evaluation and mitigation strategy is recommended for this product.

1.4 Recommendations for Post market Requirements and Commitments

I have no recommendations for any post-marketing requirements of commitments.

2. Introduction and Regulatory Background

2.1 Product information

The fixed dose combination (FDC) product submitted for review is a combination of empagliflozin (a sodium glucose cotransporter-2 [SGLT2] inhibitor) and linagliptin (a dipeptidyl peptidase-4 [DPP4] inhibitor). The sodium glucose cotransporter-2 is found in the proximal renal tubule and is responsible for reabsorption of glucose from the urine. By inhibiting urinary glucose reabsorption, empagliflozin improves glycemic control. Dipeptidyl peptidase-4 is an enzyme responsible for the breakdown of glucagon-like peptide-1 (GLP-1), which is an incretin hormone that plays a role in glucose dependent insulin secretion. By prolonging the action of native GLP-1, linagliptin improves glycemic control.

Both of these products are intended for use in the treatment of type 2 diabetes mellitus (T2DM). At the time of this review, empagliflozin is not approved for use in the United States (U.S.). Linagliptin is approved under the trade name Tradjenta. The Applicant asserts that the two drug products will be complementary due to the different mechanisms of action.

Throughout this review, the FDC product will be referred to as FDC 25/5 for the FDC dose composed of empagliflozin 25 mg/linagliptin 5 mg and FDC 10/5 for the FDC dose composed of empagliflozin 10 mg/linagliptin 5 mg. The treatment of empagliflozin 25 mg will be referred to as Empa 25, empagliflozin 10 mg will be referred to as Empa 10, and linagliptin 5 mg will be referred to as Lina 5.

2.2 Currently Available Treatments for the Proposed Indication

Several classes of drugs are currently approved for the treatment of T2DM, used either alone or

[2] Inzucchi SE., et al. "Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association and the European Association for the Study of Diabetes." *Diabetes Care*. 2012 Jun; 35 (6): 1364-1379
[3] Garber AJ, et al. "AACE comprehensive diabetes management algorithm 2013". *Endocr Pract*. 2013 Mar-Apr; 19 (2): 327-336.

in combination. These drug classes are:

- Biguanides (i.e. metformin)
- Sulfonylureas
- Thiazolidinediones
- Meglitinides
- DPP4 inhibitors
- GLP-1 analogues
- SGLT2 inhibitors
- Alpha-glucosidase inhibitors
- Amylin-mimetics
- Dopamine agonist (i.e. bromocriptine)
- Insulin and insulin analogues
- Bile acid sequestrant (i.e. colesevelam hydrochloride)

2.3 Availability of Proposed Active Ingredient in the United States

The proposed FDC product is not currently available in the U.S., or in any other country. Linagliptin was approved for use in the U.S. on May 2, 2011, and is available. Empagliflozin was approved in the U.S. on August 1, 2014.

2.4 Important Issues with Consideration to Related Drugs

Safety concerns for the SGLT2 inhibitor class of drugs include:

- Volume depletion/hypotension
- Impairment of renal function
- Genitourinary infections (especially genital mycotic infections)
- Increases in low density lipoprotein cholesterol (LDL-C)
- Hypoglycemia with concomitant insulin or insulin secretagogue therapy

Safety concerns for the DPP4 inhibitor class of drugs include:

- Pancreatitis
- Serious hypersensitivity reactions
- Hypoglycemia with concomitant insulin or insulin secretagogue therapy

2.5 Summary of Presubmission Regulatory Activity Related to Submission

April 1, 2010	Pre-IND Meeting requested with the FDA
June 17, 2010	Pre-IND Meeting Package received by the FDA
July 28, 2010	Preliminary FDA comments sent to the Applicant
	Pre-IND Meeting held

June 24, 2011	Investigational New Drug Application (IND-108388) submitted
February 25, 2013	Type C meeting requested. Meeting request denied.
May 31, 2013	Pre-NDA Meeting requested
July 1, 2013	Pre-NDA Meeting Package received by the FDA
July 26, 2013	Initial Pediatric Study Plan (PSP) received by the FDA
July 29, 2013	Preliminary FDA comments sent to the Applicant
August 14, 2013	Pre-NDA Meeting cancelled
October 18, 2013	Revised PSP received by the FDA
January 30, 2014	NDA received by the FDA

3. Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA submission is adequate for navigation and for meaningful review. Though no clinical summaries (either for efficacy or for safety are included, the full study report for the single phase 3 study which supports the NDA is submitted. The study report appears to be adequate for review, though it does not combine the population of patients with metformin background therapy with the population of patients without metformin background therapy. The other supporting studies were performed in healthy volunteers and were designed to evaluate relative bioavailability of the FDC formulation.

3.2 Compliance with Good Clinical Practice

The Applicant reports that clinical study 1275.1 was performed in compliance with the protocol, in accordance with the Declaration of Helsinki, in accordance with the International Conference on Harmonisation – Good Clinical Practice (ICH E6), and in accordance with applicable regulatory requirements.

3.3 Financial Disclosures

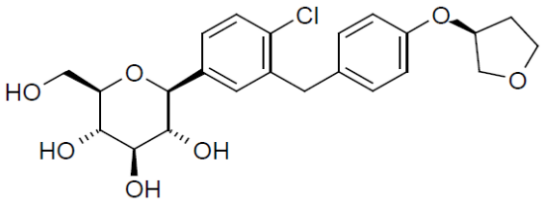
In FDA form 3454, the Applicant has certified that they have not entered into a financial arrangement with any of the clinical investigators participating in study 1275.1 that could affect the outcome of the study. See section 9.3 below for details.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing and Controls

The FDC product is a combination of empagliflozin (an SGLT2 inhibitor; Figure 1) and linagliptin (a DPP4 inhibitor; Figure 2).

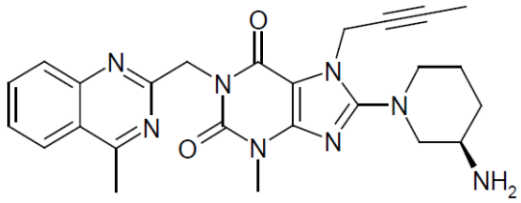
Figure 1: Chemical Structure of Empagliflozin



Source: Excerpted from the August 1, 2014 approved label for Empagliflozin

Molecular Formula of Empagliflozin: $C_{23}H_{27}ClO_7$
Molecular Weight of Empagliflozin: 450.91 g/mol

Figure 2: Chemical Structure of Linagliptin



Source: Excerpted from the May 22, 2014 approved label revision for Linagliptin

Molecular Formula of Linagliptin: $C_{25}H_{28}N_8O_2$
Molecular Weight of Linagliptin: 472.54 g/mol

For detailed discussion of the CMC, see Dr. Joseph Leginus' review. Based on his review of the data, Dr. Leginus recommends approval of the FDC product.

The FDC product is an immediate release, film-coated FDC tablet for oral administration containing empagliflozin and linagliptin. There are two dosage strengths: 10 mg empagliflozin with 5 mg linagliptin, and 25 mg empagliflozin with 5 mg linagliptin. Excipients to be included in the final dosage form include mannitol, pregelatinized starch, corn starch, copovidone, crospovidone, talc, magnesium stearate, (b) (4). The film-coat is composed of hypromellose (b) (4), mannitol, talc, titanium dioxide, polyethylene glycol (b) (4), and ferric oxide.

(b) (4)

Stabilities studies showed that the tablets remain stable through 12 months at 25°C and 60% relative humidity, and through 6 months at 40°C and 75% relative humidity. The FDC tablet appears stable at ambient and high humidity conditions for longer than the in-use period. There

are no concerns for an effect of exposure to light. Based on these studies, Dr. Leginus agrees with the Applicant's proposed expiry period of 24 months when maintained at 25°C and 60% relative humidity in the proposed container closure systems which are high density polyethylene bottles and blister cards.

The bioequivalence of the FDC tablet, proposed dissolution method and proposed quality control testing were reviewed by Dr. Kareen Riviere. See Dr. Riviere's review for a detailed discussion. Both were deemed acceptable and Dr. Riviere recommends approval of the FDC product.

To support the bioavailability of the FDC tablet compared to the individual components, the Applicant performed Study 1275.3. Dr. Riviere reviewed this study and deemed the design and analytical methods used adequate. Additionally, Dr. Riviere reviewed the data and concluded that the FDC table is bioequivalent to coadministration of the individual tablets.

For dissolution testing, the Applicant is utilizing a paddle method at rotation speeds of 50 rpm with a phosphate buffer (pH 6.8). Though the proposed dissolution method was not affected by (b) (4) Overall, the proposed dissolution method was deemed acceptable. The dissolution acceptance criterion was also found to be adequate.

For routine quality control, the Applicant has requested use of disintegration testing instead of dissolution testing. To support this request, the Applicant showed that both drugs have a high solubility throughout the physiological pH range, that the dissolution rate correlates with disintegration time, and that the disintegration and dissolution methods have similar discriminating ability. The proposal to use disintegration testing and the proposed disintegration acceptance criterion were deemed acceptable.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

For detailed discussion of the Pharmacology/Toxicology, see Dr. David Carlson's review. Dr. Carlson recommends approval of the FDC product based upon his review of the non-clinical data.

To support the FDC product, the Applicant performed several pre-clinical studies. These include in vitro studies to assess the effect combining the two drugs on hepatocyte metabolism, a single dose study of the combination of empagliflozin and linagliptin in Zucker Diabetic Fatty (ZDF) rats, a single dose pharmacokinetic/toxicokinetic study of concomitant administration in Wistar

Han rats, a 2-week repeat dose toxicity study in rats, a 13-week combination toxicity study in rats, and a study of embryofetal development in rats.

The in vitro studies suggested a limited potential for drug-drug interactions on the hepatic metabolism of linagliptin when coadministered with empagliflozin, and similar findings for the hepatic metabolism of empagliflozin when coadministered with linagliptin. The single dose study in ZDF rats suggested that there was additional benefit from combining empagliflozin and linagliptin as shown on an oral glucose tolerance tests following a single dose. The single dose pharmacokinetic/toxicokinetic study in Wistar Han rats did not demonstrate any effect of empagliflozin on the levels of linagliptin. The 2-week toxicity study in rats did not show any apparent additive toxicity. Toxicity findings were mostly limited to the high dose empagliflozin groups (either empagliflozin alone or in combination with linagliptin). The toxicity findings appeared to be due to decreased body weight and exaggerated pharmacology. In male rats, there was reproductive atrophy in the high dose combination, consistent with known toxicity of high dose DPP4 inhibitors. In the 13-week toxicity study in rats there was no apparent additive toxicity. Increases in liver enzymes were seen though histopathology could not explain this finding. These increases appeared reversible. Toxicity was generally consistent with that seen with SGLT2 inhibitors. Of note, though no drug-drug interactions were predicted from the in vitro studies, increased exposure to empagliflozin and decreased exposure to linagliptin was seen with co-administration in rats in this study. The mechanism for this is unknown. The no observed adverse effect limit from this study was 9x and 3x the maximum recommended human dose for linagliptin and empagliflozin, respectively. The embryofetal toxicity studies did no demonstrate any apparent drug interactions. There were no drug-related fetal malformations. Maternal toxicity was evidenced as reduced weight gain and lower plasma glucose which are presumably due to exaggerated pharmacologic effect. Fetal weights were also reduced. As discussed in Dr. Carlson's review, the no observed adverse event level and lowest observed adverse event level was several-fold above the maximum recommended human dose (see excerpted table below).

Human Equivalent Doses †				
Species	NOAEL (mg/kg) (lina/empa)	LOAEL (mg/kg) (lina/empa)	MRHD ($AUC_{0\text{-}24\ h}$) (lina/empa)	
			NOAEL	LOAEL
Rat (3-month)	15 / 30	20 / 100	9X / 3X	14X / 15X
Rat (Embryofetal development)	15/30 (maternal) 60/300 (fetal)	60/300 (maternal) 140/700 (fetal)	9X / 15X 227X / 199X	227X / 199X 353X / 253X

† Clinical exposure multiples based on proposed maximum human dose 5 mg linagliptin (158 nM*h) and 25 mg empagliflozin (4750 nM*h) FDC

Source: Table 7 of Dr. Carlson's review

No carcinogenicity or genotoxicity studies were performed for the combination of the two drugs. Studies of the individual drugs were deemed to be adequate for assessment of the carcinogenicity and genotoxicity of the combination.

4.4 Clinical Pharmacology

For detailed discussion of the Clinical Pharmacology, see Dr. Suryanarayana Sista's review. Based on his review of the data, Dr. Sista recommends approval of the FDC product.

4.4.1 Mechanisms of Action

The FDC product is composed of empagliflozin and linagliptin. Empagliflozin is an SGLT2 inhibitor which prevents renal glucose reabsorption, thus increasing renal glucose excretion and improving glycemic control. The amount of glucose removed is dependent on the blood glucose concentration and the glomerular filtration rate. Linagliptin is a DPP4 inhibitor and prolongs the presence of the incretin hormones which play a role in glucose dependent insulin secretion and in reducing glucagon secretion. The net result of the presence of incretin hormones is improved glycemic control.

4.4.2 Pharmacodynamics

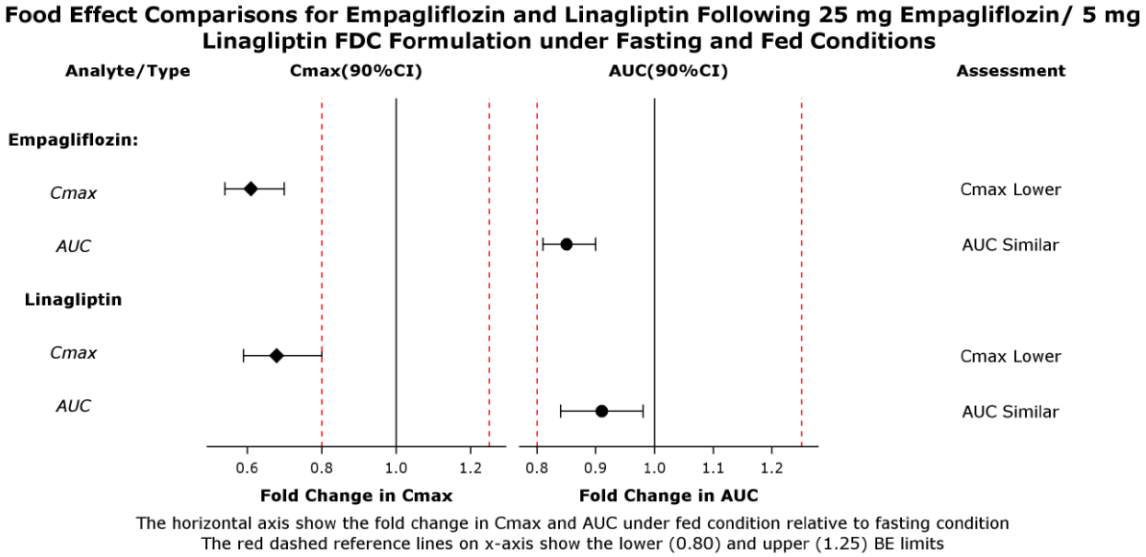
In Study 1245.30, pharmacodynamic (PD) assessment of the combination of empagliflozin and linagliptin included measurement of urinary glucose excretion and the activity of DPP4 in plasma. Inhibition of DPP4 was similar when linagliptin was given with or without empagliflozin. There was no effect on DPP4 activity when empagliflozin was administered alone. Urinary glucose excretion was slightly reduced when empagliflozin was co-administered with linagliptin vs. empagliflozin alone (mean cumulative glucose excreted in urine over 24 hours of 54.8 +/- 11.2 g and 67.2 +/- 14.6 g, respectively). This change was not felt to be meaningful.

4.4.3 Pharmacokinetics

Study 1245.30 was a multiple dose relative bioavailability study. It was originally reviewed as part of the review for the empagliflozin NDA. The steady-state bioavailability (both AUC and C_{max}) of linagliptin was not affected by concomitant administration with empagliflozin. The AUC of empagliflozin was not affected by concomitant administration with linagliptin, but the C_{max} was reduced by 12%.

When administered with food the AUC of empagliflozin and linagliptin were similar to that seen when administered fasting, but the C_{max} of empagliflozin and linagliptin was reduced by 39% and 32%, respectively (see excerpted figure below). This is consistent with the studies of the effect of food on bioavailability performed for the individual components as part of the respective NDA. In the NDA for each of the individual components, the reduction in C_{max} was

not associated with a reduction in urinary glucose excretion (for empagliflozin) or with a reduction in DPP4 inhibition (for linagliptin). Thus, this reduction is C_{max} is unlikely to be clinically significant.



Source: Figure 1 of Dr. Sista's review

5. Sources of Clinical Data

The applicant has submitted a single clinical study report to support the efficacy and safety of combining empagliflozin and linagliptin. Additional clinical studies have been performed in healthy volunteers to evaluate the bioavailability of the FDC formulation.

There are two ongoing clinical studies where empagliflozin and linagliptin are being studied in combination with each other that are not included in the NDA submission. Study 1275.9 is entitled "A phase 3, randomized, 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 glycemic control after 16 weeks treatment with linagliptin 5 mg once daily on metformin background therapy". Study 1275.10 is entitled "A phase 3, randomized, double-blind, parallel group study to evaluate the efficacy and safety of linagliptin 5 mg compared to placebo, administered as oral fixed dose combination with empagliflozin 10 mg or 25 mg for 24 weeks in patients with type 2 diabetes mellitus and insufficient glycemic control after 16 weeks of treatment with empagliflozin 10 mg or 25 mg on metformin background therapy". Information on one patient from study 1275.10 with a serious adverse event (SAE) is included in the initial NDA submission.

The four month safety update was submitted to the NDA on May 28, 2014. The date of database

lock for this update was January 30, 2014. Safety data for patients enrolled in the two ongoing studies (Study 1275.9 and Study 1275.10) are included in this update. Each of these trials contains an open-label treatment period (open-label linagliptin for Study 1275.9; open-label empagliflozin for Study 1275.10). Adverse events that occurred in the open-label period are included in the safety update.

5.1 Tables of Studies/Clinical Trials

To support the NDA, the Applicant is submitting data from three clinical trials (Table 1). Only one (study 1275.1) studied the combination of empagliflozin and linagliptin in patients with T2DM.

Table 1: Studies submitted in support of the New Drug Application

Study	Phase	Population	Objective
1275.3	1	Healthy volunteers	To evaluate the relative bioavailability of two formulations of BI 10773 25 mg/linagliptin 5 mg compared with each other and with the monocomponents.
1245.30	1	Healthy volunteers	To evaluate the relative bioavailability of multiple doses of BI 10773 50 mg and linagliptin 5 mg administered concomitantly compared to multiple doses of BI 10773 50 mg alone and linagliptin 5 mg alone
1275.1	3	Patients with T2DM, with and without a background of metformin	To evaluate the efficacy and safety of the empagliflozin/linagliptin FDC (10/5, 25/5) compared to the individual components.

BI 10773 = empagliflozin; T2DM = type 2 diabetes mellitus; FDC = fixed dose combination; 10/5 = empagliflozin 10 mg/linagliptin 5 mg; 25/5 = empagliflozin 25 mg/linagliptin 5 mg

5.2 Review Strategy

This review will focus on the findings from study 1275.1. For discussion of the CMC information, non-clinical findings, and clinical pharmacology information see the brief discussion above and the respective primary reviews.

Study 1275.1 is the only phase 3 study submitted in support of this NDA, and is the only submitted study that enrolled patients with T2DM. Efficacy and safety will be assessed based on comparisons with the included active controls from this study (i.e. empagliflozin 10 mg, empagliflozin 25 mg, and linagliptin 5 mg). Patients with a background of metformin will be examined separate from patients without a background of metformin. For efficacy and safety of the individual drug products, see the previous reviews for NDA-201280 (Linagliptin) and NDA-204629 (Empagliflozin).

5.3 Discussion of Individual Studies/Clinical Trials

Study 1275.1 was a phase 3 study designed to compare two dose strengths of the FDC product with the individual components (Table 2). There were two dose strengths of empagliflozin (10 mg and 25 mg), and one dose strength of linagliptin (5 mg). While this is submitted as a single study report, two distinct populations of patients were studied: (1) patients with T2DM and inadequate glycemic control who were treatment naïve, and (2) patients with T2DM and inadequate glycemic control despite treatment with metformin. These will be subsequently referred to as "treatment naïve" and "metformin patients", respectively. The primary endpoint was glycosylated hemoglobin (HbA1c) after 24 weeks. Treatment was extended to 52 weeks to collect additional information with regards to long term efficacy and safety.

Table 2: Treatment arms by patient population

Metformin Background	Treatment Naïve
Empagliflozin 25 mg/Linagliptin 5 mg	Empagliflozin 25 mg/Linagliptin 5 mg
Empagliflozin 10 mg/Linagliptin 5 mg	Empagliflozin 10 mg/Linagliptin 5 mg
Empagliflozin 25 mg	Empagliflozin 25 mg
Empagliflozin 10 mg	Empagliflozin 10 mg
Linagliptin 5 mg	Linagliptin 5 mg

6. Review of Efficacy

For detailed discussion of efficacy, see the Dr. Jennifer Clark's review.

6.1 Efficacy Summary

To demonstrate efficacy of the FDC product compared to the individual components, the Applicant performed a study in a metformin background therapy population and a treatment naïve population. In both populations, treatment with the FDC demonstrated greater efficacy on glycemic control than linagliptin alone. In the metformin patients, each FDC dose was better than the respective individual empagliflozin dose. In the treatment naïve patients, the FDC 25/5 arm was not statistically significantly better than empagliflozin 25 mg in reducing HbA1c. As a result of this, statistical testing stopped and comparison of the FDC 10/5 to the individual components were not statistically valid. However, comparison of the FDC 10/5 arm to the Empa 10 was nominally statistically significant for change in HbA1c.

Additional efficacy findings, which should be considered exploratory, included change in fasting plasma glucose, and use of rescue medication. For the endpoint of fasting plasma glucose, the comparison in the metformin treated patients was again statistically significant for both doses against both of the individual components. An issue was again identified in the treatment naïve population where the change in fasting plasma glucose was statistically significantly better for both doses of the FDC compared to linagliptin, but not better compared to the respective dose of

empagliflozin. Similar issues were seen for other endpoints explored such as change in body weight, percent achieving a target HbA1c, and use of rescue medication. A common theme seen across these comparisons is superiority of the FDC compared to linagliptin and less convincing evidence of the FDC compared to empagliflozin.

Despite these questions with regard to efficacy, I believe that the data is adequate to support approval. The primary efficacy issue is failure of the FDC 25/5 dose to demonstrate superiority in change in HbA1c compared to Empa 25 for the treatment naïve population. Neither I nor the Applicant is able to identify a plausible explanation for this finding. In all other comparisons, the FDC product was superior to the individual components. The Applicant is of the opinion that the finding is a chance finding and that the overall evidence of efficacy supports additional efficacy over the individual components for the FDC product. Additionally, they assert that the nominally statistically significant finding in the FDC 10/5 compared to Empa 10 support approval with the proposed language that the starting dose is FDC 10/5.

While I have concerns with accepting the failure to demonstrate a statistically significant benefit from the FDC 25/5 over Empa 25 as a chance finding, I believe that there is adequate support for efficacy of the FDC product over the individual components to recommend approval. While the testing hierarchy did not allow for acceptance of the subsequent endpoints in the treatment naïve population, the FDC 10/5 arm demonstrated a robustly statistically significant improvement in HbA1c over Empa 10 and Lina 5 (p-value < 0.0001 for both comparisons). Additionally, it was nominally statistically significantly better than Empa 25 (p-value = 0.0046). Both of these observations suggest that the FDC 10/5 dose is better than the individual components in the treatment naïve population. Assuming that all of the comparisons for the primary endpoint are valid, only the FDC 25/5 vs. Empa 25 in the treatment naïve population fails to demonstrate statistical significance making it the exception rather than the rule.

An additional consideration that influenced my recommendation is the current availability of both products. Prescribers and patients can freely use the combination of empagliflozin and linagliptin, and there is no associated limitation of use. I would not favor including a limitation of use for the combination in the treatment naïve population. As discussed in the preceding paragraph, I believe that there is sufficient evidence to support efficacy of the FDC product. With regard to the use in the treatment naïve population, current practice guidelines[4, 5] would not advocate use of this FDC as initial therapy. The product is most likely to be used as add-on to other therapy. Even if used as initial therapy, it would likely be initiated at the low dose (i.e.

[4] Inzucchi SE., et al. "Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association and the European Association for the Study of Diabetes." *Diabetes Care*. 2012 Jun; 35 (6): 1364-1379
[5] Garber AJ, et al. "AACE comprehensive diabetes management algorithm 2013". *Endocr Pract*. 2013 Mar-Aprl; 19 (2): 327-336.

FDC 10/5) which has evidence to support efficacy over the individual components.

(b) (4)

The question regarding the efficacy of the FDC product is perhaps more broadly a question about the efficacy of the Empa 25 dose. As discussed in the NDA review for empagliflozin (NDA-204629), the additional benefit of Empa 25 over Empa 10 was unclear. However, given the lack of a serious dose-related safety signal, it was ultimately felt that the higher dose could be approved based on a consistent improvement in secondary endpoints. The findings in this program again raise questions about the higher dose of empagliflozin, but there is once again an absence of a serious dose-related safety signal which would warrant withdrawal of the Empa 25 dose (see section 7 for discussion of the safety findings).

6.2 Indication

The proposed indication for this FDC product is as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus when both empagliflozin and linagliptin is appropriate.

6.2.1 Methods

This review will focus on the findings from the phase 3 study (Study 1275.1) submitted to support the FDC product. Study 1275.1 was designed to compare the two doses of the FDC product with the individual components. The patient population was divided into treatment naïve patients and metformin patients. The study was stratified and analyzed separately for the two different populations. The study was powered to analyze the two separate patient groups at 24 weeks. A separate testing procedure was followed for each patient population, and there was a pre-specified testing hierarchy.

6.2.2 Demographics

Inclusion criteria included:

- Age $\geq$ 18 years, a diagnosis of T2DM, a body mass index (BMI) $\leq$ 45 kg/m^2 at screening, and an HbA1c value $\geq$ 7.0% and $\leq$ 10.5%.
- The patient population consisted of naïve patients (i.e. no anti-diabetic therapy), and metformin patients (at a dose $\geq$ 1500 mg/day or on the maximum tolerated dose). This needed to be unchanged in the 12 weeks prior to randomization.

Exclusion criteria included:

- Uncontrolled hyperglycemia (plasma glucose > 240 mg/dL), impaired renal function (i.e.

estimated glomerular filtration rate [eGFR] by the modification of diet in renal disease [MDRD] formula < 60 ml/min/1.73m^2), acute coronary syndrome or stroke/transient ischemic attack (TIA) in the three months prior to consent, bariatric surgery, blood dyscrasias, and use of anti-obesity drugs.

For a full list of inclusion and exclusion criteria, see the study protocol.

There were 2,504 patients enrolled in the study, and 1,363 patients (686 metformin patients, 677 treatment naïve) randomized and analyzed. Randomization to treatment was 1:1:1:1:1 (Table 3).

Table 3: Distribution of patients by treatment

	FDC 25/5	FDC 10/5	Empa 25	Empa 10	Lina 5
Treatment Naïve	137	136	135	134	135
Metformin background	137	136	141	140	132
Total	**274**	**272**	**276**	**274**	**267**

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Figure 10: 1 of the Clinical Study Report for study 1275.1

There were additional patients randomized to treatment who were not included in the 1,363 analyzed. One clinical trial site was found to have evidence of scientific and data misconduct. The patients from this site (38 screened, 26 entered/randomized) are excluded from analysis and from Table 3. An additional 16 patients were found to have been randomized at multiple sites. These patients were also excluded from analysis and from the numbers in Table 3. This is acceptable.

6.2.3 Patient Disposition

A total of 2,504 patients were screened for participation in study 1275.1. Of these, 1,504 entered the two week placebo run-in period, and 1,363 were randomized and analyzed (686 patients with metformin background and 677 patients who were treatment naïve).

Patient disposition is presented at 24 weeks (primary endpoint, Table 4) and at 52 weeks (total study duration, Table 5). At 24 weeks, 8.88% of the patients discontinued study drug (9.31% of naïve patients, 8.45% of metformin patients), and 4.70% of the patients discontinued from the study (5.17% of naïve patients, 4.23% of metformin patients). By 52 weeks, 14.09% of the patients discontinued study drug (15.81% of naïve patients, 12.39% of metformin patients), and 11.89% of the patients discontinued from the study (13.88% of naïve patients, 9.91% of metformin patients). The most common reason for discontinuation of study drug was an adverse event (AE), and the most common reason for discontinuation from the study was withdrawal of consent. This was true for each patient population and at each time point with the exception of the metformin patients at 52 weeks in whom the most common reason for discontinuation of

study drug was being lost to follow-up.

While there were small differences in patient disposition between the different treatment arms for each patient population, none of the differences would be expected to significantly impact the study results.

Table 4: Disposition of patients at 24 weeks – randomized set

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5		Total	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Treatment naïve (24 weeks)	137		136		135		134		135		677	
Prematurely discontinued study drug	12	8.76	12	8.82	14	10.37	13	9.70	12	8.89	63	9.31
- Due to adverse event	7	5.11	4	2.94	3	2.22	4	2.99	2	1.48	20	2.95
- Due to withdrawal of consent, not related to adverse event	2	1.46	2	1.47	1	0.74	3	2.24	2	1.48	10	1.48
- Due to non-compliance	1	0.73	0	0.00	1	0.74	1	0.75	0	0.00	3	0.44
- Due to loss of follow-up	0	0.00	2	1.47	3	2.22	3	2.24	5	3.70	13	1.92
- Due to other reason	2	1.46	4	2.94	6	4.44	2	1.49	3	2.22	17	2.51
Prematurely discontinued from study	6	4.38	6	4.41	7	5.19	6	4.48	10	7.41	35	5.17
- Due to loss of follow-up	0	0.00	1	0.74	3	2.22	3	2.24	4	2.96	11	1.62
- Due to withdrawal of consent	6	4.38	5	3.68	4	2.96	3	2.24	6	4.44	24	3.55
- Due to death	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Metformin patients (24 weeks)	137		136		141		140		132		686	
Prematurely discontinued study drug	11	8.03	7	5.15	10	7.09	16	11.43	14	10.61	58	8.45
- Due to adverse event	3	2.19	3	2.21	2	1.42	5	3.57	4	3.03	17	2.48
- Due to withdrawal of consent, not related to adverse event	3	2.19	1	0.74	1	0.71	3	2.14	2	1.52	10	1.46
- Due to non-compliance	1	0.73	0	0.00	0	0.00	2	1.43	0	0.00	3	0.44
- Due to loss of follow-up	1	0.73	2	1.47	4	2.84	4	2.86	4	3.03	15	2.19
- Due to other reason	3	2.19	1	0.74	3	2.13	2	1.43	4	3.03	13	1.90
Prematurely discontinued from study	6	4.38	3	2.21	5	3.55	8	5.71	7	5.30	29	4.23
- Due to loss of follow-up	1	0.73	1	0.74	2	1.42	4	2.86	2	1.52	10	1.46
- Due to withdrawal of consent	5	3.65	1	0.74	3	2.13	4	2.86	5	3.79	18	2.62
- Due to death	0	0.00	1	0.74	0	0.00	0	0.00	0	0.00	1	0.15

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Tables 10.A.1:1 and 10.B.1:1 of the clinical study report for study 1275.1

Table 5: Disposition of patients at 52 weeks – randomized set

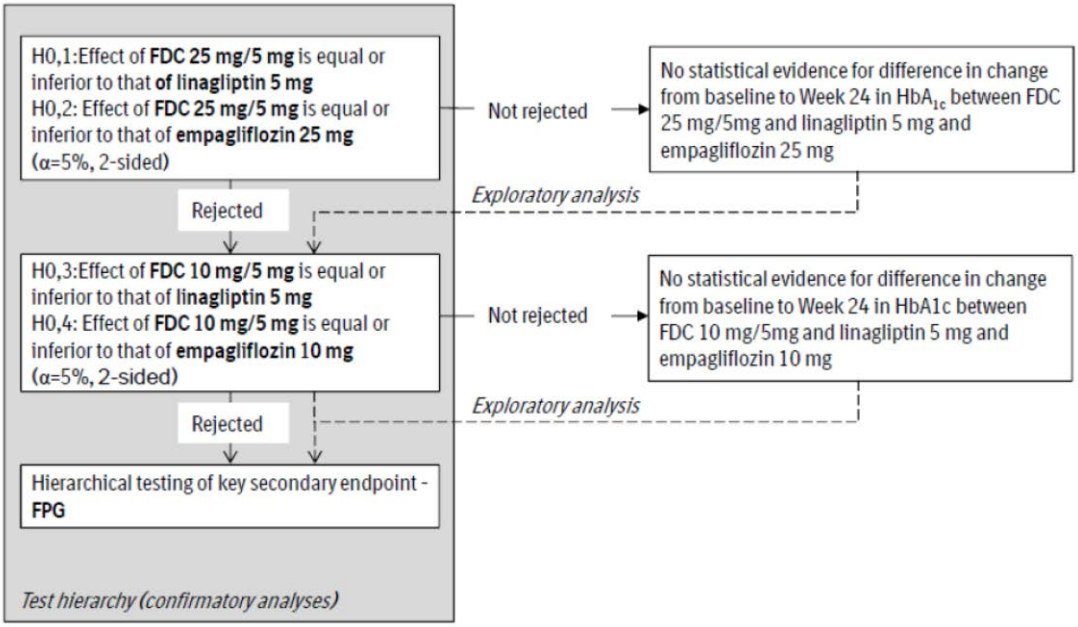
	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Treatment naive (52 weeks)	137		136		135		134		135		677	
Prematurely discontinued study drug	23	16.79	20	14.71	21	15.56	24	17.91	19	14.07	107	15.81
- Due to adverse event	9	6.57	8	5.88	5	3.70	7	5.22	2	1.48	31	4.58
- Due to withdrawal of consent, not related to adverse event	2	1.46	3	2.21	3	2.22	5	3.73	4	2.96	17	2.51
- Due to non-compliance	3	2.19	1	0.74	1	0.74	2	1.49	1	0.74	8	1.18
- Due to loss of follow-up	5	3.65	3	2.21	5	3.70	6	4.48	7	5.19	26	3.84
- Due to other reason	4	2.92	5	3.68	7	5.19	3	2.24	4	2.96	23	3.40
Prematurely discontinued from study	17	12.41	16	11.76	23	17.04	21	15.67	17	12.59	94	13.88
- Due to loss of follow-up	5	3.65	5	3.68	8	5.93	7	5.22	8	5.93	33	4.87
- Due to withdrawal of consent	12	8.76	10	7.35	12	8.89	13	9.70	9	6.67	56	8.27
- Due to death	0	0.00	1	0.74	3	2.22	1	0.75	0	0.00	5	0.74
Metformin patients (52 weeks)	137		136		141		140		132		686	
Prematurely discontinued study drug	16	11.68	12	8.82	16	11.35	22	15.71	19	14.39	85	12.39
- Due to adverse event	3	2.19	3	2.21	4	2.84	9	6.43	4	3.03	23	3.35
- Due to withdrawal of consent, not related to adverse event	5	3.65	1	0.74	2	1.42	4	2.86	3	2.27	15	2.19
- Due to non-compliance	1	0.73	0	0.00	0	0.00	2	1.43	1	0.76	4	0.58
- Due to loss of follow-up	3	2.19	3	2.21	7	4.96	4	2.86	7	5.30	24	3.50
- Due to other reason	4	2.92	4	2.94	3	2.13	3	2.14	4	3.03	18	2.62
Prematurely discontinued from study	12	8.76	10	7.35	13	9.22	18	12.86	15	11.36	68	9.91
- Due to loss of follow-up	3	2.19	5	3.68	7	4.96	5	3.57	8	6.06	28	4.08
- Due to withdrawal of consent	9	6.57	4	2.94	6	4.26	12	8.57	7	5.30	38	5.54
- Due to death	0	0.00	1	0.74	0	0.00	1	0.71	0	0.00	2	0.29

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Tables 10.A.1:4 and 10.B.1:4 of the clinical study report for study 1275.1

6.2.4 Analysis of Primary Endpoint(s)

The primary endpoint for both patient populations was change in HbA1c after 24 weeks of treatment. The primary analysis population was the full analysis set (FAS) which consisted of all patients randomized who received at least one dose of study drug, and who had a baseline and at least one on-treatment HbA1c. This set was slightly smaller than the randomized set and the treated set as some patients did not have on-treatment HbA1c values. Each of the patient populations (i.e. metformin patients and treatment naïve) were considered separately. Missing data was imputed using the last observation carried forward (LOCF) method and the data was analyzed using an analysis of covariance (ANCOVA) model. The same testing hierarchy (Figure 3) was pre-specified and used for each of the patient populations. Thus, the results for patients with a background of metformin therapy and for patients that are treatment naïve will be discussed separately.

Figure 3: Testing hierarchy



Source: From Figure 3 of Dr. Clark's review

Metformin patients:

At 24 weeks, all treatment groups showed a reduction in HbA1c from baseline (Table 6), and the FDC treated patients showed a statistically significantly greater reduction than was seen in either of the respective monocomponent arms (Table 7).

Table 6: Change in HbA1c from baseline at 24 weeks for metformin patients

	Empa25/Lina5 n=137	Empa10/Lina5 n=136	Empa 25 n=141	Empa 10 n=140	Lina 5 n=132
Mean HbA1c at Baseline	7.9	8	8	8	8
Mean HbA1c at Week 24	6.8	6.9	7.4	7.3	7.3
Mean Change from Baseline in HbA1c	-1.1	-1	-0.6	-0.7	-0.7
Adjusted change from Baseline in HbA1c (Mean, SE)	-1.2 (0.1)	-1.1 (0.1)	-0.7 (0.1)	-0.7 (0.1)	-0.8 (0.1)

Model based adjusted change from baseline included adjustment for baseline HbA1c, renal function, and region

Source: Table 6 of Dr. Clark's review

Table 7: Difference between treatments for HbA1c at 24 weeks for metformin patients

	Empa25/Lina5	Empa10/Lina5	Empa 25	Empa 10	Lina 5
Empa25/Lina5					
Empa10/Lina5	-0.1 (-0.3, 0.1) 0.215				
Empa 25	-0.6 (-0.7, -0.4) <.0001	-0.4 (-0.6, -0.3) <.0001			
Empa 10	-0.5 (-0.7, -0.4) <.0001	-0.4 (-0.6, -0.2) <.0001	0.03 (-0.1, 0.2) 0.7352		
Lina 5	-0.5 (-0.7, -0.3) <.0001	-0.4 (-0.5, -0.2) <.0001	0.1 (-0.1, 0.2) 0.4207	0.04 (-0.1, 0.2) 0.6376	

Source: Table 7 of Dr. Clark's review

Treatment naïve:

At 24 weeks, all treatment groups showed a reduction in HbA1c (Table 8). Unlike what was seen in the metformin patient population, comparison of the FDC treated patients with the respective monocomponents did not yield consistent findings of statistically significantly greater reduction (Table 9).

Table 8: Change in HbA1c from baseline at 24 weeks for treatment naive

	Empa25/Lina5 n=137	Empa10/Lina5 n=136	Empa 25 n=135	Empa 10 n=134	Lina 5 n=135
Mean HbA1c at Baseline	8	8.1	8	8	8.1
Mean HbA1c at Week 24	6.9	6.8	7.1	7.2	7.4
Mean Change from Baseline in HbA1c	-1	-1.2	-0.9	-0.8	-0.7
Adjusted change in HbA1c (Mean, SE)	-1.1 (0.1)	-1.3 (0.1)	-1 (0.1)	-0.9 (0.1)	-0.7 (0.1)

Model based adjusted change from baseline included adjustment for baseline HbA1c, renal function, and region

Source: Table 14 of Dr. Clark's review

Table 9: Difference between treatments for HbA1c at 24 weeks for treatment naive

	Empa25/Lina5	Empa10/Lina5	Empa 25	Empa 10	Lina 5
Empa25/Lina5					
Empa10/Lina5	0.2 (-0.05, 0.3) 0.1348				
Empa 25	-0.1 (-0.3, 0.1) 0.1775	-0.3 (-0.5, -0.1) 0.0046			
Empa 10	-0.3 (-0.5, -0.1) 0.0112	-0.4 (-0.6, -0.2) <.0001	-0.1 (-0.3, 0.1) 0.2333		
Lina 5	-0.4 (-0.6, -0.2) <.0001	-0.6 (-0.8, -0.4) <.0001	-0.3 (-0.5, -0.1) 0.0053	-0.2 (-0.4, 0.03) 0.1106	

Source: Table 15 of Dr. Clark's review

The addition of Lina to Empa 25 did not result in a statistically significant reduction compared to Empa 25 alone. Due to the pre-specified testing hierarchy, testing stopped at this point and all further endpoints in this patient population are considered exploratory.

In considering the difference between the low dose FDC and the individual components, there was a nominally statistically significant difference. Though this is considered exploratory, this finding appears to be statistically robust and unlikely to be due to chance ($p < 0.0001$). As discussed in section 3.2.4.2 of Dr. Clark's review, this finding remains statistically significant after a conservative Bonferroni adjustment for type I error.

6.2.5 Analysis of Secondary Endpoint(s)

6.2.5.1 Fasting plasma glucose

A key secondary endpoint identified by the Applicant was change in fasting plasma glucose. Comparison between treatments was performed on the FAS population using an ANCOVA model and the LOCF method of imputing missing data.

Metformin patients:

Consistent with what was seen for the primary endpoint, reductions in fasting plasma glucose were seen for all treatments (Table 10). Treatment with the FDC resulted in a greater reduction compared to the individual components (Table 11).

Table 10: Change in fasting plasma glucose from baseline at 24 weeks for metformin patients

	Empa25/Lina5 n=137	Empa10/Lina5 n=136	Empa 25 n=141	Empa 10 n=140	Lina 5 n=132
Mean FPG at Baseline	154.5	156.5	160	162.1	155.8
Mean FPG at Week 24	121.7	125.8	141	139.6	144
Mean Change from Baseline in FPG	-30.9	-30.9	-19.3	-22.5	-12
Adjusted change in FPG (Mean, SE)	-36.6 (2.6)	-33.9 (2.6)	-20.4 (2.6)	-22.4 (2.6)	-15.1 (2.6)

Adjusted for baseline HbA1c,, baseline FPG, geography, and renal function

Source: Table 8 of Dr. Clark's review

Table 11: Difference between treatments for fasting plasma glucose at 24 weeks for metformin patients

	Empa25/Lina5	Empa10/Lina5	Empa 25	Empa 10	Lina 5
Empa25/Lina5					
Empa10/Lina5	-2.7 (-9.7, 4.3) 0.4442				
Empa 25	-16.2 (-23.2, -9.3) <.0001	-13.5 (-20.4, -6.6) 0.0001			
Empa 10	-14.3 (-21.2, -7.3) <.0001	-11.6 (-18.5, -4.6) 0.0012	2 (-4.9, 8.9) 0.5744		
Lina 5	-21.5 (-28.6, -14.5) <.0001	-18.8 (-25.9, -11.8) <.0001	-5.3 (-12.3, 1.7) 0.1376	-7.3 (-14.3, -0.2) 0.0425	

Source: Table 9 of Dr. Clark's review

Treatment naïve:

Due to failure to demonstrate a statistically significant difference between the high dose FDC and empagliflozin, this and all subsequent endpoints are considered exploratory. All treatment arms demonstrated a reduction in fasting plasma glucose (Table 12). Unlike what was seen in the metformin patients, no statistically significant difference was seen between the FDC arms and the respective empagliflozin alone arm (Table 13).

Table 12: Change in fasting plasma glucose from baseline at 24 weeks for treatment naive

	Empa25/Lina5 n=137	Empa10/Lina5 n=136	Empa 25 n=135	Empa 10 n=134	Lina 5 n=135
Mean FPG at Baseline	155.7	157.4	152	159.9	155.7
Mean FPG at Week 24	126.6	129.1	130	137.4	150.3
Mean Change from Baseline in FPG	-29.1	-28.2	-22	-22.5	-5.4
Adjusted change in FPG (Mean, Std Err)	-30.5 (2.8)	-29 (2.8)	-25.3 (2.8)	-21.7 (2.8)	-6.7 (2.8)

Adjusted for baseline HbA1c,, baseline FPG, geography, and renal function

Source: Table 18 of Dr. Clark's review

Table 13: Difference between treatments for fasting plasma glucose at 24 weeks for treatment naive

	Empa25/Lina5	Empa10/Lina5	Empa 25	Empa 10	Lina 5
Empa25/Lina5					
Empa10/Lina5	-1.6 (-9.1, 6) 0.6729				
Empa 25	-5.2 (-12.7, 2.4) 0.1803	-3.6 (-11.2, 4) 0.359			
Empa 10	-8.9 (-16.5, -1.3) 0.0227	-7.3 (-14.9, 0.3) 0.0631	-3.7 (-11.3, 3.9) 0.3472		
Lina 5	-23.8 (-31.3, -16.2) <.0001	-5.2 (-12.7, 2.4) <.0001	-18.5 (-26.1, -11) <.0001	-14.8 (-22.4, -7.2) 0.0001	

Source: Table 19 of Dr. Clark's review

6.2.5.2 Body weight

Obesity and weight gain are important consideration in the treatment of T2DM. Many of the approved therapies for T2DM are associated with weight gain. The SGLT2 inhibitors are associated with some weight loss, and the DPP4 inhibitors are generally thought to be weight neutral. Given this, a key secondary endpoint in study 1275.1 was change in body weight with treatment.

Metformin patients:

Weight loss was seen in each of the treatment arms for the metformin patients (Table 14). While the FDC arms resulted in a statistically significant greater weight loss than the linagliptin arm, there was no statistically significant difference between the FDC arms and the respective empagliflozin arm (Table 15). As a result, all of the subsequent endpoints in this patient population are considered exploratory.

Table 14: Change in body weight from baseline at 24 weeks for metformin patients

	Empa25/Lina5 n=137	Empa10/Lina5 n=136	Empa 25 n-141	Empa 10 n=140	Lina 5 n=132
Mean Weight at Baseline	85.3	86.4	87.8	85.7	85.4
Mean Weight at Week 24	82.4	83.8	84.9	83.2	84.6
Mean Change from Baseline in Weight	-2.9	-2.6	-2.9	-2.4	-0.7
Adjusted change in Weight (Mean, SE)	-3.1 (0.3)	-2.8 (0.3)	-3.1 (0.3)	-2.7 (0.3)	-1 (0.3)

Adjusted for baseline HbA1c,, baseline FPG, geography, and renal function

Source: Table 10 of Dr. Clark's review

Table 15: Difference between treatments for body weight at 24 weeks for metformin patients

	Empa25/Lina5	Empa10/Lina5	Empa 25	Empa 10	Lina 5
Empa25/Lina5					
Empa10/Lina5	-0.3 (-1, 0.4) 0.348				
Empa 25	-0.1 (-0.8, 0.6) 0.8359	0.3 (-0.4, 1) 0.4603			
Empa 10	-0.5 (-1.2, 0.2) 0.1822	-0.1 (-0.8, 0.6) 0.6974	-0.4 (-1.1, 0.3) 0.2565		
Lina 5	-2.2 (-2.9, -1.5) <.0001	-1.9 (-2.6, -1.1) <.0001	-2.1 (-2.8, -1) <.0001	-1.7 (-2.4, -1) <.0001	

Source: Table 11 of Dr. Clark's review

Treatment naïve:

Weight loss was seen in each treatment arm for the treatment naïve patient population (Table 16). Similar to what was seen in the metformin patient population, the FDC resulted in a statistically significantly greater reduction in body weight compared to linagliptin (Table 17). For the FDC compared to the respective empagliflozin dose, the difference was not statistically significant. Again, it is important to note that this endpoint is exploratory due to failure to demonstrate a statistically significant difference between the high dose FDC and empagliflozin 25 for the primary endpoint.

Table 16: Change in body weight from baseline at 24 weeks for treatment naïve

	Empa25/Lina5 n=137	Empa10/Lina5 n=136	Empa 25 n=135	Empa 10 n=134	Lina 5 n=135
Mean Weight at Baseline	88.4	87.4	86.6	87.8	89.3
Mean Weight at Week 24	86.4	84.7	84.4	85.5	88.4
Mean Change from Baseline in Weight	-2	-2.7	-2.2	-2.3	-0.9
Adjusted change in Weight (Mean, SE)	-2.1 (0.4)	-2.8 (0.4)	-2.3 (0.4)	-2.5 (0.4)	-0.9 (0.4)

Adjusted for baseline HbA1c,, baseline FPG, geography, and renal function

Source: Table 20 of Dr. Clark's review

Table 17: Difference between treatments for body weight at 24 weeks for treatment naïve

	Empa25/Lina5	Empa10/Lina5	Empa 25	Empa 10	Lina 5
Empa25/Lina5					
Empa10/Lina5	0.7 (-0.3, 1.7) 0.1575				
Empa 25	0.2 (-0.8, 1.2) 0.6609	-0.5 (-1.5, 0.5) 0.3309			
Empa 10	0.4 (-0.6, 1.4) 0.4706	-0.3 (-1.3, 0.6) 0.4916	0.1 (-0.8, 1.1) 0.7775		
Lina 5	-1.2 (-2.2, -0.2) 0.0195	-1.9 (-2.9, -0.9) 0.0002	-1.4 (-2.4, -0.4) 0.0058	-1.5 (-2.5, -0.5) 0.0024	

Source: Table 21 of Dr. Clark's review

6.2.5.3 Ability to achieve target HbA1c

The ability to achieve a target HbA1c was considered to be a key secondary endpoint. Analysis of the ability to achieve the target HbA1c of less than 7% was performed using a noncompleters considered failure (NCF) approach. Missing data due to premature discontinuation was assumed to be a failure to achieve the target HbA1c. Only patients that had an HbA1c above 7% at baseline were included in this analysis.

Metformin patients:

Due to failure to demonstrate statistical significance for the preceding endpoint, the findings for this endpoint are considered exploratory. Treatment with the FDC resulted in a greater likelihood of achieving a target HbA1c < 7% if the baseline HbA1c was ≥ 7% (Table 18).

Table 18: Ability to achieve an HbA1c < 7% if baseline HbA1c ≥ 7% - full analysis set, non-completers considered failure, metformin patients

	FDC 25/5	FDC 10/5	Empa 25	Empa 10	Lina 5
N	**123**	**128**	**132**	**125**	**119**
At 24 weeks					
Patients achieving HbA1c < 7.0%, n (%)	76 (61.8)	74 (57.8)	43 (32.6)	35 (28.0)	43 (36.1)
Vs. Empa[2]					
– Odds ratio[1]	4.191	4.500			
– 95% CI (LL, UL)	2.319, 7.573	2.474, 8.184			
– p-value	< 0.0001	< 0.0001			
Vs. Lina					
– Odds ratio[1]	3.495	2.795			
– 95% CI (LL, UL)	1.920, 6.363	1.562,5.001			
– p-value	< 0.0001	0.0005			

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; CI = confidence interval; LL = lower limit; UL = upper limit
[1] Odds ratio estimated based on logistic regression; [2] FDC compared to respective dose of empagliflozin
Source: Adapted from Table 11.A.4.1.2.3: 1 of study 1275.1

Treatment naïve:

Treatment with the FDC in the treatment naïve patient population resulted in a greater likelihood of achieving a target HbA1c of < 7% than the respective individual components (Table 19). The high dose FDC demonstrated a nominally statistically significant improvement compared to Empa 25 for this endpoint (p = 0.0224).

Table 19: Ability to achieve an HbA1c < 7% if baseline HbA1c ≥ 7% - full analysis set, non-completers considered failure, treatment naive

	FDC 25/5	FDC 10/5	Empa 25	Empa 10	Lina 5
N	**121**	**122**	**118**	**121**	**127**
At 24 weeks					
Patients achieving HbA1c < 7.0%, n (%)	67 (55.4)	76 (62.3)	49 (41.5)	47 (38.8)	41 (32.3)
Vs. Empa[2]					
– Odds ratio[1]	1.893	2.961			
– 95% CI (LL, UL)	1.095, 3.274	1.697, 5.169			
– p-value	0.0224	0.0001			
Vs. Lina					
– Odds ratio[1]	3.065	4.303			
– 95% CI (LL, UL)	1.768, 5.314	2.462, 7.522			
– p-value	< 0.0001	< 0.0001			

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; CI = confidence interval; LL = lower limit; UL = upper limit
[1] Odds ratio estimated based on logistic regression; [2] FDC compared to respective dose of empagliflozin
Source: Adapted from Table 11.B.4.1.2.3: 1 of study 1275.1

6.2.6 Other Endpoint(s)

The following endpoints are not discussed in Dr. Clark's review and are considered exploratory.

6.2.6.1 Changes in blood pressure

Metformin patients:

Changes in blood pressure (BP) from baseline at 24 weeks and at 52 weeks were assessed using the FAS (LOCF) population with an ANCOVA model. Reductions in both systolic blood pressure (SBP) and diastolic blood pressure (DBP) were seen with the FDC and empagliflozin treated patients (Table 20 and Table 21). The linagliptin treated patients had a small reduction in SBP and DBP at 24 weeks. At 52 weeks, a small increase in SBP and a small decrease in DBP were seen. The FDC was not statistically different from the respective dose of empagliflozin for either SBP or DBP at 24 or 52 weeks. Compared to linagliptin, there was a statistically significant greater reduction in SBP at 24 and 52 weeks. For DBP, the FDC 25/5 arm has a statistically significant greater reduction in DBP at 24 and 52 weeks, but the FDC 10/5 arm did not. The clinical significance of these changes is not known.

Treatment naïve:

In the treatment naïve population, reductions in BP were seen at 24 and 52 weeks (Table 22 and Table 23). This was assessed using the FAS (LOCF) population with an ANCOVA model. Only change in SBP for FDC 10/5 compared to linagliptin at 24 weeks demonstrated a statistically significant difference. All other comparisons did not demonstrate a statistically significant difference. The clinical significance of these changes is not known.

Table 20: Adjusted mean change in systolic blood pressure – full analysis set, last observation carried forward, metformin patients

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
N	134		135		140		137		128	
	mmHg	**SE**	**mmHg**	**SE**	**mmHg**	**SE**	**mmHg**	**SE**	**mmHg**	**SE**
Week 24										
Mean baseline	130.9	1.4	130.5	1.3	129.2	1.1	131.6	1.2	128.4	1.1
Mean at 24 weeks	125.0	1.2	126.3	1.2	124.5	1.0	126.9	1.2	128.1	1.1
Adj[1] mean at 24 weeks	124.5	0.9	126.1	0.9	125.1	0.9	126.1	0.9	129.1	0.9
Adj mean change	-5.6	0.9	-4.1	0.9	-5.1	0.9	-4.0	0.9	-1.0	0.9
Vs. Empa[2]										
– Adj mean change at 24 week	-0.6	1.3	0.0	1.3						
– 95% CI (LL, UL)	-3.0, 1.9		-2.5, 2.4							
– p-value	0.6509		0.9715							
Vs. Lina										
– Adj mean change at 24 week	-4.6	1.3	-3.0	1.3						
– 95% CI (LL, UL)	-7.1, -2.1		-5.6, -0.5		-					
– p-value	0.0004		0.0176							
Week 52										
Mean baseline	130.9	1.4	130.5	1.3	129.2	1.1	131.6	1.2	128.4	1.1
Mean at 52 weeks	127.0	1.3	127.5	1.2	126.8	1.0	127.4	1.2	129.5	1.2
Adj mean at 52 weeks	126.6	0.9	127.3	0.9	127.3	0.9	126.6	0.9	130.4	1.0
Adj mean change	-2.03	0.38	-1.59	0.38	-2.37	0.39	-2.34	0.39	-0.29	0.39
Vs. Empa[2]										
– Adj mean change at 52 weeks	-0.7	1.3	0.7	1.3						
– 95% CI (LL, UL)	-3.3, 1.9		-1.9, 3.3							
– p-value	0.5781		0.6092							

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
N	**134**		**135**		**140**		**137**		**128**	
	mmHg	**SE**	**mmHg**	**SE**	**mmHg**	**SE**	**mmHg**	**SE**	**mmHg**	**SE**
Vs. Lina										
– Adj mean change at 52 weeks	-3.8	1.4	-3.1	1.4						
– 95% CI (LL, UL)	-6.5, -1.2		-5.7, -0.4							
– p-value	0.0049		0.0221							

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; mmHg = millimeters of mercury; SE = standard error; Adj = adjusted; CI = confidence interval; LL = lower limit; UL = upper limit
[1] adjustments included treatment, renal function, region, baseline HbA1c, and baseline blood pressure; [2] FDC compared to respective dose of empagliflozin
Source: Adapted from Tables 11.A.4.1.3.2: 1 and 11.A.4.1.3.2: 3 of study 1275.1

Table 21: Adjusted mean change in diastolic blood pressure – full analysis set, last observation carried forward, metformin patients

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
N	**134**		**135**		**133**		**132**		**133**	
	mmHg	**SE**	**mmHg**	**SE**	**mmHg**	**SE**	**mmHg**	**SE**	**mmHg**	**SE**
Week 24										
Mean baseline	77.9	0.8	78.4	0.7	78.7	0.8	79.4	0.8	78.2	0.8
Mean at 24 weeks	77.1	0.7	77.8	0.7	77.2	0.8	77.8	0.8	78.4	0.8
Adj[1] mean at 24 weeks	77.1	0.7	77.8	0.7	77.2	0.8	77.8	0.8	78.4	0.8
Adj mean change	-1.1	0.6	-0.7	0.6	-1.4	0.6	-1.2	0.6	0.1	0.6
Vs. Empa[2]										
– Adj mean change at 24 week	0.3	0.8	0.5	0.8						
– 95% CI (LL, UL)	-1.3, 2.0		-1.2, 2.1							
– p-value	0.7054		0.5787							
Vs. Lina										
– Adj mean change at 24 week	-1.1	0.8	-0.8	0.8						
– 95% CI (LL, UL)	-2.8, 0.5		-2.4, 0.9							
– p-value	0.1806		0.3568							
Week 52										
Mean baseline	77.9	0.8	78.4	0.7	78.7	0.8	79.4	0.8	78.2	0.8
Mean at 52 weeks	77.6	0.8	78.7	0.7	77.0	0.8	78.2	0.8	78.3	0.7
Adj mean at 52 weeks	78.0	0.6	78.7	0.6	77.0	0.6	77.7	0.6	78.5	0.6
Adj mean change	-0.6	0.6	-0.2	0.6	-1.6	0.6	-0.9	0.6	0.0	0.6

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
N	**134**		**135**		**133**		**132**		**133**	
	mmHg	**SE**	**mmHg**	**SE**	**mmHg**	**SE**	**mmHg**	**SE**	**mmHg**	**SE**
Vs. Empa[2]										
– Adj mean change at 52 weeks	1.0	0.9	1.0	0.9						
– 95% CI (LL, UL)	-0.7, 2.7		-0.7, 2.7							
– p-value	0.2450		0.2307							
Vs. Lina										
– Adj mean change at 52 weeks	-0.5	0.9	0.2	0.9						
– 95% CI (LL, UL)	-2.2, 1.2		-1.5, 1.9							
– p-value	0.5399		0.8089							

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; mmHg = millimeters of mercury; SE = standard error; Adj = adjusted; CI = confidence interval; LL = lower limit; UL = upper limit
[1] adjustments included treatment, renal function, region, baseline HbA1c, and baseline blood pressure; [2] FDC compared to respective dose of empagliflozin
Source: Adapted from Tables 11.A.4.1.3.2: 2 and 15.4.2.3.2.2: 1 of study 1275.1

Table 22: Adjusted mean change in systolic blood pressure – full analysis set, last observation carried forward, treatment naïve

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
N	**134**		**135**		**133**		**132**		**133**	
	mmHg	**SE**	**mmHg**	**SE**	**mmHg**	**SE**	**mmHg**	**SE**	**mmHg**	**SE**
Week 24										
Mean baseline	128.3	1.3	127.4	1.2	129.1	1.3	129.1	1.4	127.7	1.2
Mean at 24 weeks	125.4	1.0	124.3	1.1	126.2	1.2	126.5	1.3	127.8	1.3
Adj[1] mean at 24 weeks	125.4	1.0	124.7	1.0	125.8	1.0	126.1	1.0	128.1	1.0
Adj mean change	-2.9	1.0	-3.6	1.0	-2.5	1.0	-2.2	1.0	-0.3	1.0
Vs. Empa[2]										
– Adj mean change at 24 week	-0.4	1.4	-1.4	1.4						
– 95% CI (LL, UL)	-3.0, 2.3		-4.1, 1.3							
– p-value	0.7905		0.2998							
Vs. Lina										
– Adj mean change at 24 week	-2.6	1.4	-3.4	1.4						
– 95% CI (LL, UL)	-5.3, 0.0		-6.0, -0.7		-					
– p-value	0.0522		0.0126							

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
N	**134**		**135**		**133**		**132**		**133**	
	mmHg	**SE**	**mmHg**	**SE**	**mmHg**	**SE**	**mmHg**	**SE**	**mmHg**	**SE**
Week 52										
Mean baseline	128.3	1.3	127.4	1.2	129.1	1.3	129.1	1.4	127.7	1.2
Mean at 52 weeks	15.8	1.0	125.8	1.1	126.6	1.3	126.5	1.2	127.6	1.1
Adj mean at 52 weeks	125.9	1.0	126.2	1.0	126.3	1.0	126.1	1.0	127.9	1.0
Adj mean change	-2.5	1.0	-2.1	1.0	-2.1	1.0	-2.2	1.0	-0.3	1.0
Vs. Empa[2]										
– Adj mean change at 52 weeks	-0.4	1.4	0.1	1.4						
– 95% CI (LL, UL)	-3.0, 2.3		-2.6, 2.8							
– p-value	0.7776		0.9429							
Vs. Lina										
– Adj mean change at 52 weeks	-2.0	1.4	-1.7	1.4						
– 95% CI (LL, UL)	-4.7, 0.6		-4.4, 0.9							
– p-value	0.1365		0.2071							

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; mmHg = millimeters of mercury; SE = standard error; Adj = adjusted; CI = confidence interval; LL = lower limit; UL = upper limit
[1] adjustments included treatment, renal function, region, baseline HbA1c, and baseline blood pressure; [2] FDC compared to respective dose of empagliflozin
Source: Adapted from Tables 11.B.4.1.3.2: 1 and 11.B.4.1.3.2: 3 of study 1275.1

Table 23: Adjusted mean change in diastolic blood pressure – full analysis set, last observation carried forward, treatment naive

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
N	**134**		**135**		**140**		**137**		**128**	
	mmHg	**SE**	**mmHg**	**SE**	**mmHg**	**SE**	**mmHg**	**SE**	**mmHg**	**SE**
Week 24										
Mean baseline	78.6	0.8	79.0	0.7	79.9	0.7	80.2	0.8	77.7	0.8
Mean at 24 weeks	75.2	0.8	76.5	0.7	77.1	0.7	77.7	0.8	77.0	0.7
Adj[1] mean at 24 weeks	75.5	0.6	76.5	0.6	76.6	0.6	77.0	0.6	77.9	0.6
Adj mean change	-3.6	0.6	-2.6	0.6	-2.5	0.6	-2.1	0.6	-1.2	0.6
Vs. Empa[2]										
– Adj mean change at 24 week	-1.2	0.8	-0.5	0.8						
– 95% CI (LL, UL)	-2.7, 0.4		-2.1, 1.1							
– p-value	0.150.3		0.5514							

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
N	134		135		140		137		128	
	mmHg	**SE**	**mmHg**	**SE**	**mmHg**	**SE**	**mmHg**	**SE**	**mmHg**	**SE**
Vs. Lina										
– Adj mean change at 24 week	-2.5	0.8	-1.4	0.8						
– 95% CI (LL, UL)	-4.1, -0.9		-3.0, 0.2							
– p-value	0.0025		0.0769							
Week 52										
Mean baseline	78.6	0.8	79.0	0.7	79.9	0.7	80.2	0.8	77.7	0.8
Mean at 52 weeks	76.6	0.8	76.9	0.6	77.6	0.7	78.0	0.8	77.7	0.7
Adj mean at 52 weeks	76.9	0.6	76.9	0.6	77.2	0.6	77.3	0.6	78.5	0.6
Adj mean change	-2.0	0.6	-2.2	0.6	-1.9	0.6	-1.8	0.6	-0.6	0.6
Vs. Empa[2]										
– Adj mean change at 52 weeks	-0.3	0.8	-0.4	0.8						
– 95% CI (LL, UL)	-1.9, 1.3		-2.0, 1.2							
– p-value	0.7026		0.6201							
Vs. Lina										
– Adj mean change at 52 weeks	-1.6	0.8	-1.6	0.8						
– 95% CI (LL, UL)	-3.2, 0.0		-3.2, 0.0							
– p-value	0.0496		0.0517							

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; mmHg = millimeters of mercury; SE = standard error; Adj = adjusted; CI = confidence interval; LL = lower limit; UL = upper limit

[1] adjustments included treatment, renal function, region, baseline HbA1c, and baseline blood pressure; [2] FDC compared to respective dose of empagliflozin

Source: Adapted from Tables 11.B.4.1.3.2: 2 and 11.B.4.1.3.2: 4 of study 1275.1

6.2.6.2 Need for rescue medication

Need for rescue medication was defined by the Applicant as the use of additional antidiabetic medication, increase in background medication above the baseline dose for seven days or more (or until treatment discontinuation), or discontinuation of study drug due to lack of efficacy and addition or increase in dose of antidiabetic medication the next day.

Metformin patients:

Only small numbers of patients required rescue (Table 24). At 24 weeks, there was no statistically significant difference between any of the treatment groups (Table 25). Of note, the FDC 10/5 arm appeared to more likely require rescue than the Empa 10 arm. At 52 weeks, both FDC arms appeared to be better than the Lina 5 arm. This suggests that the FDC product is no worse than the individual components with regard to the need for rescue medication, and that it may be better than treatment with linagliptin for this endpoint.

Table 24: Rescue medication use – full analysis set, metformin patients

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Patients exposed	**134**		**135**		**140**		**137**		**128**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
24 weeks										
Patients rescued	1	0.7	3	2.2	6	4.3	1	0.7	4	3.1
- Dose increase	0	0.0	0	0.0	3	2.1	0	0.0	0	0.0
- Additional medication	1	0.7	3	2.2	3	2.1	1	0.7	4	3.1
- Sulfonylurea	1	0.7	3	2.2	2	1.4	1	0.7	4	3.1
- Glitazone	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- α-glucosidase inhibitor	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Insulin	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Other	0	0.0	0	0.0	1[1]	0.7	0	0.0	0	0.0
52 weeks										
Patients rescued	5	3.7	7	5.2	13	9.3	6	4.4	21	16.4
- Dose increase	1	0.7	1	0.7	4	2.9	0	0.0	0	0.0
- Additional medication	4	3.0	6	4.4	10	7.1	6	4.4	21	16.4
- Sulfonylurea	4	3.0	6	4.4	8	5.7	5	3.6	17	13.3
- Glitazone	0	0.0	0	0.0	2	1.4	1	0.7	3	2.3
- α-glucosidase inhibitor	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8
- Insulin	0	0.0	0	0.0	1	0.7	0	0.0	1	0.8
- Other	0	0.0	0	0.0	1[1]	0.7	0	0.0	1	0.8

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin

[1] Patient incorrectly categorized as "Other". Actually rescued with sulfonylurea.

Source: Adapted from Tables 11.A.4.1.3.4: 1 and 11.A.4.1.3.4: 2 from the clinical study report for 1275.1

Table 25: Odds ratio for rescue medication use – full analysis set, logistic regression, metformin patients

	OR	95% CI		p-value
		LL	UL	
24 weeks				
FDC 25/5 vs. Empa 25	0.189	0.220	1.612	0.1277
FDC 10/5 vs. Empa 10	3.750	0.374	37.627	0.2613
FDC 25/5 vs. Lina 5	0.280	0.030	2.583	0.2613
FDC 10/5 vs. Lina 5	0.802	0.172	3.740	0.7785
52 weeks				
FDC 25/5 vs. Empa 25	0.420	0.142	1.239	0.1159
FDC 10/5 vs. Empa 10	1.420	0.446	4.520	0.5527
FDC 25/5 vs. Lina 5	0.212	0.075	0.596	0.0033
FDC 10/5 vs. Lina 5	0.284	0.112	0.715	0.0076

OR = odds ratio; CI = confidence interval; LL = lower limit; UL = upper limit; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Tables 15.2.2.3.4: 2 and 15.5.2.3.4: 2 from the clinical study report for 1275.1

Treatment naïve:

Only small numbers of patients required rescue therapy (Table 26). At 24 weeks, both FDC arms appeared to be better than the Lina 5 arm (Table 27). The FDC product did not appear to be statistically significantly better than treatment with the respective empagliflozin dose. Of note, the FDC 25/5 arm appeared to more likely require rescue than the Empa 25 arm. At 52 weeks, both of the FDC arms again appeared to be better than the Lina 5 arm. This suggests that the FDC product is no worse than the individual components with regard to the need for rescue medication, and that it may be better than treatment with Lina 5.

Table 26: Rescue medication use – full analysis set, treatment naive

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
	N	%	N	%	N	%	N	%	N	%
Patients exposed	134		135		133		132		128	
24 week										
Rescued	2	1.5	1	0.7	1	0.8	4	3.0	11	8.3
- Metformin	2	1.5	0	0.0	1	0.8	3	2.3	6	4.5
- Sulfonylurea	0	0.0	1	0.7	0	0.0	1	0.8	6	4.5
- Insulin	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Other	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
52 week										
Rescued	6	4.5	5	3.7	6	4.5	12	9.1	27	20.3
- Metformin	3	2.2	5	3.7	5	3.8	9	6.8	15	11.3
- Sulfonylurea	3	2.2	1	0.7	0	0.0	3	2.3	16	12.0
- Insulin	0	0.0	0	0.0	1	0.8	0	0.0	0	0.0
- Other	0	0.0	0	0.0	1	0.8	0	0.0	0	0.0

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Tables 11.B.4.1.3.4: 1 and 11.B.4.1.3.4: 2 from the clinical study report for 1275.1

Table 27: Odds ratio of rescue medication use – logistic regression, full analysis set, treatment naïve

	OR	95% CI		p-value
		LL	UL	
24 weeks				
FDC 25/5 vs. Empa 25	2.072	0.184	23.343	0.5554
FDC 10/5 vs. Empa 10	0.245	0.027	2.247	0.2135
FDC 25/5 vs. Lina 5	0.167	0.036	0.777	0.0225
FDC 10/5 vs. Lina 5	0.076	0.010	0.609	0.0152
52 weeks				
FDC 25/5 vs. Empa 25	1.013	0.314	3.272	0.9828
FDC 10/5 vs. Empa 10	0.383	0.129	1.141	0.0850
FDC 25/5 vs. Lina 5	0.175	0.069	0.448	0.0003
FDC 10/5 vs. Lina 5	0.136	0.049	0.372	0.0001

OR = odds ratio; CI = confidence interval; LL = lower limit; UL = upper limit; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Tables 15.1.2.3.4: 2 and 15.4.2.3.4: 2 from the clinical study report for 1275.1

6.2.7 Subpopulations

Subgroups of interest included groupings by age, baseline HbA1c, gender, and baseline eGFR. Again, the analysis was done separately for the metformin patients and treatment naïve patients. Discussion of subgroups for efficacy will be limited to the primary endpoint of change in HbA1c.

6.2.7.1 By baseline HbA1c

Metformin patients:

As would be expected, patients with a higher baseline HbA1c had a greater reduction in HbA1c (Table 28). The 95% confidence interval for the difference between the FDC treatment arms and Lina 5 did not cross zero for any of the groups. Of note, the upper bound approached zero at 24 weeks for patients with a baseline HbA1c < 8.0%. For patients with HbA1c ≥ 9.0% at baseline, the 95% confidence interval for the difference between the FDC treatment arms and the respective empagliflozin dose crossed zero. This was true 24 and at 52 weeks. This may have been due to the smaller number of patients from this subgroup.

Treatment naïve:

Patients with higher baseline HbA1c had a greater reduction in HbA1c (Table 29). The 95% confidence interval for the difference between FDC 10/5 and Lina 5 did not cross zero for any of the groups. Of note, the upper bound approached zero at 24 weeks for patients with a baseline HbA1c < 8.0%. The upper bound of the 95% confidence interval for the difference between

FDC 25/5 and Empa 25 crossed zero for all sub-groups at 24 and at 52 weeks. For the comparison between FDC 25/5 and Lina 5, the 95% confidence interval was noted to again cross zero at 24 weeks. This is consistent with other efficacy findings described above, and again raises concern that combining the two agents does not offer an advantage over Empa 25.

Table 28: Adjusted mean change in HbA1c by baseline HbA1c subgroup – full analysis set, last observation carried forward, metformin patients

	FDC 25/5	FDC 10/5	Empa 25	Empa 10	Lina 5
24 weeks					
< 8.0%					
Number of patients	81	77	73	80	69
Mean HbA1c at baseline (SE)	7.35 (0.34)	7.37 (0.31)	7.39 (0.34)	7.40 (0.38)	7.36 (0.35)
Adjusted[1] mean change (SE)	-0.82 (0.08)	-0.79 (0.08)	-0.30 (0.09)	-0.38 (0.08)	-0.57 (0.09)
vs. Empa[2] (95% CI)	-0.51 (-0.74, -0.28)	-0.42 (-0.65, -0.19)			
vs. Lina (95% CI)	-0.25 (-0.48, -0.01)	-0.22 (-0.46, 0.01)			
8.0 to < 9.0%					
Number of patients	34	42	48	35	39
Mean HbA1c at baseline (SE)	8.41 (0.28)	8.40 (0.24)	8.33 (0.29)	8.36 (0.31)	8.33 (0.26)
Adjusted[1] mean change (SE)	-1.51 (0.12)	-1.22 (0.11)	-0.77 (0.11	-0.78 (0.12)	-0.74 (0.12)
vs. Empa[2] (95% CI)	-0.74 (-10.8, -0.42)	-0.44 (-0.77, -0.11)			
vs. Lina (95% CI)	-0.77 (-1.11, -0.44)	-0.48 (-0.80, -0.16)			
≥ 9.0%					
Number of patients	19	16	19	22	20
Mean HbA1c at baseline (SE)	9.29 (0.23)	9.53 (0.38)	9.61 (0.43)	9.64 (0.66)	9.67 (0.51)
Adjusted[1] mean change (SE)	-1.97 (0.17)	-1.96 (0.18)	-1.59 (0.17)	-1.57 (0.16)	-1.17 (0.16)
vs. Empa[2] (95% CI)	-0.38 (-0.84, 0.09)	-0.40 (-0.87, 0.08)			
vs. Lina (95% CI)	-0.79 (-1.25, -0.33)	-0.79 (-1.27, -0.31)			
52 weeks					
< 8.0%					
Number of patients	81	77	73	80	69
Mean HbA1c at baseline (SE)	7.35 (0.34)	7.37 (0.31)	7.39 (0.34)	7.39 (0.38)	7.38 (0.35)
Adjusted[1] mean change (SE)	-0.86 (0.06)	-0.80 (0.10)	-0.32 (0.13)	-0.35 (0.08_	-0.39 (0.08)
vs. Empa[2] (95% CI)	-0.55 (-0.82, -0.28)	-0.46 (-0.73, -0.20)			
vs. Lina (95% CI)	-0.50 (-0.78, -0.23)	-0.44 (-0.71, 0.16)			

	FDC 25/5	FDC 10/5	Empa 25	Empa 10	Lina 5
8.0 to < 9.0%					
Number of patients	34	42	48	35	39
Mean HbA1c at baseline (SE)	8.41 (0.28)	8.40 (0.24)	8.33 (0.29)	8.35 (0.31)	8.33 (0.26)
Adjusted[1] mean change (SE)	-1.39 (0.14)	-1.17 (0.13)	-0.75 (0.12)	-0.90 (0.14)	-0.51 (0.14)
vs. Empa[2] (95% CI)	-0.64 (-1.02, -0.27)	-0.27 (-0.65, -0.11)			
vs. Lina (95% CI)	-0.89 (-1.28, -0.50)	-0.66 (-1.03, -0.29)			
≥ 9.0%					
Number of patients	19	16	19	22	20
Mean HbA1c at baseline (SE)	9.29 (0.23)	9.53 (0.38)	9.61 (0.43)	9.64 (0.66)	9.67 (0.51)
Adjusted[1] mean change (SE)	-2.09 (0.19)	-1.83 (0.21)	-1.79 (0.19)	-1.64 (0.18)	-0.97 (0.19)
vs. Empa[2] (95% CI)	-0.30 (-0.84, 0.24)	-0.14 (-0.69, 0.41)			
vs. Lina (95% CI)	-1.11 (-1.64, -0.58)	-0.86 (-1.42, -0.30)			

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; HbA1c = glycosylated hemoglobin; SE = standard error; CI = confidence interval
[1] adjusted for region, treatment, baseline HbA1c, eGFR and treatment by baseline HbA1c interaction; [2] FDC compared with respective empagliflozin dose
Source: Adapted from Tables 11.A.4.1.1.2: 3 and 11.A.11.2: 6 of the study report for study 1275.1

Table 29: Adjusted mean change in HbA1c by baseline HbA1c subgroup – full analysis set, last observation carried forward, treatment naïve

	FDC 25/5	FDC 10/5	Empa 25	Empa 10	Lina 5
24 weeks					
< 8.0%					
Number of patients	72	69	73	72	70
Mean HbA1c at baseline (SE)	7.23 (0.36)	7.29 (0.36)	7.27 (0.35)	7.28 (0.38)	7.36 (0.29)
Adjusted[1] mean change (SE)	-0.56 (0.10)	-0.81 (0.10)	-0.49 (0.10)	-0.52 (0.10)	-0.40 (0.10)
vs. Empa[2] (95% CI)	-0.06 (-0.33, 0.21)	-0.29 (-0.57, -0.02)			
vs. Lina (95% CI)	-0.15 (-0.43, 0.12)	-0.41 (-0.68, -0.13)			
8.0 to < 9.0%					
Number of patients	38	43	35	32	41
Mean HbA1c at baseline (SE)	8.49 (0.24)	8.36 (0.28)	8.35 (0.29)	8.36 (0.23)	8.38 (0.24)
Adjusted[1] mean change (SE)	-1.42 (0.13)	-1.49 (0.13)	-1.10 (0.14)	-0.88 (0.15)	-0.85 (0.13)
vs. Empa[2] (95% CI)	-0.32 (-0.70, 0.06)	-0.60 (-0.98, -0.22)			
vs. Lina (95% CI)	-0.57 (-0.94, -0.20)	-0.64 (-0.99, -0.28)			
≥ 9.0%					
Number of patients	24	23	25	28	22
Mean HbA1c at baseline (SE)	9.47 (0.43)	9.69 (0.52)	9.59 (0.49)	9.66 (0.59)	9.63 (0.50)

	FDC 25/5	FDC 10/5	Empa 25	Empa 10	Lina 5
Adjusted[1] mean change (SE)	-2.03 (0.17)	-2.12 (0.17)	-1.98 (0.17)	-1.63 (0.16)	-1.28 (0.18)
vs. Empa[2] (95% CI)	-0.05 (-0.52, 0.41)	-0.49 (-0.94, -0.03)			
vs. Lina (95% CI)	-0.75 (-1.23, -0.27)	-0.84 (-1.33, -0.35)			
52 weeks					
< 8.0%					
Number of patients	72	69	73	72	70
Mean HbA1c at baseline (SE)	7.23 (0.36)	7.29 (0.36)	7.27 (0.35)	7.28 (0.38)	7.36 (0.29)
Adjusted[1] mean change (SE)	-0.65 (0.12)	-0.75 (0.12)	-0.63 (0.11)	-0.62 (0.12)	-0.27 (0.12)
vs. Empa[2] (95% CI)	-0.02 (-0.34, 0.30)	-0.13 (-0.45, 0.19)			
vs. Lina (95% CI)	-0.8 (-0.70, -0.06)	-0.48 (-0.80, -0.15)			
8.0 to < 9.0%					
Number of patients	38	43	35	32	41
Mean HbA1c at baseline (SE)	8.49 (0.24)	8.36 (0.28)	8.35 (0.29)	8.36 (0.23)	8.38 (0.24)
Adjusted[1] mean change (SE)	-1.49 (0.16)	-1.47 (0.15)	-1.20 (0.17)	-0.82 (0.17)	-0.65 (0.13)
vs. Empa[2] (95% CI)	-0.29 (-0.74, 0.16)	-0.65 (-1.10, -0.20)			
vs. Lina (95% CI)	-0.84 (-1.28, -0.41)	-0.82 (-1.23, -0.40)			
≥ 9.0%					
Number of patients	24	23	25	28	22
Mean HbA1c at baseline (SE)	9.47 (0.43)	9.69 (0.52)	9.59 (0.49)	9.66 (0.59)	9.63 (0.50)
Adjusted[1] mean change (SE)	-2.13 (0.20)	-2.23 (0.20)	-1.78 (0.19)	-1.52 (0.18)	-1.08 (0.21)
vs. Empa[2] (95% CI)	-0.35 (-0.89, 0.20)	-0.70 (-1.24, -0.16)			
vs. Lina (95% CI)	-1.06 (-1.62, -0.49)	-1.15 (-1.72, -0.58)			

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; HbA1c = glycosylated hemoglobin; SE = standard error; CI = confidence interval
[1] adjusted for region, treatment, baseline HbA1c, eGFR and treatment by baseline HbA1c interaction; [2] FDC compared with respective empagliflozin dose
Source: Adapted from Tables 11.B.4.1.1.2: 3 and 11.B.1.1.2: 6 of the study report for study 1275.1

6.2.7.2 By Age

Metformin patients:

The efficacy of SGLT2 inhibitors appears to wane with age, possibly due to declining renal function with age. In comparing between age groups, there were few patients > 75 years of age. To increase the numbers of patient in the age subgroups, examination of change in HbA1c was performed for patients < 65 and ≥ 65 years of age (Table 30). At 24 and 52 weeks, findings in patients < 65 years of age were consistent with the general population. For patients ≥ 65 years of age, the FDC compared favorably against the respective empagliflozin dose at 24 weeks. At 52 weeks, the difference for FDC 25/5 to Empa 25 was barely statistically significant. While both doses of the FDC were numerically better than linagliptin at 24 weeks, neither was statistically significantly better. However, at 52 weeks both doses of the FDC were statistically significantly better than linagliptin.

Treatment naïve patients:

The efficacy of SGLT2 inhibitors appears to wane with age, possibly due to declining renal function with age. In comparing between age groups, there were few patients > 75 years of age. To increase the numbers of patient in the age subgroups, examination of change in HbA1c was performed for patients < 65 and ≥ 65 years of age (Table 31). As was seen with the general population, the FDC 25/5 arm was not statistically significantly better than Empa 25 for either age group at 24 or 52 weeks. At both 24 and 52 weeks, treatment with FDC 10/5 was better than Empa 10 in patients < 65 years of age, but not in patients ≥ 65 years of age. The FDC was better than linagliptin for patients < 65 years of age at 24 and 52 weeks. In the ≥ 65 years of age sub-group, the FDC was not better than linagliptin at either 24 or 52 weeks with the exception of FDC 10/5 at 52 weeks which barely met nominal statistical significance.

Table 30: Adjusted mean change in HbA1c by age subgroup – full analysis set, last observation carried forward, metformin patients

	FDC 25/5	FDC 10/5	Empa 25	Empa 10	Lina 5
24 weeks					
< 65 years					
Number of patients	102	110	115	111	101
Mean HbA1c at baseline (SE)	7.94 (0.08)	7.96 (0.08)	8.07 (0.08)	8.07 (0.09)	8.04 (0.09)
Adjusted[1] mean change (SE)	-1.23 (0.07)	-1.07 (0.07)	-0.62 (0.07)	-0.70 (0.07)	-0.66 (0.07)
vs. Empa[2] (95% CI)	-0.60 (-0.80, -0.41)	-0.37 (-0.55, -0.18)			
vs. Lina (95% CI)	-0.56 (-0.76, -0.37)	-0.41 (-0.60, -0.21)			
≥ 65 years					
Number of patients	32	25	25	26	27
Mean HbA1c at baseline (SE)	7.78 (0.14)	7.87 (0.14)	7.78 (0.14)	7.73 (0.13)	7.93 (0.15)
Adjusted[1] mean change (SE)	-1.09 (0.13)	-1.13 (0.14)	-0.61 (0.14)	-0.46 (0.14)	-0.82 (0.14)
vs. Empa[2] (95% CI)	-0.48 (-0.86, -0.11)	-0.67 (-1.06, -0.27)			
vs. Lina (95% CI)	-0.27 (-0.64, 0.09)	-0.31 (-0.70, 0.08)			
52 weeks					
< 65 years					
Number of patients	102	110	115	111	101
Mean HbA1c at baseline (SE)	7.94 (0.08)	7.96 (0.08)	8.07 (0.08)	8.07 (0.09)	8.04 (0.09)
Adjusted[1] mean change (SE)	-1.24 (0.08)	-1.02 (0.08)	-0.63 (0.08)	-0.74 (0.08)	-0.45 (0.08)
vs. Empa[2] (95% CI)	-0.60 (-0.83, -0.38)	-0.28 (-0.50, -0.06)			
vs. Lina (95% CI)	-0.78 (-1.01, -0.55)	-0.57 (-0.79, -0.34)			
≥ 65 years					
Number of patients	32	25	25	26	27
Mean HbA1c at baseline (SE)	7.78 (0.14)	7.87 (0.14)	7.78 (0.14)	7.73 (0.13)	7.93 (0.15)
Adjusted[1] mean change (SE)	-1.13 (0.15)	-1.18 (0.17)	-0.68 (0.17)	-0.46 (0.16)	-0.57 (0.16)
vs. Empa[2] (95% CI)	-0.44 (-0.88, 0.00)	-0.72 (-1.18, -0.26)			
vs. Lina (95% CI)	-0.55 (-0.98, -0.12)	-0.61 (-1.07, -0.16)			

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; HbA1c = glycosylated hemoglobin; SE = standard error; CI = confidence interval
[1] adjusted for region, treatment, baseline HbA1c, eGFR and treatment by age groups interaction; [2] FDC compared with respective empagliflozin dose
Source: Adapted from Tables 15.2.2.1.2.4.1: 3, 15.2.2.1.2..4.1: 4, 15.5.2.1.4.1: 3, and 15.5.2.1.4.1: 4 of the study report for study 1275.1

Table 31: Adjusted mean change in HbA1c by age subgroup – full analysis set, last observation carried forward, treatment naïve

	FDC 25/5	FDC 10/5	Empa 25	Empa 10	Lina 5
24 weeks					
< 65 years					
Number of patients	111	110	112	112	109
Mean HbA1c at baseline (SE)	8.04 (0.09)	8.09 (0.09)	7.98 (0.09)	8.07 (0.10)	8.11 (0.09)
Adjusted[1] mean change (SE)	-1.13 (0.08)	-1.26 (0.08)	-0.96 (0.08)	-0.83 (0.08)	-0.63 (0.08)
vs. Empa[2] (95% CI)	-0.17 (-0.39, 0.04)	-0.43 (-0.64, -0.21)			
vs. Lina (95% CI)	-0.51 (-0.72, -0.29)	-0.63 (-0.85, -0.41)			
≥ 65 years					
Number of patients	23	25	21	20	24
Mean HbA1c at baseline (SE)	7.73 (0.18)	7.84 (0.19)	8.07 (0.23)	7.95 (0.24)	7.76 (0.12)
Adjusted[1] mean change (SE)	-0.85 (0.17)	-1.15 (0.16)	-0.88 (0.18)	-0.81 (0.18)	-0.87 (0.17)
vs. Empa[2] (95% CI)	0.03 (-0.45, 0.52)	-0.32 (-0.82, 0.15)			
vs. Lina (95% CI)	0.03 (-0.44, 0.50)	-0.27 (-0.74, 0.19)			
52 weeks					
< 65 years					
Number of patients	102	110	115	111	101
Mean HbA1c at baseline (SE)	8.04 (0.09)	8.09 (0.09)	7.98 (0.09)	8.07 (0.10)	8.11 (0.09)
Adjusted[1] mean change (SE)	-1.22 (0.09)	-1.19 (0.09)	-1.03 (0.09)	-0.86 (0.09)	-0.44 (0.09)
vs. Empa[2] (95% CI)	-0.19 (-0.45, 0.06)	-0.34 (-0.59, -0.08)			
vs. Lina (95% CI)	-0.78 (-1.03, -0.52)	-0.75 (-1.00, -0.49)			
≥ 65 years					
Number of patients	32	25	25	26	27
Mean HbA1c at baseline (SE)	7.73 (0.18)	7.84 (0.19)	8.07 (0.23)	7.95 (0.24)	7.76 (0.12)
Adjusted[1] mean change (SE)	-0.95 (0.20)	-1.35 (0.19)	-0.95 (0.21)	-0.81 (0.22)	-0.80 (0.20)
vs. Empa[2] (95% CI)	0.00 (-0.57, 0.57)	-0.54 (-1.11, 0.03)			
vs. Lina (95% CI)	-0.15 (-0.70, 0.40)	-0.55 (-1.09, -0.01)			

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; HbA1c = glycosylated hemoglobin; SE = standard error; CI = confidence interval
[1] adjusted for region, treatment, baseline HbA1c, eGFR and treatment by age groups interaction; [2] FDC compared with respective empagliflozin dose
Source: Adapted from Tables 15.1.2.1.2.4.1: 3, 15.1.2.1.2..4.1: 4, 15.4.2.1.4.1: 3, and 15.4.2.1.4.1: 4 of the study report for study 1275.1

6.2.7.3 By estimated glomerular filtration rate

Both of the approved SGLT2 inhibitors have labeling which excludes use in patients with varying degrees of renal impairment. Consistent with this, patients with severe renal impairment (i.e. eGFR < 30 ml/min/1.73 m^2) were excluded from the study. There were few patients with moderate renal impairment (i.e. eGFR 30 to 60 ml/min/1.73 m^2). Thus, subgroups were examined using patients with an eGFR of ≥ 90 ml/min/1.73 m^2 (i.e. normal) versus those with an eGFR from 60 to 90 ml/min/1.73 m^2 (i.e. mild renal impairment).

Metformin patients:

Both doses of the FDC were numerically and statistically significantly better than the individual components for both renal function subgroups (Table 32). This was true at both 24 and 52 weeks. The FDC 25/5 also appeared to be numerically superior to the FDC 10/5 dose.

Treatment naïve:

The 10/5 dose of the FDC was numerically and statistically significantly better than the individual components for patients in both renal function subgroups at 24 and 52 weeks except when compared to empagliflozin 10 at 52 weeks (Table 33). As was seen with the primary analysis and with other analyses, the 25/5 dose of the FDC was not statistically significantly better than empagliflozin 25 for patients with an eGFR ≥ 90 ml/min/1.73 m^2 at either 24 or 52 weeks, or for patients with an eGFR between 60 and 90 ml/min/1.73 m^2 at 52 weeks.

Table 32: Adjusted mean change in HbA1c by baseline renal function using estimated glomerular filtration rate by modification of diet in renal disease formula– full analysis set, last observation carried forward, metformin patients

	FDC 25/5	FDC 10/5	Empa 25	Empa 10	Lina 5
24 weeks					
≥ 90					
Number of patients	58	57	60	64	57
Mean HbA1c at baseline (SE)	7.96 (0.11)	8.14 (0.11)	7.96 (0.10)	7.99 (0.12)	8.10 (0.15)
Adjusted[1] mean change (SE)	-1.24 (0.09)	-1.24 (0.10)	-0.78 (0.09)	-0.72 (0.09)	-0.72 (0.10)
vs. Empa[2] (95% CI)	-0.47 (-0.72, -0.21)	-0.51 (-0.77, -0.26)			
vs. Lina (95% CI)	-0.52 (-0.76, -0.26)	-0.52 (-0.78, -0.25)			
60 to < 90					
Number of patients	72	77	78	68	65
Mean HbA1c at baseline (SE)	7.81 (0.09)	7.79 (0.71)	8.06 (0.10)	8.03 (0.12)	7.96 (0.09)
Adjusted[1] mean change (SE)	-1.17 (0.08)	-0.95 (0.08)	-0.51 (0.08)	-0.64 (0.09)	-0.67 (0.09)
vs. Empa[2] (95% CI)	-0.66 (-0.89, -0.43)	-0.31 (-0.54, -0.07)			
vs. Lina (95% CI)	-0.50 (-0.74, -0.26)	-0.28 (-0.52, -0.04)			
52 weeks					
≥ 90					
Number of patients	58	57	60	64	57
Mean HbA1c at baseline (SE)	7.96 (0.11)	8.14 (0.11)	7.96 (0.10)	7.99 (0.12)	8.10 (0.15)
Adjusted[1] mean change (SE)	-1.22 (0.11)	-1.11 (0.11)	-0.76 (0.11)	-0.75 (0.10)	-0.49 (0.11
vs. Empa[2] (95% CI)	-0.46 (-0.76, -0.16)	-0.36 (-0.66, -0.06)			
vs. Lina (95% CI)	-0.73 (-1.03, -0.42)	-0.62 (-0.92, -0.31)			
60 to < 90					
Number of patients	72	77	78	68	65
Mean HbA1c at baseline (SE)	7.81 (0.09)	7.79 (0.71)	8.06 (0.10)	8.03 (0.12)	7.96 (0.09)
Adjusted[1] mean change (SE)	-1.21 (0.10)	-1.00 (0.09)	-0.57 (0.10)	-0.71 (0.10)	-0.50 (0.10)
vs. Empa[2] (95% CI)	-0.64 (-0.90, -0.37)	-0.29 (-0.56, -0.02)			
vs. Lina (95% CI)	-0.72 (-0.99, -0.44)	-0.50 (-0.78, -0.23)			

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; HbA1c = glycosylated hemoglobin; SE = standard error; CI = confidence interval
[1] adjusted for region, treatment, baseline HbA1c, eGFR, and treatment by baseline eGFR interaction; [2] FDC compared with respective empagliflozin dose
Source: Adapted from Tables 15.2.2.1.2.4.10: 1, 15.2.2.1.2.4.10: 2, 15.5.2.1.4.10: 1, and 15.5.2.1.4.10: 2 of the study report for study 1275.1

Table 33: Adjusted mean change in HbA1c by baseline renal function using estimated glomerular filtration rate by modification of diet in renal disease formula– full analysis set, last observation carried forward, treatment naive

	FDC 25/5	FDC 10/5	Empa 25	Empa 10	Lina 5
24 weeks					
≥ 90					
Number of patients	62	54	58	59	57
Mean HbA1c at baseline (SE)	7.98 (0.12)	8.08 (0.14)	7.99 (0.13)	8.15 (0.13)	8.24 (0.13)
Adjusted[1] mean change (SE)	-1.06 (0.10)	-1.16 (0.11)	-1.13 (0.11)	-0.86 (0.11)	-0.62)0.11)
vs. Empa[2] (95% CI)	0.07 (-0.23, 0.36)	-0.30 (-0.61, 0.00)			
vs. Lina (95% CI)	-0.44 (-0.74, -0.14)	-0.55 (-0.85, -0.24)			
60 to < 90					
Number of patients	67	76	72	70	75
Mean HbA1c at baseline (SE)	8.02 (0.12)	8.04 (0.11)	7.99 (0.11)	7.94 (0.12)	7.91 (0.09)
Adjusted[1] mean change (SE)	-1.08 (0.10)	-1.31 (0.09)	-0.80 (0.10)	-0.79 (0.10)	-0.72 (0.10)
vs. Empa[2] (95% CI)	-0.28 (-0.55, -0.01)	-0.52 (-0.79, -0.25)			
vs. Lina (95% CI)	-0.36 (-0.63, -0.09)	-0.58 (-0.85, -0.32)			
52 weeks					
≥ 90					
Number of patients	62	54	58	59	57
Mean HbA1c at baseline (SE)	7.98 (0.12)	8.08 (0.14)	7.99 (0.13)	8.15 (0.13)	8.24 (0.13)
Adjusted[1] mean change (SE)	-1.10 (0.12	-1.08 (0.13)	-1.14 (0.13)	-0.86 (0.13)	-0.38 (0.13)
vs. Empa[2] (95% CI)	0.04 (-0.31, 0.39)	-0.22 (-0.58, 0.14)			
vs. Lina (95% CI)	-0.72 (-1.07, -0.37)	-0.70 (-1.06, -0.34)			
60 to < 90					
Number of patients	67	76	72	70	75
Mean HbA1c at baseline (SE)	8.02 (0.12)	8.04 (0.11)	7.99 (0.11)	7.94 (0.12)	7.91 (0.09)
Adjusted[1] mean change (SE)	-1.20 (0.12)	-1.35 (0.11)	-0.91 (0.11)	-0.86 (0.12)	-0.61 (0.11)
vs. Empa[2] (95% CI)	-0.29 (-0.61, 0.03)	-0.49 (-0.80, -0.17)			
vs. Lina (95% CI)	-0.58 (-0.90, -0.27)	-0.73 (-1.04, -0.42)			

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; HbA1c = glycosylated hemoglobin; SE = standard error; CI = confidence interval
[1] adjusted for region, treatment, baseline HbA1c, eGFR, and treatment by baseline eGFR interaction; [2] FDC compared with respective empagliflozin dose
Source: Adapted from Tables 15.1.2.1.2.4.10: 1, 15.1.2.1.2.4.10: 2, 15.4.2.1.4.10: 1, and 15.4.2.1.4.10: 2 of the study report for study 1275.1

6.2.7.4 By region

Metformin patients:

Examining the efficacy of the FDC by region showed results generally consistent with whole population (Table 34). The one region where efficacy of the FDC was not as apparent was in Latin America. Additionally, the FDC 10/5 arm did not appear to be clearly more effective in Europe compared to Empa 10 or Lina 5.

Treatment naïve:

Examining the efficacy of the FDC by region showed results generally consistent with whole population (Table 35). The efficacy in the FDC 25/5 arm was again numerically greater than Empa 25, but it did not achieve nominal statistical significance in any region. Superiority of FDC 10/5 over Empa 10 was nominally statistically significant in North America only. Compared to Lina 5, neither dose of the FDC was nominally statistically significantly better in Asia. In Europe, the FDC 25/5 arm did not achieve nominal statistical significance compared to Lina 5.

Table 34: Adjusted mean change in HbA1c from baseline by region – 24 weeks, full analysis set, last observation carried forward, analysis of covariance model, metformin patients

	FDC 25/5	FDC 10/5	Empa 25	Empa 10	Lina 5
24 weeks					
Europe[1]					
Number of patients	39	37	37	39	39
Adjusted mean change (SE)	-1.32 (0.11)	-1.03 (0.12)	-0.81 (0.12)	-0.82 (0.12)	-0.95 (0.11)
vs. Empa (95% CI)	-0.51 (-0.83, -0.19)	-0.21 (-0.53, 0.11)			
vs. Lina (95% CI)	-0.38 (-0.69, -0.06)	-0.08 (-0.40, 0.24)			
North America[2]					
Number of patients	59	63	65	62	54
Adjusted mean change (SE)	-1.08 (0.09)	-0.96 (0.09)	-0.41 (0.09)	-0.45 (0.09)	-0.48 (0.10)
vs. Empa (95% CI)	-0.67 (-0.92, -0.41)	-0.50 (-0.75, -0.25)			
vs. Lina (95% CI)	-0.59 (-0.86, -0.33)	-0.47 (-0.73, -0.21)			
Latin America[3]					
Number of patients	18	18	20	19	18
Adjusted mean change (SE)	-1.12 (0.17)	-1.24 (0.17)	-0.95 (0.16)	-0.87 (0.16)	-0.72 (0.17)
vs. Empa (95% CI)	-0.18 (-0.63, 0.28)	-0.37 (-0.84, 0.09)			
vs. Lina (95% CI)	-0.40 (-0.87, 0.07)	-0.52 (-0.98, -0.05)			
Asia[4]					
Number of patients	18	17	18	17	17
Adjusted mean change (SE)	-1.39 (0.17)	-1.45 (0.17)	-0.57 (0.17)	-0.80 (0.17)	-0.83 (0.17)
vs. Empa (95% CI)	-0.82 (-1.29, -0.35)	-0.65 (-1.13, -0.17)			
vs. Lina (95% CI)	-0.55 (-1.03, -0.08)	-0.62 (-1.10, -0.14)			

[1] includes Australia, Bulgaria, Denmark, Estonia, Hungary, Italy, Poland, Romania, Russia, Spain, Sweden; [2] includes Canada, United States; [3] includes Argentina, Brazil, Columbia, Mexico, Peru; [4] Lebanon, Malaysia, Philippines, Taiwan
FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; SE = standard error; CI = confidence interval
Source: Adapted from Table 15.2.2.1.2.4.5: 1 of the study report for Study 1275.1

Table 35: Adjusted mean change in HbA1c from baseline by region – 24 weeks, full analysis set, last observation carried forward, analysis of covariance model, treatment naive

	FDC 25/5	FDC 10/5	Empa 25	Empa 10	Lina 5
24 weeks					
Europe[1]					
Number of patients	34	35	33	33	34
Adjusted mean change (SE)	-1.02 (0.14)	-1.22 (0.14)	-0.93 (0.14)	-0.95 (0.14)	-0.77 (0.14)
vs. Empa (95% CI)	-0.09 (-0.49, 0.30)	-0.27 (-0.66, 0.12)			
vs. Lina (95% CI)	-0.25 (-0.65, 0.14)	-0.45 (-0.84. -0.06)			
North America[2]					
Number of patients	56	55	53	55	54
Adjusted mean change (SE)	-1.02 (0.11)	-1.16 (0.11)	-0.76 (0.11)	-0.61 (0.11)	-0.50 (0.11)
vs. Empa (95% CI)	-0.27 (-0.58, 0.05)	-0.56 (-0.86, -0.25)			
vs. Lina (95% CI)	-0.52 (-0.83, -0.21)	-0.66 (-0.97, -0.35)			
Latin America[3]					
Number of patients	28	31	30	31	28
Adjusted mean change (SE)	-1.14 (0..16)	-1.28 (0.15)	-1.17 (0.15)	-1.05 (0.15)	-0.68 (0.16)
vs. Empa (95% CI)	0.03 (-0.40, 0.45)	-0.23 (-0.64, 0.19)			
vs. Lina (95% CI)	-0.47 (-0.90, -0.03)	-0.60 (-1.03, -0.18)			
Asia[4]					
Number of patients	16	14	17	13	17
Adjusted mean change (SE)	-1.32 (0.21)	-1.47 (0.22)	-1.23 (0.20)	-0.89 (0.23)	-1.03 (0.20)
vs. Empa (95% CI)	-0.09 (-0.65, 0.48)	-0.58 (-1.20, 0.05)			
vs. Lina (95% CI)	-0.29 (-0.85, 0.28)	-0.44 (-1.02, 0.15)			

[1] includes Australia, Bulgaria, Denmark, Estonia, Hungary, Italy, Poland, Romania, Russia, Spain, Sweden; [2] includes Canada, United States; [3] includes Argentina, Brazil, Columbia, Mexico, Peru; [4] Lebanon, Malaysia, Philippines, Taiwan
FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; SE = standard error; CI = confidence interval
Source: Adapted from Table 15.1.2.1.2.4.5: 1 of the study report for Study 1275.1

6.2.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Formal comparison between the two FDC doses was not performed. Numerically, FDC 25/5 was better than FDC 10/5 in the metformin treated patients for reduction in HbA1c. In the treatment naïve patients, FDC 25/5 was not numerically better than FDC 10/5. This raises a question with regard to the benefit of the higher dose for efficacy.

The optimal dose for approval was also an issue in the empagliflozin review. While there were settings in which Empa 25 was better than Empa 10 for reducing HbA1c, this was not universally true in the empagliflozin development program. Empa 25 appeared to be better than Empa 10 for reduction in HbA1c in treatment naïve patients, in the setting of pioglitazone +/- metformin background therapy, and in the setting of metformin background therapy. In the setting of metformin plus a sulfonylurea, Empa 25 did not appear better than Empa 10. Additional consideration of secondary efficacy endpoints and slight differences in safety led to the decision to recommend both doses for approval.

Given the findings in study 1275.1, the question is raised again regarding additional efficacy with the higher dose (i.e. 25/5) over the lower dose (i.e. 10/5). The added efficacy of using the combination is questionable, particularly when compared to empagliflozin alone. Additionally, there is no clearly apparent benefit from the higher dose over the lower dose.

6.2.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

To assess the persistence of efficacy, the patients were followed beyond the 24 week primary endpoint to 52 weeks.

Metformin patients:

At 52 weeks, all treatment arms showed a reduction in HbA1c compared to baseline (Table 36). As was seen at 24 weeks, the FDC arms appeared to have a greater reduction than the comparator arms. This difference was nominally statistically significant for all of the comparisons (Table 37).

Table 36: Change in HbA1c from baseline to 52 weeks – full analysis set, last observation carried forward, analysis of covariance model, metformin patients

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
N	**134**		**135**		**140**		**137**		**128**	
	%	**SE**	**%**	**SE**	**%**	**SE**	**%**	**SE**	**%**	**SE**
Mean baseline HbA1c	7.90	0.07	7.95	0.07	8.02	0.07	8.00	0.08	8.02	0.08
Mean HbA1c at 52 weeks	6.72	0.06	6.92	0.09	7.36	0.10	7.30	0.07	7.50	0.09
Mean adjusted[1] HbA1c at 52 weeks	6.76	0.07	6.92	0.07	7.33	0.07	7.29	0.07	7.50	0.07
Change from baseline										
- Mean change	-1.17	0.07	-1.03	0.09	-0.66	0.10	-0.70	0.08	-0.51	0.07
- Adjusted mean change	-1.21	0.07	-1.05	0.07	-0.64	0.07	-0.69	0.07	-0.48	0.07

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; SE = standard error; HbA1c = glycosylated hemoglobin
[1] model adjustments for treatment, renal function, region, and baseline HbA1c
Source: Adapted from Table 11.A.4.1.1.2: 4 of the clinical study report for study 1275.1

Table 37: Reduction in HbA1c with fixed dose combination product compared to the individual components – 52 weeks, full analysis set, last observation carried forward, analysis of covariance model, metformin patients

	Adjusted[1] mean change (%)	SE	95% CI		p-value
			LL	UL	
FDC 25/5					
- vs. Empa 25	-0.57	0.10	-0.77	-0.37	< 0.0001
- vs. Lina 5	-0.73	0.10	-0.93	-0.53	< 0.0001
FDC 10/5					
- vs. Empa 10	-0.36	0.10	-0.56	-0.17	0.0003
- vs. Lina 5	-0.57	0.10	-0.77	-0.37	< 0.0001

SE = standard error; 95% CI = 95% confidence interval; LL = lower limit; UL = upper limit; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
[1] model adjustments for treatment, renal function, region, and baseline HbA1c
Source: Adapted from Table 11.A.4.1.1.2: 4 of the clinical study report for study 1275.1

Treatment naïve:

At 52 weeks, all treatment arms showed a reduction in HbA1c compared to baseline (Table 38). The FDC arms had a numerically greater reduction than the comparator arms. As was seen at 24 weeks, the difference between the FDC 25/5 arm and Empa 25 did not demonstrate a statistically significant difference (Table 39). All other comparisons had a nominally statistically significant difference.

Table 38: Change in HbA1c from baseline to 52 weeks – full analysis set, last observation carried forward, analysis of covariance model, treatment naïve

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
N	**134**		**135**		**133**		**132**		**133**	
	%	**SE**	**%**	**SE**	**%**	**SE**	**%**	**SE**	**%**	**SE**
Mean baseline HbA1c	7.99	0.08	8.04	0.08	7.99	0.08	8.05	0.09	8.05	0.08
Mean HbA1c at 52 weeks	6.83	0.08	6.81	0.09	6.99	0.09	7.19	0.10	7.52	0.10
Mean adjusted[1] HbA1c at 52 weeks	6.85	0.08	6.80	0.08	7.01	0.08	7.17	0.08	7.51	0.08
Change from baseline										
- Mean change	-1.15	0.09	-1.23	0.10	-1.00	0.08	-0.86	0.09	-0.53	0.10
- Adjusted mean change	-1.17	0.08	-1.22	0.08	-1.01	0.08	-0.85	0.08	-0.51	0.08

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; SE = standard error; HbA1c = glycosylated hemoglobin
[1] model adjustments for treatment, renal function, region, and baseline HbA1c
Source: Adapted from Table 11.B.4.1.1.2: 4 of the clinical study report for study 1275.1

Table 39: Reduction in HbA1c with fixed dose combination product compared to the individual components – 52 weeks, full analysis set, last observation carried forward, analysis of covariance model, treatment naïve

	Adjusted[1] mean change (%)	SE	95% CI		p-value
			LL	UL	
FDC 25/5					
- vs. Empa 25	-0.16	0.12	-0.39	0.07	0.1764
- vs. Lina 5	-0.66	0.12	-0.90	-0.43	< 0.0001
FDC 10/5					
- vs. Empa 10	-0.37	0.12	-0.60	-0.14	0.0017
- vs. Lina 5	-0.71	0.12	-0.94	-0.48	< 0.0001

SE = standard error; 95% CI = 95% confidence interval; LL = lower limit; UL = upper limit; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
[1] model adjustments for treatment, renal function, region, and baseline HbA1c
Source: Adapted from Table 11.B.4.1.1.2: 4 of the clinical study report for study 1275.1

6.2.10 Additional Efficacy Analyses

In addition to the primary analysis utilizing the FAS, the Applicant analyzed the results using additional patient groupings (Table 40). These additional groupings included a full analysis set – completers only (FAS-completers), a per protocol set (PPS), and a per protocol set – completers only (PPS-completers). The FAS-completers included all randomized patients with at least one dose of study medication, a baseline HbA1c, and an on-treatment HbA1c who did not prematurely discontinue from the trial. The PPS included all randomized patients without important protocol violations. The PPS-completers included patients from the PPS who did not prematurely discontinue from the trial.

Table 40: Analysis sets

	FDC 25/5	FDC 10/5	Empa 25	Empa 10	Lina 5	Total
	N	N	N	N	N	N
Treatment naïve						
Randomized set	137	136	135	134	135	677
Treated set	136[1]	136	135	135[1]	135	677
FAS	134	135	133	132	133	667
FAS-completers (24 weeks)	121	125	119	122	119	606
FAS-completers (52 weeks)	110	110	112	106	114	552
PPS (24 weeks)	116	124	123	118	126	607
PPS-completers (24 weeks)	112	116	114	110	115	567
Metformin patients						
Randomized set	137	136	141	140	132	686
Treated set	137	136	141	140	132	686
FAS	134	135	140	137	128	674
FAS-completers (24 weeks)	124	130	129	126	120	629
FAS-completers (52 weeks)	117	124	123	116	113	593
PPS (24 weeks)	124	129	132	124	115	624
PPS-completers (24 weeks)	118	126	123	120	110	597

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; FAS = full analysis set; PPS = per protocol set
[1] One patient (1275.0001.098584) was randomized to FDC 25/5 but was mistakenly treated with Empa 10 for the first six weeks. The patient was analyzed as FDC 25/5 for efficacy.
Source: Adapted from Tables 15.1.1.3: 1, 15.2.1.3: 1, 15.4.1.3: 1, and 15.5.1.3: 1 from the clinical study report for 1275.1

Additional analyses using these different analysis sets yielded similar results to that seen with the primary analysis set.

6.2.11 Discussion of Efficacy Issue(s)

The main efficacy issue is failure of the high dose FDC to demonstrate improved efficacy compared to empagliflozin in the treatment naïve population. As noted in the discussion of efficacy above, the treatment naïve population did not demonstrate a statistically significant difference between the high dose FDC and Empa 25. As a result of this, the testing hierarchy stopped and all of the endpoints in this patient population are considered exploratory. Additionally, comparison of the high dose FDC with the low dose FDC did not demonstrate an improvement in efficacy for this population. The question is how to reconcile this finding with the efficacy seen in the metformin patient population.

At the mid-cycle meeting, the Applicant was made aware of this concern. This finding was acknowledged, but no explanation was provided at that time. At the late-cycle meeting, this issue was again discussed. Additional analysis to explore difference between the treatment arms that might explain this finding were performed by the Applicant and submitted to the Agency for consideration. Additionally, the Applicant suggested that the finding may be spurious and due to chance, and stated their opinion that the overall evidence for efficacy supports the conclusion

that combining the two drugs yields improved efficacy.

I am similarly unable to provide a plausible explanation for this finding. However, I believe that overall the efficacy findings support approval of the FDC product. Though the statistical testing scheme was to have stopped after the FDC 25/5 comparison in the treatment naïve population, it is difficult to ignore the efficacy findings for the FDC 10/5 compared to the individual components. The associated p-value for this finding suggests that it is likely to be statistically significant and robust. If one accepts the efficacy findings of the FDC 10/5 in the treatment naïve population and the finding for the FDC 25/5 compared to linagliptin as valid, then the FDC demonstrates efficacy over the individual components in seven of eight comparisons. Though eight of eight would be ideal, this seems to adequately support the efficacy of the FDC, particularly in the metformin treated population. Considering all of these factors, I feel that the FDC product can be approved.

Due to the question of the additional benefit of combining Empa 25 and Lina 5 compared to Empa 25 in the treatment naïve population, inclusion of a limitation of use against initial therapy with the FDC is a possible consideration. However, I do not favor including a limitation of use against use of the FDC as initial therapy. Current practice guidelines would not encourage use of this FDC as initial therapy, and guidelines which recommend the use of multiple drug therapy as initial therapy typically recommend that one of those drugs be metformin. Thus, it seems unlikely that this combination would be used without metformin. Additionally, though it was not valid based on the statistical testing hierarchy, the FDC 10/5 dose demonstrated additional efficacy over Empa 10 alone. The current labeling language for empagliflozin is to initiate at 10 mg and increase if additional glycemic lowering is needed. The proposed FDC label similarly recommends starting with the lower dose then increasing dosage if needed. Thus, if the FDC were used as initial therapy it would likely be the FDC 10/5 dose which I feel has adequate evidence to support added benefit over the monocomponents.

7. Review of Safety

7.1 Safety Summary

As there was no placebo arm for Study 1275.1, the analysis of safety for the FDC product was entirely against active comparators. Comparing the apparent safety profiles of the combination product with the individual components yields safety findings consistent with might be expected if treated with both empagliflozin and linagliptin.

Treatment with the FDC did not produce any notable difference in deaths or nonfatal serious adverse events compared to the individual components. Adverse events of special interest evaluated in this study included volume depletion, changes in renal function, hepatic safety, urinary tract infections, genital infections, pancreatitis, hypersensitivity, hypoglycemia,

malignancies, skin lesions, and cardiovascular events. Findings for these adverse events with the FDC were consistent with the individual components, and use of the FDC product resulted in a safety profile consistent with the combined safety profile of the individual components. There did not appear to be any synergism which would suggest an increased risk with the FDC over the individual components. Additionally, no new safety signals were identified during review of the NDA.

Overall, the safety profile of the FDC is consistent with the individual components. There were no new safety signals identified, and there were no notable differences from what might be predicted given the profile of the individual components.

7.2 Methods

7.2.1 Studies/Clinical Trials Used to Evaluate Safety

For details on the safety of the individual components which make up the FDC product, refer to the previous reviews for the individual products.

This review will focus on the findings from the phase 3 study (Study 1275.1) submitted to support the FDC product at 52 weeks. Study 1275.1 was designed to compare the two doses of the FDC product with the individual components. The patient population was divided into naïve patients and metformin patients. These two populations are analyzed separately by the Applicant. A pooled analysis is also presented.

7.2.2 Categorization of Adverse Events

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 16.0.

Adverse events were defined in accordance with ICH E6 guidelines as any untoward medical occurrence in a subject who was administered a pharmaceutical product, regardless of assigned causality.

Serious adverse events (SAEs) were defined as any AE that was immediately life threatening, was a congenital anomaly/birth defect, resulted in persistent or significant disability/incapacity, requires or prolonged hospitalization, or resulted in death. It could also be any other AE deemed serious if it was a medically important event based upon medical judgment which might jeopardize the patient and require medical/surgical intervention to prevent one of the previously listed outcomes.

Intensity of the AE was determined by the investigator as mild (awareness of signs/symptoms, easily tolerated), moderate (cause interference in usual activity), or severe (incapacitating or

causing inability to perform usual activities/work).

Worsening of an underlying condition was not recorded as an AE unless:

- It could be classified as an SAE
- The study drug was discontinued, or the dose was changed
- Additional treatment was required
  Or,
- In the investigator's opinion the deterioration from baseline was unexpected

Protocol pre-specified significant adverse events were events that required immediate reporting to the drug safety center, and collection of additional unscheduled laboratory tests including a sample for pharmacokinetics. These events included:

- Hypersensitivity reactions (e.g. angioedema, anaphylaxis)
- Skin reactions (e.g. exfoliative rash, skin necrosis, bullous dermatitis)
- Pancreatitis
- Decreased renal function (defined as serum creatinine increase ≥ 2x baseline and above the upper limit of the reference range [ULRR])
- Hepatic injury (defined as alteration of liver parameters after randomization such that ALT and/or AST was ≥ 3x ULRR with an elevation of bilirubin ≥ 2x ULRR)

Adverse events of special interest (AESIs) included the protocol pre-specified significant adverse events. They additionally included:

- Hypoglycemic events
- Urinary tract infections
- Genital infections
- Adverse events related to volume depletion
- Malignancies

Cardiovascular events were adjudicated by an independent external committee. Adjudication endpoints were:

- Cardiovascular death
- Non-cardiovascular death
- Non-fatal myocardial infarction
- Hospitalization for unstable angina
- Stent thrombosis
- Transient ischemic attack
- Stroke

7.2.2.1 Criteria for Withdrawal/Early Discontinuation

Patients could be withdrawn from the study if the patient withdrew consent (no justification

needed to be provided), or the patient became pregnant. Study medication was to be discontinued if there was a need to concomitant medications that would interfere with the study drug, the patient was no longer able to participate due to a medical reason, the introduction of rescue therapy failed to produce sufficient glycemic control, hypoglycemia that could put the patient at risk occurred, or there was suspicion of pancreatitis. Patients who discontinued from treatment were to be followed until the end of the study (week 52).

7.2.3 Pooling of Data Across Clinical Trials to Estimate and Compare Incidence

Not applicable. Though the submitted study assesses two distinct sub-groups of patients (i.e. treatment naïve patients and metformin patients), only one clinical trial was performed. No pooling is performed.

7.3 Adequacy of Safety Assessments

7.3.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

For analysis of safety, the analysis population was the treated set (TS). This population was composed of all patients treated with at least one dose of randomized study drug. The Applicant performed analyses at 24 weeks and at 52 weeks. The focus of this review will be the 52 week data as it covers a greater duration of exposure. As with the rest of the analyses, the Applicant examined this population by background therapy (i.e. metformin patients and treatment naïve).

Metformin patients:

Exposure to study drug was similar between the different study arms (Table 41). The study was planned to extend to 52 weeks, and the majority of patients continued study drug exposure through the 46 to 54 week time period.

Table 41: Exposure to randomized study drug – treated set, metformin background

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	137		136		141		140		132	
Exposure (weeks)	N	%	N	%	N	%	N	%	N	%
> 0-4	5	3.6	2	1.5	2	1.4	3	2.1	4	3.0
> 4-8	0	0.0	0	0.0	0	0.0	3	2.1	3	2.3
> 8-14	2	1.5	0	0.0	3	2.1	5	3.6	1	0.8
> 14-20	1	0.7	2	1.5	3	2.1	2	1.4	1	0.8
> 20-28	5	3.6	3	2.2	2	1.4	3	2.1	5	3.8
> 28-36	1	0.7	1	0.7	2	1.4	2	1.4	2	1.5
> 36-46	1	0.7	4	2.9	3	2.1	4	2.9	2	1.5
> 46-54	121	88.3	124	91.2	126	89.4	118	84.3	114	86.4
> 54	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	137		136		141		140		132	
Exposure (days)										
Mean (SD)	338.3	83.5	349.7	60.5	343.5	72.3	329.6	94.2	333.0	90.5
Median	364.0		365.0		364.0		364.0		364.5	
Range	1	379	7	375	1	378	1	377	1	378
Total exposure (pt-yrs)	126.9		130.2		132.6		126.3		120.3	

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; SD = standard deviation; pt-yrs = patient-years (number of patients x mean exposure in days / 365.25)
Source: Adapted from Table 15.5.3.1: 1 of the clinical study report for study 1275.1

In general, patient demographics were similar between treatment arms (Table 42). The majority of subjects identified as White, and as non-Hispanic. Approximately half of the patients in each treatment arm were between 50 and 65 years of age. The majority of patients had a baseline estimated glomerular filtration rate (eGFR) as calculated by the modification of diet in renal disease (MDRD) equation > 60 ml/min/1.73 m^2.

Table 42: Baseline demographics – full analysis set, metformin patients

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
	N	%	N	%	N	%	N	%	N	%
Number of patients	134		135		140		137		128	
Gender										
Male	72	53.7	83	61.5	65	46.4	78	56.9	64	50.0
Female	62	46.3	52	38.5	75	53.6	59	43.1	64	50.0
Race										
White	97	72.4	102	75.6	100	71.4	104	75.9	96	75.0
Black	7	5.2	12	8.9	13	9.3	8	5.8	9	7.0
Asian	22	16.4	18	13.3	20	14.3	19	13.9	14	10.9
Other	8	6.0	3	2.2	7	5.0	6	4.4	9	7.0
Ethnicity										
Hispanic/Latino	34	25.4	32	23.7	38	27.1	44	32.1	39	30.5
Non-Hispanic/Latino	100	74.6	103	76.3	102	72.9	93	67.9	89	69.5
Region										
Europe	39	29.1	37	27.4	37	26.4	39	28.5	39	30.5
North America	59	44.0	63	46.7	65	46.4	62	45.3	54	42.2
Latin America	18	13.4	18	13.3	20	14.3	19	13.9	18	14.1
Asia	18	13.4	17	12.6	18	12.9	17	12.4	17	13.3
Age (years)										
< 50	27	20.1	32	23.7	38	27.1	37	27.0	36	28.1
50 to < 65	75	56.0	78	57.8	77	55.0	74	54.0	65	50.8
65 to < 75	28	20.9	21	15.6	21	15.0	19	13.9	24	18.8
≥ 75	4	3.0	4	3.0	4	2.9	7	5.1	3	2.3
BMI (kg/m^2)										
< 25	17	12.7	19	14.1	10	7.1	15	10.9	20	15.6
25 to < 30	59	44.0	49	36.3	46	32.9	48	35.0	41	32.0

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
	N	%	N	%	N	%	N	%	N	%
30 to < 35	29	21.6	34	25.2	43	30.7	44	32.1	41	32.0
≥ 35	29	21.6	33	24.4	41	29.3	30	21.9	26	20.3
eGFR[1] (ml/min/1.73m^2)										
> 90	58	43.3	57	42.2	60	42.9	64	46.7	57	44.5
60 to < 90	72	53.7	77	57.0	78	55.7	68	49.6	65	50.8
30 to < 60	3	2.2	1	0.7	2	1.4	5	3.6	6	4.7
< 30	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; SD = standard deviation; BMI = body mass index; eGFR = estimated glomerular filtration rate
[1] estimated glomerular filtration rate as calculated by the modification of diet in renal disease equation (eGFR = 175 x SerumCr$^{-1.154}$ * age$^{-0.203}$ * 1.212 [if patient is black] * 0.742 [if female])
Source: Adapted from Table 15.5.1.4.1: 1 of the clinical study report for study 1275.1

Treatment Naïve:

Exposure to study drug was similar between the different study arms (Table 43). The study was planned to extend to 52 weeks, and the majority of patients continued study drug exposure through the 46 to 54 week mark.

Table 43: Exposure to randomized study drug – treated set, treatment naive

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	136		136		135		135		135	
Exposure (weeks)	N	%	N	%	N	%	N	%	N	%
> 0-4	2	1.5	1	0.7	2	1.5	2	1.5	4	3.0
> 4-8	3	2.2	2	1.5	2	1.5	3	2.2	3	2.2
> 8-14	2	1.5	4	2.9	2	1.5	1	0.7	3	2.2
> 14-20	4	2.9	1	0.7	6	4.4	2	1.5	0	0.0
> 20-28	3	2.2	5	3.7	3	2.2	7	5.2	5	3.7
> 28-36	4	2.9	3	2.2	2	1.5	2	1.5	1	0.7
> 36-46	4	2.9	4	2.9	4	3.0	7	5.2	3	2.2
> 46-54	112	82.4	115	84.6	112	83.0	110	81.5	113	83.7
> 54	2	1.5	1	0.7	2	1.5	1	0.7	3	2.2
Exposure (days)										
Mean (SD)	331.9	87.7	335.5	81.7	332.9	85.9	332.8	85.7	332.7	91.8
Median	364.0		364.0		364.0		364.0		365.0	
Range	1	386	1	392	7	393	4	441	1	398
Total exposure (pt-yrs)	123.6		124.9		123.0		123.0		123.0	

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; SD = standard deviation; pt-yrs = patient-years (number of patients x mean exposure in days / 365.25)
Source: Adapted from Table 15.4.3.1: 1 of the clinical study report for study 1275.1

In general, patient demographics were similar between treatment arms (Table 44). The majority of subjects identified as White, and as non-Hispanic. Approximately half of the patients in each treatment arm were between 50 and 65 years of age. The majority of patients had a baseline

eGFR as calculated by MDRD equation > 60 ml/min/1.73 m^2.

Table 44: Baseline demographics – full analysis set, treatment naïve

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
	N	%	N	%	N	%	N	%	N	%
Number of patients	134		135		133		132		133	
Gender										
Male	70	52.2	73	54.1	77	57.9	64	48.5	75	56.4
Female	64	47.8	62	45.9	56	42.1	68	51.5	58	43.6
Race										
White	104	77.6	100	74.1	93	69.9	99	75.0	103	77.4
Black	9	6.7	12	8.9	10	7.5	9	6.8	5	3.8
Asian	12	9.0	14	10.4	19	14.3	13	9.8	17	12.8
Other	9	6.7	9	6.7	11	8.3	11	8.3	8	6.0
Ethnicity										
Hispanic/Latino	45	33.6	45	33.3	43	32.3	45	34.1	40	30.1
Non-Hispanic/Latino	89	66.4	90	66.7	90	67.7	87	65.9	93	69.9
Region										
Europe	34	25.4	35	25.9	33	24.8	33	25.0	34	25.6
North America	56	41.8	55	40.7	53	39.8	55	41.7	54	40.6
Latin America	28	20.9	31	23.0	30	22.6	31	23.5	28	21.1
Asia	16	11.9	14	10.4	17	12.8	13	9.8	17	12.8
Age (years)										
< 50	44	32.8	34	25.2	29	21.8	40	30.3	40	30.1
50 to < 65	67	50.0	76	56.3	83	62.4	72	54.5	69	51.9
65 to < 75	22	16.4	23	17.0	19	14.3	18	13.6	22	16.5
≥ 75	1	0.7	2	1.5	2	1.5	2	1.5	2	1.5
BMI (kg/m^2)										
< 25	14	10.4	17	12.6	15	11.3	15	11.4	13	9.8
25 to < 30	38	28.4	39	28.9	47	35.3	43	32.6	47	35.3
30 to < 35	45	33.6	47	34.8	37	27.8	36	27.3	29	21.8
≥ 35	37	27.6	32	23.7	34	25.6	38	28.8	44	33.1
eGFR[1] ($ml/min/1.73m^2$)										
> 90	62	46.3	54	40.0	58	43.6	59	44.7	57	42.9
60 to < 90	67	50.0	76	56.3	72	54.1	70	53.0	75	56.4
30 to < 60	5	3.7	5	3.7	3	2.3	3	2.3	1	0.8
< 30	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; SD = standard deviation; BMI = body mass index; eGFR = estimated glomerular filtration rate

[1] estimated glomerular filtration rate as calculated by the modification of diet in renal disease equation (eGFR = 175 x $SerumCr^{-1.154}$ * $age^{-0.203}$ * 1.212 [if patient is black] * 0.742 [if patient is female])

Source: Adapted from Table 15.4.1.4.1: 1 of the clinical study report for study 1275.1

4-month Safety Update:

A total of 868 patients have been enrolled in the Study 1275.9 and Study 1275.10. Of these patients, 301 patients have completed the open-label treatment period and been randomized and potentially exposed to the combination of empagliflozin and linagliptin (n=91 for Study 1275.9; n=210 for Study 1275.10). Treatment assignment remains blinded for these patients.

7.3.2 Explorations for Dose Response

Two doses of empagliflozin were studied and one dose of linagliptin was studied. The two doses for empagliflozin studied here are the same two doses studied in the empagliflozin development program. The one dose of linagliptin studied here is the approved dose. As a result of the selected doses, there were two possible doses of the FDC product. No formal comparison of the doses was performed by the Applicant. Comparison of events between the two doses of empagliflozin will allow for some assessment of the relationship between dose and safety.

7.3.3 Special Animal and/or *In Vitro* Testing

See the dedicated Pharmacology/Toxicology review for discussion of any special animal and/or *in vitro* testing.

7.3.4 Routine Clinical Testing

Vital signs, HbA1c, and fasting plasma glucose were measured at every visit after initiation of study drug. Fasting plasma glucose was also measured in the placebo run-in, and HbA1c was measured at screening. Routine laboratory tests were performed at screening, placebo run-in, initiation of study treatment, and at weeks 12, 24, 32, 40, 52, and 56. These tests included complete blood count, serum electrolytes, liver enzymes, markers of renal function, and lipase. Lipids were measured at initiation of study treatment, and at weeks 6, 24, and 51. Home blood glucose monitors were reviewed at every visit after starting study drug. The routine testing appears to be adequate.

7.3.5 Metabolic, Clearance, and Interaction Workup

See the Clinical Pharmacology review for discussion of metabolism, clearance, and interactions.

7.3.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The Applicant has included the following as adverse events of special interest:

- Hypoglycemic events
- Urinary tract infections
- Genital infections
- Adverse events related to volume depletion
- Malignancies
- Hepatic injury
- Decreased renal function
- Hypersensitivity reactions
- Skin reactions

- Pancreatitis

Given the known safety concerns with the two individual components of the FDC product, this list appears to be adequate to evaluate for AEs related to the two drug classes.

For all antidiabetic medications, cardiovascular events are of concern. Cardiovascular events were centrally adjudicated by an independent adjudication committee as recommended in the FDA Guidance for Industry *Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.* The FDA Guidance to Industry recommends performing a meta-analysis across the phase 2 and phase 3 trials. The FDC development program is comprised of a single phase 3 study. Thus, this could not be performed for the FDC product. However, an evaluation of cardiovascular risk has been performed for the individual components. A postmarketing cardiovascular outcomes trial is typically expected. Again, this is being performed for the individual components.

7.4 Major Safety Results

7.4.1 Deaths

There were a total of six reported deaths in the study patients. Of these, two were in the metformin patients, and four were in the treatment naïve patients. There was no evident link between the different causes of death, and there was no evident link between the study treatment and death. Study subject identification (ID) numbers, treatment arm, and reported cause of death are provided in Table 45. A review of the narratives follows below in 7.4.1.1.

Table 45: Patient deaths

Subject ID	Background	Treatment	Reported Cause of Death
1275.0001.090242	Metformin	Empa 10	Metastatic non-small cell lung cancer
1275.0001.091001	Naïve	Empa 25	Tuberculous meningitis
1275.0001.095051	Naïve	Empa 25	Hepatic mass
1275.0001.097041	Metformin	FDC 10/5	Hypertensive heart disease
1275.0001.098439	Naïve	FDC 10/5	Lung adenocarcinoma, Hemorrhagic stroke
1275.0001.099111	Naïve	Empa 10	Car accident, Cerebral edema

ID = identification number; Empa = empagliflozin; FDC = fixed dose combination

One additional death is noted in review of the submitted datasets. This 62 year old, treatment naïve, Black male (study subject ID 1275.0001.092300) discontinued study drug on day 151. The death appears to have occurred > 30 days after discontinuation of study drug. On day (b) (6), adverse events of gastrointestinal bleeding, renal failure, and pneumonia are reported. He died on day (b) (6). No narrative of this death is provided for review. Given the time between the last dose of study drug and the events leading to his death, a relationship seems unlikely. He is not considered in the analysis of deaths.

The overall incidence of death was low in this study (0.4%). No deaths were reported in either the FDC 25/5 or Lina 5 arm. There were two deaths in each of the remaining three arms, and the incidence of death was < 1% for each of these arms (0.7% for Empa 10, 0.7% for Empa 25, 0.7% for FDC 10/5). There was no evidence of imbalance in death between the treatment arms.

7.4.1.1 Narratives of Deaths

Subject ID 1275.0001.090242 (Metformin patient, Empa 10): Metastatic lung cancer
This 61 year old White male with a past medical history including tobacco use, hypertension, and hyperlipidemia with a diagnosis of T2DM for one to five years at the time of study entry was started on blinded treatment with Empa 10. Concomitant medication in the two weeks prior to the diagnosis of lung cancer included amoxicillin/clavulanate, furosemide, hydrochlorothiazide, lisinopril, metoprolol, albuterol inhaler, and simvastatin. On day 283 since randomization, he was diagnosed with an upper respiratory infection. On day 345, he was diagnosed with pneumonia. On day 365, a computerized tomography (CT) scan showed a right middle lobe lung mass. Study drug was discontinued that same day due to completion of the study. A biopsy was performed on day (b) (6) which led to the diagnosis of non-small cell lung cancer. Further evaluation led to the diagnosis of stage IV non-small cell lung cancer with bone metastasis. No treatment was reported, and the patient died on day (b) (6)

Reviewer Comment:
Lung cancer was identified in the empagliflozin review as an event with an imbalance between the empagliflozin treated patients and the comparator treated patients. This case is confounded by the patient's history of tobacco use.

Subject ID 1275.0001.091001 (Treatment naïve, Empa 25): Tuberculous meningitis
This 77 year old Black male with a past medical history including coronary artery disease status post (s/p) stent placement, hypertension, dyslipidemia, gastro esophageal reflux disease, and glaucoma with a diagnosis of T2DM for one to five years at the time of study entry was started on blinded treatment with Empa 25. Concomitant medication in the two weeks prior to the diagnosis of tuberculous meningitis included aspirin, atorvastatin, amlodipine, carvedilol, bitamoprost eye drops, and rabeprazole. Symptoms of cold sweats and night sweats were reported on day 113. On an unspecified date, the patient had presented with fever and mental status changes. Lumbar puncture performed as part of the patient's evaluation suggested viral meningitis/encephalitis. On day (b) (6) since randomization, he was diagnosed with tuberculous meningitis. Study medication was discontinued the same day due to the event. Treatment was reportedly administered (exact treatment not specified) and the patient was improved. He was discharged to a skilled nursing facility but was subsequently admitted to the intensive care unit (dates not specified). He died on day (b) (6)

Reviewer Comment:
Insufficient information is provided to confirm the diagnosis as that of tuberculous meningitis versus another type of central nervous system infection. Regardless, neither of the components of the FDC is associated with central nervous infections or tuberculosis. This death is unlikely to be related to study treatment.

Subject ID 1275.0001.095051 (Treatment naïve, Empa 25): Hepatic mass, hepatocellular carcinoma
This 61 year old Asian male with a past medical history of hypertension and eosinophilia with a diagnosis of T2DM for < 1 year at the time of study entry was started on blinded treatment with Empa 25. Concomitant medications taken in the two weeks before diagnosis of the hepatic mass include amlodipine and losartan. There was no reported history of alcohol, hepatotoxic drugs, or of any other liver disorder. A liver ultrasound was performed on day 137 for evaluation of increased liver transaminases identified on day 87. The ultrasound identified parenchymal liver disease and ascites. No further evaluation or treatment was reported. Laboratory values continued to show elevations in liver transaminases. Total bilirubin was noted to be elevated on day 284. Computed tomography performed on day 312 showed a mass in the right lobe of the liver. Repeat CT scan performed with contrast on day 317 showed the mass to be 8.9 x 8.8 x 8.1 cm, concerning for hepatocellular carcinoma. On day 319, abdominal enlargement was reports, and alpha-fetoprotein was noted to be elevated. Study medication was stopped on day 326, and the patient was admitted on day (b) (6) with vomiting. During his hospitalization, a repeat CT scan was performed showing an unchanged mass but interval development of massive ascites. Tests were negative for hepatitis C, and hepatitis B. Surgical treatment of the liver mass was not felt to be an option, and he was started on medical therapy to reduce ascites. A drain was placed on day 351. Examination of the ascites was negative for malignant cells and negative for mycobacterium. He was discharged from the hospital on day (b) (6) with the drain in place. He was readmitted for abdominal pain, nausea, and vomiting on day (b) (6) Laboratory tests showed increased ALT, potassium, and lipase. Hypotension was reported on day 375, and he died on day (b) (6). No autopsy was performed. In the final follow-up, the diagnosis was confirmed as hepatocellular carcinoma.

Reviewer Comment:
This patient does not have any evident risk factors for the development of hepatocellular carcinoma. The absence of findings of a liver mass on ultrasound and the subsequent appearance of a large liver mass less than six months later raises some concerns about a potential contribution from study treatment, but there is no apparent mechanistic rationale nor is there other evidence of a relationship in the rest of the safety information submitted.

Subject ID 1275.0001.097041 (Metformin patient, FDC 10/5): Hypertensive heart disease
This 52 year old White male with a past medical history including hypertension, hyperlipidemia,

depression, low back pain, and obesity with a diagnosis of T2DM for < 1 year at the time of study entry was started on blinded treatment with FDC 10/5. He also reported a history of alcohol abuse, but this was not a current issue at the time of study enrollment. Concomitant medications taken in the two weeks prior to the event included duloxetine, lisinopril, and methocarbamol. The patient was found dead at home on day (b) (6) The autopsy report listed the cause of death as hypertensive cardiovascular disease. Reported blood pressure readings during his participation suggest that his blood pressure was poorly controlled.

Reviewer Comment:
There is minimal information regarding this death. This may have been a stroke or myocardial infarction. It is considered in the discussion of cardiovascular events below.

Subject ID 1275.0001.098439 (Treatment naïve, FDC 10/5): Lung cancer, hemorrhagic stroke
This 63 year old White male with a past medical history of coronary artery disease, atrial fibrillation, hyperlipidemia, and spondylodiscitis with a diagnosis of T2DM for < 1 year at the time of study entry was started on blinded treatment with FDC 10/5. Concomitant medications taken in the two weeks prior to the event included acenocoumarol, atenolol, chlorthalidone, and losartan. There is no reported history of smoking. On day 154, he was diagnosed with pulmonary adenocarcinoma on the basis of a biopsy. Acenocoumarol was started after this diagnosis. On day (b) (6) he was found unconscious on the floor. He was hospitalized and CT scan showed a left hemorrhagic stroke. No treatment is reported for either event, and the patient died on day (b) (6) as a result of the hemorrhagic stroke.

Reviewer Comment:
The finding of lung cancer occurred less than six months from the start of study drug exposure. The short duration of exposure before the event does not support a causative role for study treatment. The indication for starting anticoagulation is unclear, but likely played a role in the hemorrhagic stroke. No measure of anticoagulation is reported, but bleeding is a known complication of treatment with vitamin K antagonists. There is no known interaction between either of the individual components of the FDC and vitamin K antagonists.

Subject ID 1275.0001.099111 (Treatment naïve, Empa 10): Car accident, cerebral edema
This 74 year old Native American male with a past medical history of dyslipidemia, Hashimoto's thyroiditis, obesity, and benign prostatic hypertrophy with a diagnosis of T2DM between five and ten years at the time of study entry was started on blinded study treatment with Empa 10. He completed treatment with study medication on day 364. He was in a motor vehicle accident on day (b) (6) and suffered a head injury. He was admitted to the hospital and found to have an intracranial hemorrhage and cerebral edema. He died the same day.

Reviewer Comment:
This event is unlikely to be related to study drug. The patient had been off study drug for nearly one week, and the event leading to death stemmed from a motor vehicle accident. While hypoglycemia could have contributed to the event, it is unknown if the patient was receiving antidiabetic medications at the time of the event.

7.4.2 Nonfatal Serious Adverse Events

There were a total of 67 patients (36 metformin patients, 31 treatment naïve) that reported a total of 113 treatment emergent nonfatal serious adverse events (SAEs). There is no clear suggestion that use of the FDC product results in notably higher treatment emergent nonfatal SAEs (Table 46). An additional nine reported nonfatal SAEs are identified based on review of the submitted datasets (six metformin patients, three treatment naïve) but are not included in the patients discussed in the clinical study report (CSR). Inclusion of these additional patients does not result in any meaningful change in the incidence of treatment emergent nonfatal SAEs. Review of the associated narratives for these additional patients supports their exclusion from the analysis of treatment emergent nonfatal SAEs. Most of these were related to preexisting conditions, or occurred beyond seven days from completion of study drug treatment. In the metformin patients, the FDC 10/5 and the Empa 25 treatment arms had the highest incidence of treatment emergent nonfatal SAEs (Table 46). The lowest incidence of treatment emergent nonfatal SAEs was seen in the Lina 5 arm in the treatment naïve patients.

Table 46: Treatment emergent nonfatal serious adverse events – treated set

	N	n	%
Metformin patients			
FDC 25/5	137	6	4.4
FDC 10/5	136	9	6.6
Empa 25	141	11	7.8
Empa 10	140	5	3.6
Lina 5	132	5	3.8
Treatment naïve			
FDC 25/5	136	6	4.4
FDC 10/5	136	7	5.1
Empa 25	135	7	5.2
Empa 10	135	9	6.7
Lina 5	135	2	1.5

N = number exposed; n = number with nonfatal serious adverse event; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Tables 12.A.3.2: 1, 12.A.3.2:2, 12.B.3.2:1, and 12.B.3.2:2 of the study report for 1275.1

Also included in the NDA submission is a narrative/case report form for a patient in study 1275.10 who experienced an SAE of atrial fibrillation the same day as starting study drug (empagliflozin 10 mg). This case does not substantially impact the observations from study 1275.1.

7.4.2.1 Narratives of Non-fatal Serious Adverse Events

All of the supplied narratives for the treatment emergent nonfatal SAEs were reviewed. Those cases from patients treated with the FDC product which were not summarized previously and would benefit from additional comment are discussed in more detail below.

Subject ID 1275.0001.090448 (Treatment naïve, FDC 10/5): Hypotension
This 65 year old White male with a past medical history of hypertension, hypercholesterolemia, coronary artery disease, benign prostatic hyperplasia, and atrial fibrillation with a diagnosis of T2DM for one to five years before study entry was started on treatment with FDC 10/5. Concomitant medication in the two weeks prior to the event included hydrochlorothiazide, pravastatin, tamsulosin, and valsartan. On day (b) (6) of study drug treatment, he was hospitalized with hypotension. His valsartan dose was reduced and he was discharged from the hospital with a diagnosis of hypotension, likely due to over medication.

Reviewer Comment:
This could be consistent with a volume depletion event.

Subject ID 1275.0001.092010 (Treatment naïve, FDC 25/5): Clear cell renal carcinoma
This 60 year old White male with a past medical history of hypertension, recurrent urinary tract infections, hyperlipidemia, chronic nephrolithiasis, benign prostatic hyperplasia, and chronic prostatitis with a diagnosis of T2DM for one to five years before study entry was started on treatment with FDC 25/5. Concomitant medications in the two weeks prior to the event included Bactrim, nitrofurantoin, fluconazole, tamsulosin, lovastatin, metoprolol, and diltiazem. He has a history of smoking. On day 91, he presented with hematuria. Evaluation of the hematuria led to the diagnosis clear cell carcinoma of the kidney on day 133. On day 142, he was also found to have a bladder stone. This event resolved. Study drug was stopped on day 162 as a result of the renal carcinoma. A nephrectomy was performed on day 168, and the event was considered resolved.

Reviewer Comment:
Renal cancer was a concern in the canagliflozin review. This case was diagnosed before six months of exposure to study drug. The short exposure speaks against a causal relationship. There are too few cases to detect an imbalance for renal carcinoma with the FDC product compared to the individual components.

Subject ID 1275.0001.096967 (Metformin patient, FDC 25/5): Breast cancer
This 57 year old White female with a past medical history of hypertension, hyperlipidemia, and psoriasis with a diagnosis of T2DM for less than one year before study entry was started on treatment with FDC 25/5. Concomitant medications in the two weeks before the event included

benazepril, methotrexate, and rosuvastatin. In the month prior to initiation of study drug, the patient had a mammogram. A breast biopsy was subsequently performed (date not provided) for a 1.7 x 1.6 cm mass. A lumpectomy was performed on day (b) (6) resulting in the diagnosis of breast cancer. No action was taken with respect to the study drug.

Reviewer Comment:
Breast cancer was a concern discussed in the dapagliflozin review. Given the presence of concerning findings on mammogram prior to starting study drug and the short time from initiation of study drug to diagnosis, this event is unlikely to be related to study drug use.

Subject ID 1275.0001.098248 (Metformin patient, FDC 25/5): Renal carcinoma
This 65 year old White male with a past medical history of hypertension with a diagnosis of T2DM for one to five years at the time of study entry was started on treatment with FDC 25/5. Concomitant medications in the two weeks prior to the event included perindopril and indapamide. On day 282 of treatment, he reported fatigue, weight loss, pain, and cough. He was hospitalized on day (b) (6) (indication not reported), and a renal biopsy was performed. The biopsy results were reported as renal carcinoma on day 338. A left adrenal mass was also reported. The patient discontinued from study drug on day 351.

Reviewer Comment:
Renal carcinoma was a concern raised in the canagliflozin review. While the occurrence of the event after more than six months of exposure to study treatment may indicate a relationship, there is insufficient information to confidently state that the event was associated with study drug treatment. There are too few cases to detect an imbalance for renal carcinoma with the FDC product compared to the individual components.

Subject ID 1275.0001.098289 (Metformin patient, FDC 10/5): Gastrointestinal cancer
This 64 year old White male with a past medical history of hypertension, gout, eczema, and hyperlipidemia with a diagnosis of T2DM for five to ten years at the time of study entry was started on treatment with FDC 10/5. Concomitant medications in the two weeks prior to the vent include atenolol, pravastatin, and betamethasone. He has a family history of gastrointestinal cancer. The patient reported symptoms of constipation on day 202. A colonoscopy was performed on day 304 which led to the diagnosis of rectosigmoid colon adenocarcinoma. No action was taken with regard to study drug.

Reviewer Comment:
A variety of malignancies were reported amongst the different SGLT2 inhibitors. Colon cancer was not one of them. The duration of exposure prior to the event may support a relationship between the event and study treatment, but there is insufficient information to confidently state that the event was associated with study drug treatment. There are too few cases to detect an

imbalance with the FDC product compared to the individual components.

Subject ID 1275.0001.099315 (Treatment naïve, FDC 25/5): Coronary artery disease
This 50 year old White male with a past medical history of dyslipidemia with a diagnosis of T2DM for one to five years at study entry was started on treatment with FDC 25/5. The patient completed the study treatment period on day 373. At the study visit scheduled for day 374, new changes were seen on an electrocardiogram which were concerning for ischemic heart disease. The patient was started on aspirin therapy at that time, and the diagnosis of coronary artery disease was made on day 379 by coronary angiography.

Reviewer Comment:
The specific electrocardiogram changes are not reported. While a diagnosis of coronary artery disease was made, there does not appear to be any information to suggest that this case met criteria for adjudication.

4-month Safety Update:

There were only eight patients with non-fatal serious adverse events during blinded treatment reported in the safety update (n=5 for study 1275.9, n=3 for study 1275.10). There was no evident trend for a particular adverse event. The information included in the safety update does not change the safety observations from the original NDA submission.

Table 47: Non-fatal serious adverse events reported in the 4 month safety update

System organ class - Preferred term	Study 1275.9		Study 1275.10	
	N	%	N	%
	91	--	210	--
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	1.1	0	0.0
- Bladder cancer	1	1.1	0	0.0
Metabolism and nutrition disorders	1	1.1	0	0.0
- Metabolic acidosis	1	1.1	0	0.0
Psychiatric disorders	1	1.1	0	0.0
- Mania	1	1.1	0	0.0
Nervous system disorders	1	1.1	0	0.0
- Hydrocephalus	1	1.1	0	0.0
Cardiac disorders	2	2.2	0	0.0
- Atrial fibrillation	1	1.1	0	0.0
- Coronary artery disease	1	1.1	0	0.0
Injury, poisoning and procedural complications	1	1.1	0	0.0
- Accidental overdose	1	1.1	0	0.0
- Fall	0	0.0	1	0.5
Musculoskeletal and connective tissue disorders	0	0.0	2	1.0
- Hemarthrosis	0	0.0	1	0.5
- Rotator cuff syndrome	0	0.0	1	0.5

System organ class - Preferred term	Study 1275.9		Study 1275.10	
	N	%	N	%
	91	--	210	--
Investigations	0	0.0	1	0.5
- Hepatic enzyme increased	0	0.0	1	0.5

Source: Adapted from Table 1 and Table 2 of the 4-month Safety Update

7.4.3 Dropouts and/or Discontinuations

Premature discontinuation of study drug and premature discontinuation from the study are discussed in section 10 of the submitted study report (Table 48). Premature discontinuation of study drug due to an AE is also discussed in section 12 of the submitted study report (Table 49). Comparison of the information presented in these sections identified small discrepancies in the number of patients with premature discontinuation due to an AE, but these differences do not markedly impact the findings.

In the metformin patient population, there were 58 patients that discontinued study medication before week 24, and 29 that prematurely discontinued from the study. At week 52, there were 85 patients that discontinued study medication prior to week 52, and 68 that prematurely discontinued from the study. The Empa 10 treatment arms had the highest incidence of premature discontinuation of study drug and premature discontinuation from the study at both of these time points.

In the treatment naïve patients, there were 63 patients that discontinued from study medication before week 24, and 35 that prematurely discontinued from the study. The Empa 25 treatment arm had the highest incidence of premature discontinuation of study drug, while the Lina 5 treatment arm had the highest incidence of premature discontinuation from study at this time point. At week 52, there were 107 patients that discontinued study medication prior to week 52, and 94 that prematurely discontinued from the study. The Empa 10 treatment arm had the highest incidence of premature discontinuation of study drug, while the Empa 25 treatment arm had the highest incidence of premature discontinuation from study at this time point

For the metformin patients, premature discontinuation of study drug due to an AE was more common in the Empa 10 treatment arm at 24 and 52 weeks. For treatment naïve patients, treatment with FDC 25/5 led to more premature discontinuation of study drug due to an AE. No individual term or cluster of terms that might suggest a single reason for this was observed.

Table 48: Premature discontinuation of study drug and premature discontinuation from study at 24 and 52 weeks – treated set, metformin patients and treatment naive

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
	N	%	N	%	N	%	N	%	N	%
Metformin patients – treated	**137**		**136**		**141**		**140**		**132**	
24 weeks										
Prematurely discontinued study drug	11	8.0	7	5.1	10	7.1	16	11.4	14	10.6
- due to AE	3	2.2	3	2.2	2	1.4	5	3.6	4	3.0
- due to lack of efficacy	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Prematurely discontinued from study	6	4.4	3	2.2	5	3.5	8	5.7	7	5.3
52 weeks										
Prematurely discontinued study drug	16	11.7	12	8.8	16	11.3	22	15.7	19	14.4
- due to AE	3	2.2	3	2.2	4	2.8	9	6.4	4	3.0
- due to lack of efficacy	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
Prematurely discontinued from study	12	8.8	10	7.4	13	9.2	18	12.9	15	11.4
Treatment naïve - treated	**137**		**136**		**135**		**134**		**135**	
24 weeks										
Prematurely discontinued study drug	12	8.8	12	8.8	14	10.4	13	9.7	12	8.9
- due to AE	7	5.1	4	2.9	3	2.2	4	3.0	2	1.5
- due to lack of efficacy	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Prematurely discontinued from study	6	4.4	6	4.4	7	5.2	6	4.5	10	7.4
52 weeks										
Prematurely discontinued study drug	23	16.8	20	14.7	21	15.6	24	17.9	19	14.1
- due to AE	9	6.6	8	5.9	5	3.7	7	5.2	2	1.5
- due to lack of efficacy	0	0.0	0	0.0	0	0.0	1	0.7	1	0.7
Prematurely discontinued from study	17	12.4	16	11.8	23	17.0	21	15.7	17	12.6

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; AE = adverse event
Source: Adapted from Tables 10.A.1: 1, 10.A.1: 4, 10.B.1:1, and 10.B.1: 4 from the study report for study 1275.1

Table 49: Discontinuation of study drug due to an adverse event – treated set

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 10		Total	
	N	%	N	%	N	%	N	%	N	%	N	%
Metformin patients	**137**		**136**		**141**		**140**		**132**		**686**	
Before 24 weeks	3	2.2	3	2.2	2	1.4	6	4.3	4	3.0	18	2.6
Before 52 weeks	5	3.6	3	2.2	4	2.8	9	6.4	4	3.0	25	3.6
Treatment naïve	**136**		**136**		**135**		**135**		**135**		**677**	
Before 24 weeks	7	5.1	5	3.7	3	2.2	5	3.7	2	1.5	22	3.2
Before 52 weeks	9	6.6	9	6.6	5	3.7	7	5.2	2	1.5	32	4.7

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Tables 15.2.1.3: 1, 12.A.2.2: 2, 12.A.2.2: 3, 15.1.1.3: 1, 12.B.2.2: 3, and 12.B.2.2: 4 from the study report for 1275.1

7.4.3.1 Narratives of Discontinuations due to Adverse Events

All of the supplied narratives for the discontinuation due to an AE were reviewed. Those cases from patients treated with the FDC product which were not summarized previously and warrant additional comment are discussed in more detail below.

Subject ID 1275.0001.090248 (Treatment naïve, Empa 10): Fungal skin infection
This 64 year old male discontinued from study drug on day 304 after randomization due to recurrent penile candida dermatitis. The first event was reported on day 147. Both were treated with nystatin and resolved.

Reviewer Comment:
Increased risk for genitourinary infections is a concern with the SGLT2 inhibitor class.

Subject ID 1275.0001.091646 (Treatment naïve, FDC 25/5): Thirst and dry mouth
This 68 year old female discontinued from study drug on day 166 after randomization due to increased thirst and dry mouth.

Reviewer Comment:
The SGLT2 inhibitors create an osmotic diuresis, and thus volume depletion is a concern. This may be considered to be a volume depletion event.

4-month Safety Update:

From study 1275.9, there were three patients with discontinuation due to an adverse event. All of these occurred during the open-label linagliptin treatment period. From study 1275.10, there were 15 patients with discontinuation due to an adverse event during the open-label empagliflozin treatment period and three patients with discontinuation due to an adverse event during the blinded treatment period. One of these was due to a urinary tract infection, one was due to hyperglycemia, and one was due to abdominal pain. The patient that discontinued due to abdominal pain (patient ID 1275.0010.032424) was subsequently diagnosed with pancreatic cancer (see 1.1.1.2 and 1.1.1.1). The information included in the safety update does not substantially change the safety observations from the original NDA submission.

7.4.4 Significant Adverse Events

Protocol pre-specified significant AEs will be discussed in section 7.4.5 and are excluded from the discussion here. The review of "other significant adverse events" by the Applicant followed the ICH Guideline for Industry: Structure and Content of Clinical Study Reports (i.e. ICH E3). These include marked hematological and other laboratory abnormalities, and any events that led to an intervention (including withdrawal of study drug, change in dose, and/or significant

additional concomitant therapy), other than those reported as an SAE.

Metformin patients:

There were few patients with significant adverse events (Table 50). The treatment with the greatest number of significant adverse events was Empa 10. All of the patients included here were included due to discontinuation of study drug as a result of an AE. Review of the associated adverse events did not identify any frequently reported AEs which would raise concerns (Table 51).

Table 50: Patients with significant adverse events – treated set, metformin patients

	N	n	%
FDC 25/5	137	2	1.5
FDC 10/5	136	2	1.5
Empa 25	141	3	2.1
Empa 10	140	6	4.3
Lina 5	132	2	1.5

N = number of patients in treatment arm; n = number of patients with other significant adverse event; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Table 15.5.3.2.1: 8 and review of Tables 15.2.4.2: 2 and 15.5.4.2: 2 of the study report for 1275.1; excluded patients from Tables 15.2.4.2: 2 and 15.5.4.2: 2 with events identified as an adverse event of special interest

Table 51: Listing of patients with significant adverse events including date of onset and associated preferred term – treated set, metformin patients

Patient ID Number	Days after Randomization	Preferred Term(s)
FDC 25/5		
1275.0001.093042	2	Myalgia Asthenia
1275.0001.098248	282	Cough Weight decreased Fatigue
FDC 10/5		
1275.0001.096765	2	Headache
1275.0001.097653	3	Fatigue
Empa 25		
1275.0001.092366	11	Vulvovaginal mycotic infection
1275.0001.097928	323	Hyperglycemia
1275.0001.099813	28	Genital infection fungal
Empa 10		
1275.0001.091361	48	Vaginal hemorrhage
1275.0001.092223	236	Urinary tract infection
1275.0001.092409	226	Lipase increased
1275.0001.093365	159	Migraine
1275.0001.093627	64	Cystitis
1275.0001.096231	3	Polyuria
	8	Urge incontinence

Patient ID Number	Days after Randomization	Preferred Term(s)
Lina 5		
1275.0001.093142	15	Dizziness
1275.0001.099745	85	Blood creatine phosphokinase increased

ID = identification; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: From review of Tables 15.2.4.2: 2 and 15.5.4.2: 2 of the study report for 1275.1; excluded patients with events identified as an adverse event of special interest

Treatment naïve:

There were few patients with significant adverse events (Table 52). The treatment with the greatest number of significant adverse events was FDC 25/5. All of the patients included here were included due to discontinuation of study drug as a result of an AE. Review of the associated adverse events suggested that many of these were related to urinary concerns or changes in laboratory tests (Table 53). No clear trend was noted between the treatments, and no type of AE clearly demonstrated increased frequency in the FDC arms.

Table 52: Patients with significant adverse events – treated set, treatment naïve

	N	n	%
FDC 25/5	136	7	5.1
FDC 10/5	136	5	3.7
Empa 25	135	3	2.2
Empa 10	135	6	4.4
Lina 5	135	2	1.5

N = number of patients in treatment arm; n = number of patients with other significant adverse event; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Table 15.4.3.2.1: 8 and review of Tables 15.1.4.2: 2 and 15.4.4.2: 2 of the study report for 1275.1; excluded patients from Tables 15.1.4.2: 2 and 15.4.4.2: 2 with events identified as an adverse event of special interest

Table 53: Listing of patients with significant adverse events including date of onset and associated preferred term – treated set, treatment naïve

Patient ID Number	Days after Randomization	Preferred Term(s)
FDC 25/5		
1275.0001.091281	108	Genital herpes
	199	Genital candidiasis
1275.0001.091646	29	Thirst
	163	Dry mouth
1275.0001.092020	2	Bladder pain
1275.0001.093131	86	Post inflammatory pigmentation changes
1275.0001.093163	4	Pollakiuria
1275.0001.094298	97	Thrombosis
1275.0001.095980	73	Nausea
FDC 10/5		
1275.0001.092087	92	Lipase increased
1275.0001.093290	89	Urine odor abnormal
	110	Pruritus general

Patient ID Number	Days after Randomization	Preferred Term(s)
1275.0001.095377	230	Lipase increased
1275.0001.097161	1	Pollakiuria
	177	Blood bicarbonate decreased
1275.0001.097846	43	Pollakiuria
Empa 25		
1275.0001.091492	15	Weight decreased
	29	Rash erythematous
1275.0001.092300	127	Decreased appetite
	127	Thirst
	127	Weight decreased
	133	Nausea
	133	Vomiting
1275.0001.099807	3	Oral pain
	5	Pollakiuria
Empa 10		
1275.0001.040093	170	Polyarthritis
1275.0001.090248	147	Fungal skin infection
1275.0001.093693	143	Depression
1275.0001.096219	80	Genital infection fungal
1275.0001.096929	78	Blood creatine phosphokinase MB increased
	78	Blood creatine phosphokinase increased
1275.0001.098245	4	Depression
Lina 5		
1275.0001.097491	142	Headache
1275.0001.099742	8	Autoimmune thyroiditis

ID = identification; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: From review of Tables 15.1.4.2: 2 and 15.4.4.2: 2 of the study report for 1275.1; excluded patients with events identified as an adverse event of special interest

7.4.5 Submission Specific Safety Concerns

7.4.5.1 Hypoglycemia

All episodes of plasma glucose ≤ 70 mg/dL were to be documented. Episodes with a glucose < 54 mg/dL, symptomatic hypoglycemia, and severe hypoglycemia were to be documented as a "hypoglycemic event". "Confirmed hypoglycemia" was defined as a glucose ≤ 70 mg/dL or where assistance was required. Hypoglycemic events were categorized as follows:

Asymptomatic hypoglycemia	Measured plasma glucose concentration ≤ 70 mg/dL not accompanied by typical symptoms of hypoglycemia
Documented symptomatic hypoglycemia with plasma glucose between 54 and 70 mg/dL	Measured plasma glucose ≥ 54 mg/dL and ≤ 70 mg/dL accompanied by typical symptoms of hypoglycemia
Documented symptomatic hypoglycemia with plasma glucose < 54 mg/dL	Measured plasma glucose < 54 mg/dL accompanied by typical symptoms of hypoglycemia but no need for external assistance
Severe hypoglycemia	Hypoglycemic event requiring external assistance to actively administer carbohydrates, glucagon, or other resuscitative actions

Symptomatic hypoglycemia with plasma glucose > 70 mg/dL	Measured plasma glucose > 70 mg/dL with typical symptoms of hypoglycemia
Symptomatic hypoglycemia without plasma glucose	No measured plasma glucose with typical symptoms of hypoglycemia.

Hypoglycemic events were also analyzed using the MedDRA High Level Term (HLT) "Hypoglycemic conditions NEC" and the PT "Blood glucose decreased".

Metformin patients:

Examining the metformin patients did not reveal an imbalance in hypoglycemia. There were only a few confirmed hypoglycemic events (Table 54). None of these events required assistance. The frequency was similar between the different arms.

Table 54: Frequency of hypoglycemic events – metformin patients, treated set

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	**137**		**136**		**141**		**140**		**132**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
24 weeks										
Confirmed hypoglycemia	2	1.5	2	1.5	4	2.8	2	1.4	2	1.5
- Symptomatic	1	0.7	1	0.7	2	1.4	2	1.4	2	1.5
- Asymptomatic	1	0.7	1	0.7	2	1.4	0	0.0	1	0.8
By severity										
- Asymptomatic, ≤ 70 mg/dL	1	0.7	1	0.7	2	1.4	0	0.0	0	0.0
- Symptomatic, 54 to 70 mg/dL	1	0.7	1	0.7	2	1.4	2	1.4	2	1.5
- Symptomatic, < 54 mg/dL	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Requiring assistance	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
52 weeks										
Confirmed hypoglycemia	5	3.6	3	2.2	5	3.5	2	1.4	3	2.3
- Symptomatic	4	2.9	2	1.5	3	2.1	2	1.4	3	2.3
- Asymptomatic	1	0.7	1	0.7	2	1.4	0	0.0	0	0.0
By severity										
- Asymptomatic, ≤ 70 mg/dL	1	0.7	1	0.7	2	1.4	0	0.0	0	0.0
- Symptomatic, 54 to 70 mg/dL	4	2.9	2	1.5	3	2.1	2	1.4	3	2.3
- Symptomatic, < 54 mg/dL	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Requiring assistance	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

FDC = fixed dose combination; Empa = empagliflozin; Lina= linagliptin
Source: Adapted from Table 12.A.3.3.1: 1 and 15.5.3.2.3: 4 from study report for 1275.1

The time to the first confirmed hypoglycemic event was also analyzed. There was no clear evidence to suggest that treatment with the FDC increased the risk for earlier hypoglycemia (Table 55).

Table 55: Time to first confirmed hypoglycemic episode – metformin patients, treated set

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	**137**		**136**		**141**		**140**		**132**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Time to first episode										
> 7 to ≤ 28 days	1	0.7	0	0.0	0	0.0	0	0.0	1	0.8
> 28 to ≤ 84 days	0	0.0	1	0.7	2	1.4	2	1.4	1	0.8
> 84 days	4	2.9	2	1.5	3	2.1	0	0.0	1	0.8

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Table 15.5.3.2.3: 4 from the study report for 1275.1

Treatment naïve:

Examining the treatment naive patients did not reveal an imbalance in hypoglycemia. The frequency of confirmed hypoglycemia was low in all arms of the treatment naïve pool. No events were reported in either of the FDC arms at 24 or 52 weeks.

Table 56: Frequency of hypoglycemic events – treatment naïve, treated set

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	**136**		**136**		**135**		**135**		**135**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
24 weeks										
	136		136		135		135		135	
Confirmed hypoglycemia	0	0.0	0	0.0	2	1.5	1	0.7	1	0.7
- Symptomatic	0	0.0	0	0.0	1	0.7	0	0.0	1	0.7
- Asymptomatic	0	0.0	0	0.0	1	0.7	1	0.7	0	0.0
By severity										
- Asymptomatic, ≤ 70 mg/dL	0	0.0	0	0.0	1	0.7	1	0.7	0	0.0
- Symptomatic, 54 to 70 mg/dL	0	0.0	0	0.0	1	0.7	0	0.0	1	0.7
- Symptomatic, < 54 mg/dL	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Requiring assistance	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
52 weeks										
Confirmed hypoglycemia	0	0.0	0	0.0	1	0.7	4	3.0	1	0.7
- Symptomatic	0	0.0	0	0.0	1	0.7	2	1.5	1	0.7
- Asymptomatic	0	0.0	0	0.0	0	0.0	2	1.5	0	0.0
By severity										
- Asymptomatic, ≤ 70 mg/dL	0	0.0	0	0.0	0	0.0	2	1.5	0	0.0
- Symptomatic, 54 to 70 mg/dL	0	0.0	0	0.0	1	0.7	1	0.7	1	0.7
- Symptomatic, < 54 mg/dL	0	0.0	0	0.0	0	0.0	1	0.7	0	0.0
- Requiring assistance	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

FDC = fixed dose combination; Empa = empagliflozin; Lina= linagliptin
Source: Adapted from Table 12.B.3.3.1: 1 and 15.4.3.2.3: 4 from study report for 1275.1

The time to the first confirmed hypoglycemic event was also analyzed. There was no clear evidence to suggest that treatment with the FDC increased the risk for earlier hypoglycemia (Table 57).

Table 57: Time to first confirmed hypoglycemic episode – treatment naive, treated set

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	**136**		**136**		**135**		**135**		**135**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Time to first episode										
> 7 to ≤ 28 days	0	0.0	0	0.0	0	0.0	0	0.0	1	0.7
> 28 to ≤ 84 days	0	0.0	0	0.0	1	0.7	1	0.7	0	0.0
> 84 days	0	0.0	0	0.0	0	0.0	3	2.2	0	0.0

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Table 15.4.3.2.3: 4 from the study report for 1275.1

7.4.5.2 Urinary tract infections

Urinary tract infections were analyzed using a CMQ. The preferred terms included in the urinary tract infection CMQ can be found in section 0.

Metformin patients:

Based on analysis of the CMQ, there was no suggestion of an increased incidence of urinary tract infections with the FDC product compared to the individual components (Table 58). This was also true when examining the incidence by gender. Of these events, there were three serious adverse events that were related to urinary tract infections. None of these subjects received treatment with the FDC product (one subject each in the Empa 10, Empa 25, and Lina 5 arms). There was one discontinuation due to an adverse event included in the urinary tract infection CMQ. This occurred in a patient receiving Empa 10.

Table 58: Incidence of urinary tract infections based on a customized MedDRA query – treated set, metformin patients, 52 weeks

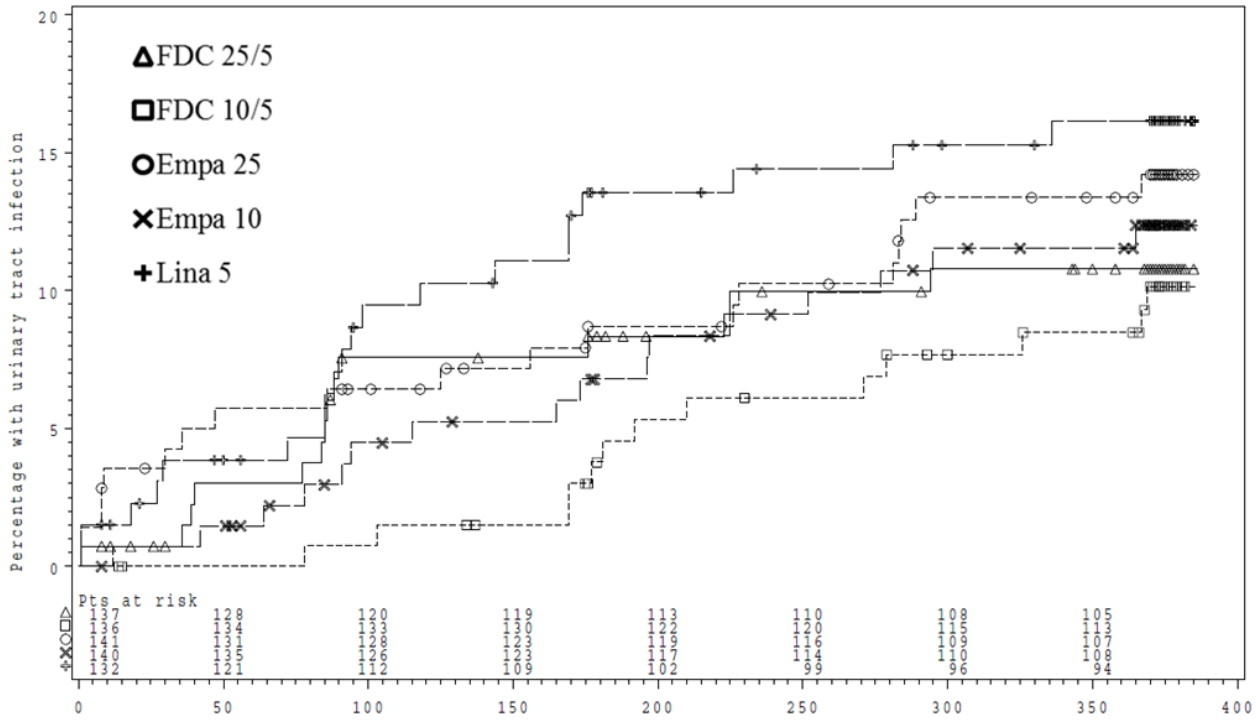
	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	**137**		**136**		**141**		**140**		**132**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
CMQ	**14**	**10.2**	**13**	**9.6**	**19**	**13.5**	**16**	**11.4**	**20**	**15.2**
Preferred term										
Urinary tract infection	12	8.8	12	8.8	17	12.1	13	9.3	15	11.4
Cystitis	2	1.5	0	0.0	1	0.7	2	1.4	4	3.0
Asymptomatic bacteriuria	0	0.0	0	0.0	1	0.7	0	0.0	1	0.8
Pyelonephritis acute	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8
Escherichia urinary tract infection	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
Genitourinary tract infection	0	0.0	0	0.0	0	0.0	1	0.7	0	0.0
Pyelonephritis	0	0.0	0	0.0	0	0.0	1	0.7	0	0.0
Pyelonephritis chronic	0	0.0	0	0.0	1	0.7	0	0.0	0	0.0
Urosepsis	0	0.0	0	0.0	0	0.0	1	0.7	0	0.0

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	**137**		**136**		**141**		**140**		**132**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
CMQ by Gender	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
- Male	2/73	2.7	2/84	2.4	2/66	3.0	3/81	3.7	3/67	4.5
- Female	12/64	18.8	11/52	21.2	17/75	22.7	13/59	22.0	17/65	26.2

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; CMQ = customized MedDRA Query
Source: Adapted from Table 12.A.3.3.2: 2 and Table 15.5.3.2.4: 2 of the study report for 1275.1

Given that urinary tract infections are, in general, quite common and that diabetes mellitus is a risk factor for infections, the Applicant considered another measure of the effect of treatment on the development of infections. If a treatment were to predispose to certain events/infections, it may be evident on the basis of earlier onset of events/infections. To explore this possibility, the time to onset of the first urinary infection by treatment was examined by the Applicant. There was no evidence of more rapid onset of first urinary infections in the patients treated with the FDC product compared to those treated with the individual components (Figure 4).

Figure 4: Time to onset of urinary infection – treated set, metformin patients



Source: Adapted from Figure 15.5.3.2.4: 1 of the study report for study 1275.1

Treatment naïve:

Based on analysis of the CMQ, there was no suggestion of an increased incidence of urinary tract infections with the FDC product compared to the individual components (Table 59). Examining the incidence by gender showed that there was a slight increase in males with the FDC versus

linagliptin alone. This was not seen in female subjects. Only one subject had an event which was considered to be a serious adverse event. This was an event of cystitis which occurred in a patient treated with Empa 25. None of the events led to discontinuation of study drug.

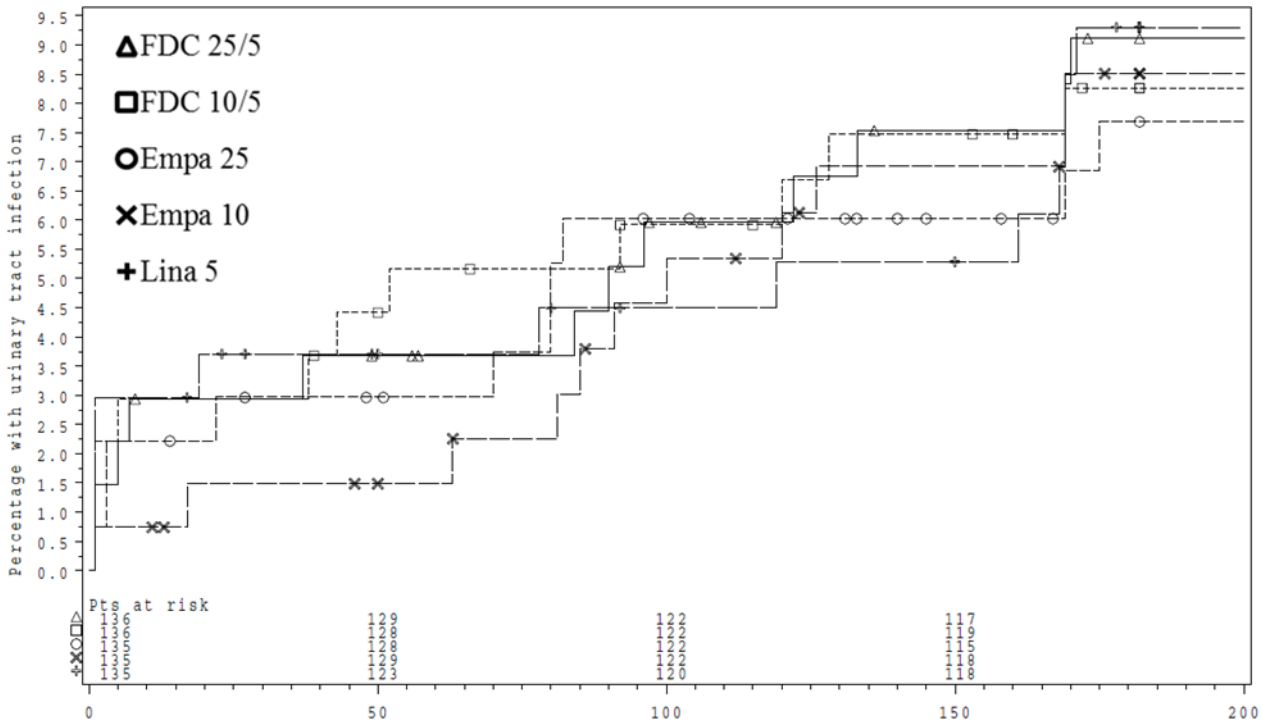
Table 59: Incidence urinary tract infections based on a customized MedDRA query – treated set, treatment naïve, 52 weeks

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	**136**		**136**		**135**		**135**		**135**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
CMQ	**17**	**12.5**	**21**	**15.4**	**14**	**10.4**	**22**	**16.3**	**14**	**10.4**
Preferred term										
Urinary tract infection	15	11.0	17	12.5	8	5.9	17	12.6	12	8.9
Cystitis	1	0.7	2	1.5	3	2.2	3	2.2	2	1.5
Asymptomatic bacteriuria	1	0.7	2	1.5	1	0.7	2	1.5	0	0.0
Bacteriuria	0	0.0	1	0.7	2	1.5	0	0.0	0	0.0
Pyelonephritis chronic	0	0.0	0	0.0	0	0.0	1	0.7	0	0.0
Urethritis	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
Urinary tract infection fungal	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
CMQ by Gender	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
- Male	4/72	5.6	5/74	6.8	3/78	3.8	6/65	9.5	2/75	2.7
- Female	13/64	20.3	16/62	25.8	11/57	19.3	16/70	22.9	12/60	20.0

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; CMQ = customized MedDRA Query
Source: Adapted from Table 12.B.3.3.2: 2 and Table 15.4.3.2.4: 2 of the study report for 1275.1

Given that urinary tract infections are, in general, quite common and that diabetes mellitus is a risk factor for infections, the Applicant considered another measure of the effect of treatment on the development of infections. If a treatment were to predispose to certain events/infections, it may be evident on the basis of earlier onset of events/infections. To explore this possibility, the time to onset of the first urinary infection by treatment was examined by the Applicant. There was no evidence of more rapid onset of first urinary infections in the patients treated with the FDC product compared to those treated with the individual components (Figure 5).

Figure 5: Time to onset of urinary infection – treated set, treatment naïve



Source: Adapted from Figure 15.1.3.2.4: 1 of the study report for study 1275.1

4-month Safety Update:

There were no cases of sepsis due to a urinary tract infection or of pyelonephritis reported in the safety update. The information included in the safety update does not change the safety observations from the original NDA submission.

7.4.5.3 Genital infections

Genital infections were analyzed using a CMQ. The preferred terms included in the genital infection CMQ can be found in section 0.

Metformin patients:

Based on analysis of the CMQ, there was no suggestion of an increased incidence of genital infections with the FDC product compared to empagliflozin (Table 60). This was true for both genders. There were no events which were considered to be a serious adverse event. There was one event with an intensity of "severe". This was an event of vulvovaginal mycotic infection (Patient ID: 1275.0001.090526) which occurred in a patient treated with Empa 10. Two patients discontinued study drug due to a genital infection adverse event. Both of these patients were in the Empa 25 arm.

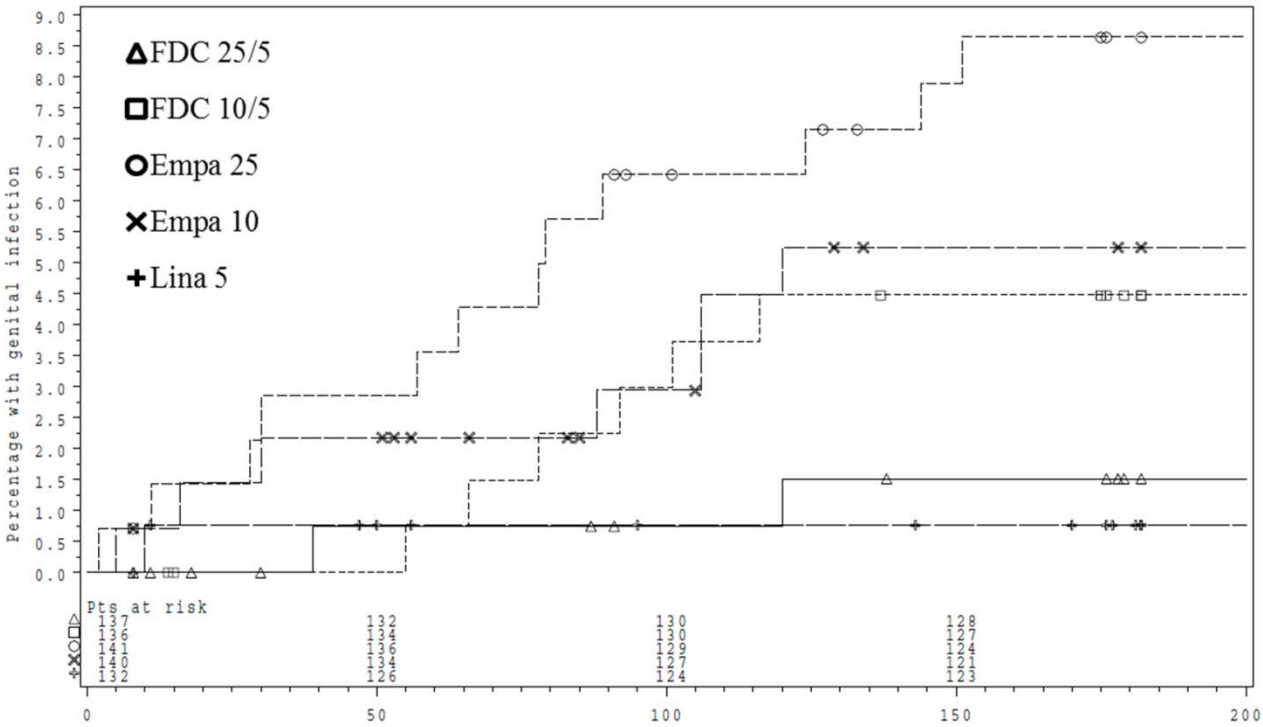
Given that infections are, in general, quite common and that diabetes mellitus is a risk factor for infections, the Applicant considered another measure of the effect of treatment on the development of infections. If a treatment were to predispose to certain events/infections, it may be evident on the basis of earlier onset of events/infections. To explore this possibility, the time to onset of the first genital infection by treatment was examined by the Applicant. There was no evidence of more rapid onset of first genital infection in the patients treated with the FDC product compared to those treated with the individual components (Figure 6).

Table 60: Incidence of genital infections based on a customized MedDRA query – treated set, metformin patients

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	**137**		**136**		**141**		**140**		**132**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
CMQ	**3**	**2.2**	**8**	**5.9**	**12**	**8.5**	**11**	**7.9**	**3**	**2.3**
Preferred term										
Vaginal infection	1	0.7	4	2.9	2	1.4	1	0.7	0	0.0
Vulvovaginal mycotic infection	0	0.0	0	0.0	3	2.1	1	0.7	0	0.0
Vulvovaginal candidiasis	0	0.0	1	0.7	2	1.4	1	0.7	0	0.0
Balanitis	1	0.7	2	1.5	2	1.4	1	0.7	0	0.0
Genital infection fungal	1	0.7	0	0.0	2	1.4	2	1.4	0	0.0
Balanitis candida	0	0.0	0	0.0	0	0.0	1	0.7	0	0.0
Genital candidiasis	0	0.0	0	0.0	1	0.7	0	0.0	0	0.0
Penile infection	0	0.0	0	0.0	0	0.0	1	0.7	0	0.0
Vulvovaginitis	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8
Orchitis	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8
Prostatitis	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8
Genital infection	0	0.0	0	0.0	0	0.0	1	0.7	0	0.0
Genitourinary tract infection	0	0.0	0	0.0	0	0.0	1	0.7	0	0.0
Vaginitis bacterial	0	0.0	1	0.7	1	0.7	1	0.7	0	0.0
CMQ by Gender	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
- Male	2/73	2.7	2/84	2.4	3/66	4.5	5/81	6.2	2/67	3.0
- Female	1/64	1.6	6/52	11.5	9/75	12.0	6/59	10.2	1/65	1.5

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; CMQ = customized MedDRA query
Source: Adapted from Table 12.A.3.3.3: 2 and Table 12.A.3.3.3: 4 of the study report for 1275.1

Figure 6: Time to onset of first genital infection – treated set, metformin patients



Source: Adapted from Figure 15.2.3.2.4: 3 of the study report for study 1275.1

Treatment naïve:

Based on analysis of the CMQ, there was no suggestion of an increased incidence of genital infections with the FDC product compared to empagliflozin (Table 60). This was true for both genders. There were no events which were considered to be a serious adverse event. Two patients discontinued study drug due to a genital infection adverse event. One of these patients was treated with FDC 25/5, and the other was in the Empa 10 arm.

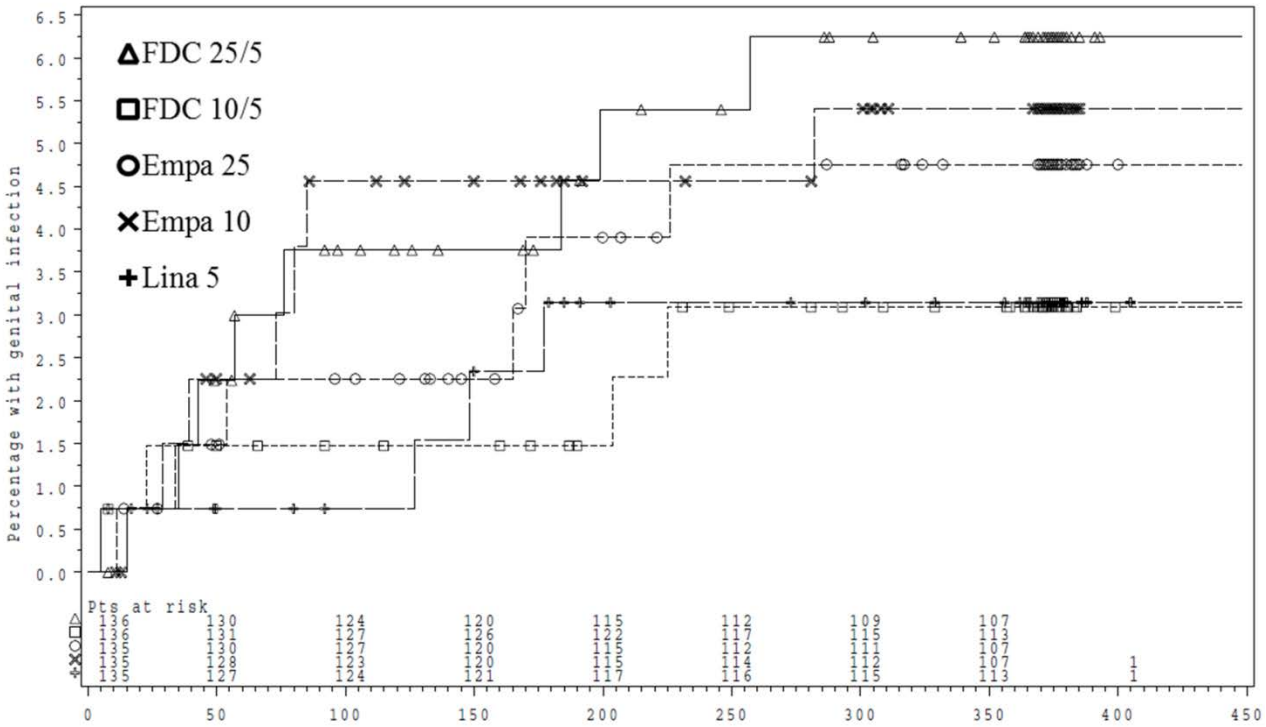
Given that infections are, in general, quite common and that diabetes mellitus is a risk factor for infections, the Applicant considered another measure of the effect of treatment on the development of infections. If a treatment were to predispose to certain events/infections, it may be evident on the basis of earlier onset of events/infections. To explore this possibility, the time to onset of the first genital infection by treatment was examined by the Applicant. There was no evidence of more rapid onset of first genital infection in the patients treated with the FDC product compared to those treated with the individual components (Figure 7).

Table 61: Incidence of genital infections based on a customized MedDRA query – treated set, treatment naïve

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	**136**		**136**		**135**		**135**		**135**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
CMQ	**8**	**5.9**	**4**	**2.9**	**6**	**4.4**	**7**	**5.2**	**4**	**3.0**
Preferred term										
Vulvovaginal candidiasis	0	0.0	1	0.7	4	3.0	0	0.0	0	0.0
Balanitis	3	2.2	1	0.7	0	0.0	0	0.0	0	0.0
Genital infection fungal	0	0.0	0	0.0	1	0.7	2	1.5	0	0.0
Vaginal infection	2	1.5	1	0.7	0	0.0	3	2.2	1	0.7
Vulvovaginal mycotic infection	0	0.0	1	0.7	1	0.7	1	0.7	2	1.5
Balanitis candida	1	0.7	0	0.0	1	0.7	0	0.0	0	0.0
Cervicitis	0	0.0	0	0.0	0	0.0	0	0.0	1	0.7
Epididymitis	0	0.0	0	0.0	0	0.0	1	0.7	0	0.0
Vaginitis bacterial	0	0.0	0	0.0	0	0.0	1	0.7	0	0.0
Vulvovaginitis	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0
Genital candidiasis	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
Pelvic inflammatory disease	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
CMQ by Gender	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**	**n/N**	**%**
- Male	3/72	4.2	0/74	0.0	1/78	1.3	2/65	3.1	1/75	1.3
- Female	2/64	3.1	2/62	3.2	4/57	7.0	4/70	5.7	3/60	5.0

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; CMQ = customized MedDRA query
Source: Adapted from Table 12.B.3.3.3: 2 and Table 12.B.3.3.3: 3 of the study report for 1275.1

Figure 7: Time to onset of first genital infection – treated set, treatment naive



Source: Adapted from figure 15.4.3.2.4: 2 of the study report for study 1275.1

7.4.5.4 Volume depletion

Volume depletion events were analyzed using a customized MedDRA query (CMQ) which included the preferred terms (PTs) "Blood pressure decreased", "Blood pressures systolic decreased", "Hypotension", "Blood pressure ambulatory decreased", "Dehydration", "Hypovolemia", "Orthostatic hypotension", and "Syncope".

In the overall study population, volume depletion events were rare (Table 62). There was no clear imbalance between treatment arms. While there is concern for a higher frequency of volume depletion events in older patients and in patients with baseline renal impairment treated with SGLT2 inhibitors, the small number of patients meeting these demographics parameters limits the ability to examine these subgroups. In the absence of additional information, it would be reasonable to assume that the subgroup of patients at risk for these events with treatment of the individual components would also be at increased risk with treatment using an FDC product.

Table 62: Frequency of volume depletion events – treated set, pooled

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	273		272		276		275		267	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Volume depletion (CMQ)	2	0.7	5	1.8	2	0.7	1	0.4	4	1.5
Preferred term										

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	**273**		**272**		**276**		**275**		**267**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
- Dehydration	1	0.4	1	0.4	1	0.4	0	0.0	2	0.7
- Hypotension	1	0.4	2	0.7	0	0.0	1	0.4	2	0.7
- Syncope	0	0.0	2	0.7	2	0.7	0	0.0	0	0.0
- Orthostatic hypotension	0	0.0	0	0.0	0	0.0	0	0.0	1	0.4

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; CMQ = customized MedDRA query
Source: Adapted from Table 15.6.3.2.6: 1

Metformin patients:

Volume depletion events were rare in the metformin patient population (Table 63). No notable imbalance between treatment arms was seen for volume depletion events. Only one event led to discontinuation of study treatment, and this occurred in a patient from the Lina 5 arm. As noted above in discussion of the pooled patient population, exploration for at risk subgroups cannot be performed with any confidence.

Table 63: Frequency of volume depletion events – treated set, metformin patients

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	**137**		**136**		**141**		**140**		**132**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Volume depletion (CMQ)	1	0.7	2	1.5	2	1.4	1	0.7	4	3.0
Preferred term										
- Dehydration	0	0.0	0	0.0	1	0.7	0	0.0	2	1.5
- Hypotension	1	0.7	1	0.7	0	0.0	1	0.7	2	1.5
- Syncope	0	0.0	1	0.7	2	1.4	0	0.0	0	0.0
- Orthostatic hypotension	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; CMQ = customized MedDRA query
Source: Adapted from Table 15.5.3.2.6: 1

Treatment naïve:

Volume depletion events were rare in the treatment naïve population (Table 64). While all of the events were reported in the FDC arms, the small number of events limits the interpretation. No notable imbalance between treatment arms was seen for volume depletion events. Only one event led to discontinuation of study treatment. This was in a patient from the FDC 10/5 arm who had a concurrent event of Alzheimer's dementia which was the reason for study drug discontinuation. As noted above in discussion of the pooled patient population, exploration for at risk subgroups cannot be performed with any confidence.

Table 64: Frequency of volume depletion events – treated set, treatment naïve

	FDC 25/5		FDC 10/5		Empa 25		Empa 5		Lina 5	
	136		136		135		135		135	
	N	%	N	%	N	%	N	%	N	%
Volume depletion (CMQ)	1	0.7	3	2.2	0	0.0	0	0.0	0	0.0
Preferred term										
- Dehydration	1	0.7	1	0.7	0	0.0	0	0.0	0	0.0
- Hypotension	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
- Syncope	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; CMQ = customized MedDRA query
Source: Adapted from Table 15.4.3.2.6: 1 of the study report for study 1275.1

While patient 1245.0001.091646 is not included in the patients analyzed for the CMQ, review of the narrative (see 7.4.3.1) suggests that dehydration may have contributed to the patient's decision to discontinue study drug (reported PT's of "thirst" and "dry mouth"). Inclusion of this patient (treated with FDC 25/5) does not substantially change the findings.

1.1.1.1 Malignancies

Malignancies were analyzed by the Applicant using the "malignancies" SMQ (#20000090). Additionally, specific malignancies were examined as being of further interest. These included pancreatic cancer (using the high level term [HLT] "pancreatic neoplasm" [#10033632]), thyroid cancer (using the HLTs "thyroid neoplasms malignant" [#10043749], "thyroid neoplasms benign" [#10043748], and the PT thyroid neoplasm [#10043744]).

In the pooled population, the FDC 25/5 arm had numerically more malignancy events (n=5, 1.8%) compared to the other arms, but the difference was small (n=2, 0.7% for the other treatment arms). No preferred term was reported more than once in each arm.

Medullary thyroid cancer and pancreatic cancer are malignancies of interest based on the current prescribing information from linagliptin. There were no reported cases of medullary thyroid cancer or of pancreatic cancer. Bladder cancer is a malignancy of interest based on the current prescribing information for dapagliflozin, a different SGLT2 inhibitor. No bladder cancer events were reported.

In the empagliflozin program, an imbalance in melanoma and lung cancer was seen. No melanomas were reported in study 1275.1. There were three events with PTs consistent with lung cancers (one with PT "lung adenocarcinoma" in the FDC 10/5 arm, one with PT "lung neoplasm" in the Empa 10 arm, and one with the PT "non-small cell lung cancer metastatic" in the Empa 10 arm). No clear imbalance in lung cancer was seen in study 1275.1.

The only cancer type which was reported in more than one subject for a treatment arm was renal cancer. There was one patient from the treatment naïve population with the PT "clear cell renal

cell carcinoma", and another patient from the metformin treated population with the PT "renal cancer". Both of these patients were from the FDC 25/5 arm. Due to the small number of events, no confident conclusion can be made regarding renal cancer. No substantial imbalance between treatments was observed.

There was no evident imbalance in either the frequency of malignancies, or of specific malignancy types seen with FDC treatment compared to treatment with the individual components.

Table 65: Frequency of malignancy events based on standardized MedDRA query – treated set

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
	N	%	N	%	N	%	N	%	N	%
Pooled Population										
Total Number of Patients	273		272		276		275		267	
Malignancy SMQ	5	1.8	2	0.7	2	0.7	2	0.7	2	0.7
Metformin Patients										
Total Number of Patients	137		136		141		140		132	
Malignancy SMQ	3	2.2	1	0.7	2	1.4	2	1.4	2	1.5
Treatment naïve										
Total Number of Patients	136		136		135		135		135	
Malignancy SMQ	2	1.5	1	0.7	0	0.0	0	0.0	0	0.0

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; SMQ = standardized MedDRA query
Source: Adapted from Tables 15.4.3.2.7: 115.5.3.2.7: 1, and 15.6.3.2.7: 1 of the study report for study 1275.1

4-month Safety Update:

There were four cases of malignancy reported in the safety update (n=1 for study 1275.9, n=3 for study 1275.10). An additional case was reported after the database lock and is also briefly discussed in section 1.1.1.2. The patient from study 1275.9 was diagnosed with bladder cancer after two months of blinded treatment. The three cases from study 1275.10 all came from the open-label empagliflozin treatment period. Two of these cases were pancreatic cancers, and the other was a hepatic nodule. I will not include discussion of the hepatic nodule. The first case of pancreatic cancer (patient ID 1275.0010.031248) was in a 71 year old female with elevated liver transaminases at the start of the study. Two weeks later she was evaluated for painless jaundice and diagnosed with pancreatic cancer. The second case of pancreatic cancer (patient ID 1275.0010.034111) was in a 56 year old male diagnosed with a pancreatic head tumor after five weeks of open-label treatment with empagliflozin.

As discussed in section 1.1.1.2, there was an additional case reported after database lock for a patient who had completed the 16 week open label empagliflozin period and had been exposed to blinded study treatment for approximately one month. The patient had symptoms of weight loss

during treatment with open-label empagliflozin. During evaluation of the elevated liver enzymes, a pancreatic tumor was identified. This was ultimately diagnosed as pancreatic cancer. Total exposure to blinded study drug was approximately one month.

The duration of exposure for all of these cases is short and unlikely to be a causative factor in the development of these cancers. The information included in the safety update does not change the safety observations from the original NDA submission.

1.1.1.2 Hepatic events

Hepatic injury was defined by the Applicant as AST and/or ALT ≥ 3x ULRR and a bilirubin ≥ 2x ULRR. To cover reported adverse events, the Applicant used narrow SMQs ("liver related investigations, signs and symptoms [#20000008], "cholestasis and jaundice of hepatic origin [#20000009], "hepatitis, non-infectious [#20000010], and "hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions [#20000013]).

Metformin patients:

There were a total of seven patients with AEs that were included in the SMQs used by the Applicant to identify hepatic events (Table 66). Three of these were reported between week 0 and week 24. The remaining four were reported between week 24 and week 52.

Two of these patients were treated with the FDC product. The PT associated with both patients was "hepatic steatosis". Neither of these patients discontinued study drug, and neither of these patients were reported to have elevated liver enzymes.

Table 66: Patients with hepatic events – treated set, metformin patients

Patient ID	Onset day	Preferred term
FDC 25/5		
1275.0001.099065	332	Hepatic steatosis
1275.0001.099383	335	Hepatic steatosis
Empa 25		
1275.0001.094602	170	Alanine aminotransferase increased, Aspartate aminotransferase increased
Empa 10		
1275.0001.092165	71	Hepatic steatosis
1275.0001.099749	167	Hepatitis toxic
1275.0001.092409	226	Liver function test abnormal
1275.0001.093210	362	Hepatic steatosis

Source: Adapted from Tables 12.A.3.3.4: 6 and 12.A.3.3.4: 7 of the study report for 1275.1

Elevations in liver enzymes were also analyzed. There were few patients with elevated liver enzymes, and there were no patients with a liver enzyme profile meeting the criteria outlined in

Hy's law[6] (Table 67).

Table 67: Frequency of elevated liver enzymes – treated set, metformin patients

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	**137**		**136**		**141**		**140**		**132**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
ALT/AST ≥ 3x ULRR	0	0.0	1	0.7	0	0.0	2	1.4	2	1.5
ALT/AST ≥ 5x ULRR	0	0.0	1	0.7	0	0.0	1	0.7	0	0.0
ALT/AST ≥ 10x ULRR	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
ALT/AST ≥ 20x ULRR	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
ALT/AST ≥ 3x ULRR, total bilirubin ≥ 2x ULRR	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Alkaline phosphatase < 2x ULRR	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Alkaline phosphatase ≥ 2x ULRR	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULRR = upper limit of reference range
Source: Adapted from Table 15.5.3.3.2: 1 of the study report for 1275.1

Treatment naïve:

There were a total of 20 patients with AEs that were included in the SMQs used by the Applicant to identify hepatic events (Table 68). Eight of these were reported between week 0 and week 24. The remaining 12 were reported between week 24 and week 52.

Five patients were treated with the FDC product. One of these patients (1275.0001.094928) had the preferred term "hepatic steatosis". Mild, intermittent elevations in alkaline phosphatase were reported, but no elevations in ALT, AST, or total bilirubin were reported. The remaining four patients all had elevations in liver enzymes. One of these patients (1275.0001.092686) had mild elevations at baseline, and while the post-randomization liver enzymes rose they did not exceed 3x ULRR. All of these were also confounded by concurrent medications. None of these were SAEs or fatal events.

Table 68: Patients with hepatic events – treated set, treatment naïve

Patient ID	Onset day	Preferred term
FDC 25/5		
1275.0001.094206	87	Alanine aminotransferase increased, Aspartate aminotransferase increased
1275.0001.094928	157	Hepatic steatosis
FDC 10/5		
1275.0001.092686	177	Hepatic enzyme increased
1275.0001.099626	91	Hepatocellular injury
1275.0001.099194	199	Hepatic enzyme increased

[6] Hy's law: (1) 3x or greater elevation of ALT or AST above the upper limit of the reference range, (2) 2x or greater elevation in total bilirubin without 2x or greater elevation in alkaline phosphatase, and (3) there is no other explanation for the laboratory abnormalities.

Patient ID	Onset day	Preferred term
Empa 25		
1275.0001.094609	169	Alanine aminotransferase increased
1275.0001.099563	3	Hepatic steatosis
1275.0001.092691	217	Hepatic steatosis, Hepatomegaly
1275.0001.095051	312	Hepatic mass
1275.0001.096921	204	Hepatic steatosis
Empa 25		
1275.0001.094602	170	Alanine aminotransferase increased, Aspartate aminotransferase increased
Empa 10		
1275.0001.092165	71	Hepatic steatosis
1275.0001.099749	167	Hepatitis toxic
1275.0001.092409	226	Liver function test abnormal
1275.0001.093210	362	Hepatic steatosis
Lina 5		
1275.0001.094939	94	Hepatic steatosis
1275.0001.097539	169	Alanine aminotransferase increased, Aspartate aminotransferase increased
1275.0001.092923	229	Gamma glutamyl transpeptidase increased
1275.0001.094612	365	Alanine aminotransferase increased, Aspartate aminotransferase increased
1275.0001.094937	238	Gamma glutamyl transpeptidase increased

Source: Adapted from Tables 12.B.3.3.4: 5 and 12.B.3.3.4: 6 of the study report for 1275.1

Elevations in liver enzymes were also analyzed. There were few patients with elevated liver enzymes, and there were no patients with a liver enzyme profile meeting the criteria outlined in Hy's law (Table 69).

Table 69: Frequency of elevated liver enzymes – treated set, treatment naïve

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	**136**		**136**		**135**		**135**		**135**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
ALT/AST ≥ 3x ULRR	2	1.5	3	2.2	0	0.0	0	0.0	1	0.7
ALT/AST ≥ 5x ULRR	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
ALT/AST ≥ 10x ULRR	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
ALT/AST ≥ 20x ULRR	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
ALT/AST ≥ 3x ULRR, total bilirubin ≥ 2x ULRR	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Alkaline phosphatase < 2x ULRR	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Alkaline phosphatase ≥ 2x ULRR	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULRR = upper limit of reference range
Source: Adapted from Table 15.4.3.3.2: 1 of the study report for 1275.1

4-month Safety Update:

There were no cases that met criteria for Hy's Law in the safety update. Two patients were

noted to have an increase in liver transaminases > 5x the upper limit of the reference range (ULRR) while receiving open-label linagliptin in study 1275.9, and one patient was noted to have an increase in liver transaminases > 5x ULRR while on blinded treatment in study 1275.10

The one patient with elevated liver enzymes (patient ID 1275.0010.032424) while receiving blinded treatment was a 64 year old male treated with open-label empagliflozin followed by blinded treatment to either the empagliflozin/linagliptin FDC or to empagliflozin/placebo. He was found to have elevated liver enzymes and at the time of database lock for the safety update and had been diagnosed with mild hepatitis. At the time of the event he had completed the 16 week open label treatment period and had received blinded study drug for approximately one month. Further updated information was provided after database lock and reported a diagnosis of pancreatic cancer. This case will be discussed again in section 1.1.1.1.

Overall, the additional information in the safety update does not substantially change the safety observations from the original NDA submission.

1.1.1.3 Changes in renal function

Decreased renal function was defined by the Applicant as creatinine ≥ 2x baseline and above the upper limit of the reference range (ULRR). To cover reported adverse events, the Applicant used a narrow standardized MedDRA query (SMQ) for "acute renal failure (#20000003).

Metformin patients:

There were four patients with AEs that had associated PTs included in the analysis of renal events (Table 70). Three of these patients were treated with the FDC product. One of these patients (1275.0001.092681) did not receive study drug prior to the event. One patient (1275.0001.093282) had a single instance of elevated creatinine on day 1 with subsequent normal creatinine values. This event was confounded by concurrent use of Bactrim. The last patient (1275.0001.093721) had a transient decrease in estimated glomerular filtration rate and a reported verbatim term of "worsening MDRD". The investigator posited that it was related to diarrhea and dehydration. Subsequent laboratory tests showed a return to baseline.

Table 70: Patients with renal events – treated set, metformin patients

Patient ID	Onset day	Preferred term
FDC 25/5		
1275.0001.093282	1	Renal impairment
1275.0001.092681	1	Blood creatinine increased
1275.0001.093721	246	Nephropathy

Patient ID	Onset day	Preferred term
Lina 5		
1275.0001.097081	15	Renal failure acute

Source: Adapted from Tables 12.A.3.3.4: 1 and 12.A.3.3.4: 2 of the study report for 1275.1

Additional evaluation of renal related laboratory tests was performed to further explore changes in renal function. There was no notable change in either mean serum creatinine or mean eGFR by MDRD (Table 71). From this, it appears that compared with the individual components that make up the FDC product, the FDC product does not result in an increase in renal events (either reported as an AE or by changes in laboratory tests).

Table 71: Mean change in laboratory parameters of renal function – treated set, metformin patients

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	**137**		**136**		**141**		**140**		**132**	
Serum creatinine (mg/dL)										
Baseline mean (SD)	0.84	0.21	0.84	0.17	0.81	0.17	0.82	0.18	0.82	0.19
Mean change from baseline::										
- Week 12 (SD)	0.01	0.10	0.02	0.14	0.00	0.09	-0.01	0.10	-0.01	0.08
- Week 24 (SD)	0.01	0.12	0.01	0.10	-0.01	0.10	-0.01	0.09	0.00	0.10
- Week 52 (SD)	0.02	0.11	0.01	0.10	0.00	0.10	0.00	0.10	0.01	0.10
- 4 week follow-up (SD)	-0.03	0.17	-0.01	0.14	-0.03	0.11	-0.03	0.09	0.01	0.10
eGFR (ml/min/1.73m^2)										
Baseline mean (SD)	87.46	17.98	89.13	18.31	90.15	18.27	91.06	19.61	89.63	20.17
Mean change from baseline:										
- Week 12 (SD)	-1.00	10.47	-0.90	13.53	-0.33	11.86	0.61	12.36	1.13	11.92
- Week 24 (SD)	-0.62	11.97	-0.26	11.27	2.24	12.97	0.75	11.35	-0.01	13.38
- Week 52 (SD)	-1.72	10.60	0.19	11.95	1.10	12.65	-0.13	11.87	-1.70	12.39
- 4 week follow-up (SD)	3.27	13.40	2.04	13.51	4.78	13.69	3.67	11.53	-0.50	12.97

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; SD = standard deviation; eGFR = estimated glomerular filtration rate calculated by MDRD equation
Source: Adapted from Tables 12.A.3.3.4: 2 and 12.A.3.3.4: 3 of the study report for study 1275.1

There were too few patients for confident analysis of changes in creatinine by age. Similarly, there were too few patients for confident analysis of changes in eGFR for patients with a baseline eGFR < 60 ml/min/1.73 m^2. In the absence of additional information, it would be reasonable to assume that the subgroup of patients at risk for these events with treatment of the individual components would also be at increased risk with treatment using an FDC product.

Treatment naïve:

No patients had AEs that qualified for analysis as a renal adverse event. Additional evaluation of renal related laboratory tests was performed to further explore changes in renal function. There

was no notable change in either mean serum creatinine or mean eGFR by MDRD (Table 72). From this, it appears that compared with the individual components that make up the FDC product, the FDC product does not results in an increase in renal events (either reported as an AE or by changes in laboratory tests).

Table 72: Mean change in laboratory parameters of renal function – treated set, treatment naive

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	**136**		**136**		**135**		**135**		**135**	
Serum creatinine (mg/dL)										
Baseline mean (SD)	0.82	0.19	0.84	0.18	0.84	0.17	0.83	0.19	0.83	0.17
Mean change from baseline:										
- Week 12 (SD)	0.00	0.12	0.01	0.11	-0.01	0.09	-0.01	0.08	-0.01	0.08
- Week 24 (SD)	0.00	0.10	0.00	0.09	-0.02	0.08	-0.03	0.09	0.00	0.09
- Week 52 (SD)	-0.01	0.10	0.00	0.11	0.00	0.10	-0.01	0.09	0.00	0.09
- 4 week follow-up (SD)	-0.03	0.13	-0.02	0.10	-0.03	0.09	-0.03	0.10	-0.02	0.09
eGFR (ml/min/1.73m^2)										
Baseline mean (SD)	90.32	19.60	87.81	17.58	88.75	18.53	88.42	19.00	89.70	20.19
Mean change from baseline:										
- Week 12 (SD)	-0.79	11.88	-0.33	12.62	1.61	11.50	1.65	11.23	1.10	10.52
- Week 24 (SD)	0.21	12.07	0.30	11.07	1.72	10.11	3.14	12.47	-0.03	11.18
- Week 52 (SD)	0.76	11.64	1.47	11.40	0.18	11.85	0.99	12.50	-0.52	10.85
- 4 week follow-up (SD)	3.94	12.66	3.97	11.74	3.30	11.06	3.66	12.36	1.52	11.49

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; SD = standard deviation; eGFR = estimated glomerular filtration rate calculated by MDRD equation
Source: Tables 12.B.3.3.4: 1 and 12.B.3.3.4: 2 from the study report for study 1275.1

There were too few patients for confident analysis of changes in creatinine by age. Similarly, there were too few patients for confident analysis of changes in eGFR for patients with a baseline eGFR < 60 ml/min/1.73 m^2. In the absence of additional information, it would be reasonable to assume that the subgroup of patients at risk for these events with treatment of the individual components would also be at increased risk with treatment using the FDC product.

1.1.1.1 Hypersensitivity reactions

The Applicant analyzed hypersensitivity reactions using narrow SMQs ("anaphylactic reaction [#20000021], "angioedema" [#20000024], and "asthma/bronchospasm" [#20000025]).

Few hypersensitivity reactions were reported in study 1275.1 (Table 73). No clear imbalance between treatment arms was seen. This was the case for the pool of any background therapy and for the two different background therapy populations.

Table 73: Incidence of hypersensitivity reactions – treated set

Preferred Term	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
	N	%	N	%	N	%	N	%	N	%
All background										
Number of patients	273		272		276		275		267	
Asthma	0	0.0	1	0.4	0	0.0	2	0.7	0	0.0
Urticaria	0	0.0	1	0.4	2	0.7	0	0.0	0	0.0
Angioedema	1	0.4	0	0.0	0	0.0	0	0.0	1	0.4
Asthmatic crisis	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0
Eyelid edema	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0
Pharyngeal edema[1]	0	0.0	0	0.0	0	0.0	1	0.4	0	0.0
Metformin patients										
Number of patients	137		136		141		140		132	
Asthma	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Urticaria	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
Angioedema	1	0.7	0	0.0	0	0.0	0	0.0	1	0.8
Asthmatic crisis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Eyelid edema	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Pharyngeal edema[1]	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
Treatment naïve										
Number of patients	136		136		135		135		135	
Asthma	0	0.0	1	0.7	0	0.0	2	1.5	0	0.0
Urticaria	0	0.0	0	0.0	2	1.5	0	0.0	0	0.0
Angioedema	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Asthmatic crisis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Eyelid edema	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
Pharyngeal edema[1]	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
[1] not included in the prespecified term for this adverse event of special interest
Source: Adapted from Tables 15.4.3.2.8: 1, 15.5.3.2.8: 1 and 15.6.3.2.8: 1 of the study report for study 1275.1 and from review of the study report

4-month Safety Update:

There were five cases of hypersensitivity reactions reported in the safety update (n=4 for study 1275.9, n=1 for study 1275.10). All occurred in the open-label treatment period. The information included in the safety update does not change the safety observations from the original NDA submission.

1.1.1.1 Skin lesions

The Applicant analyzed skin lesions using the "severe cutaneous adverse reactions" SMQ (#20000020). There were no AEs that met the prespecified terms for this adverse event of special interest. There was one patient (subject ID 1275.0001.094711) with the PT "drug eruption". This patient was from the treatment naïve population and was treated with FDC 25/5. After 18 days of study drug exposure a pruritic skin rash was reported on the upper and lower limbs. Study drug was stopped for 12 days without improvement, so treatment was restarted.

Treatment included topical steroids and topical anti-fungal. Skin biopsy was performed and reported a diagnosis of drug reaction. There were no concerning signals for serious skin reactions.

1.1.1.2 Pancreatitis

Pancreatitis was analyzed by the Applicant using the "acute pancreatitis" SMQ (#20000022) and the PT "chronic pancreatitis". There were only two cases reported in the study (Table 74). No evident imbalance between treatment arms was noted.

In the metformin patients, there were no cases of acute pancreatitis. One patient had an AE of "chronic pancreatitis". This patient was treated with Lina 5. A mild elevation in lipase was noted leading to evaluation. Repeat laboratory testing was within the reference range; abdominal ultrasound showed waviness and indistinct structure of the pancreas as well as a "sealing structure". No abdominal pain was reported. Later in the course of study participation, the patient reported abdominal distention after eating with alternating constipation and diarrhea. The investigator diagnosed the patient with chronic pancreatitis and started treatment with pancreatic enzyme replacement.

In the treatment naïve patients, there was one patient with acute pancreatitis. This patient was treated with FDC 25/5. The patient presented (b) (6) days after randomization to the emergency room with three days of abdominal pain. Laboratory tests and imaging studies were performed but are not available for review. The patient was treated with anti-emetics, opioid analgesics, and intravenous hydration. The patient was discharged from the emergency room the same day. The abdominal pain resolved on day 315. The event was reported to the investigator on day 345, and study drug was discontinued at that time.

Both of these cases lack sufficient data to confidently make the diagnosis of pancreatitis. No assessment of risk can be made with this small number of cases.

The PT "lipase increased" was reported in 18 patients who were not reported to have pancreatitis (Table 74). While this appeared to be more frequent in the FDC treated patients, the clinical significance of this is unclear.

There does not appear to be evidence of increased risk for pancreatitis with the FDC product. While there appears to be an increased frequency of elevated lipase associated with treatment with the FDC product, it is of unclear significance.

Table 74: Incidence of treatment emergent pancreatitis and increased lipase – treated set

Preferred Term	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
	N	%	N	%	N	%	N	%	N	%
All background										
Number of patients	273		272		276		275		267	
Lipase increased[1]	8	2.9	4	1.5	2	0.7	2	0.7	3	1.1
Pancreatitis acute	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0
Pancreatitis chronic	0	0.0	0	0.0	0	0.0	0	0.0	1	0.4
Metformin patients										
Number of patients	137		136		141		140		132	
Lipase increased[1]	6	4.4	0	0.0	1	0.7	2	1.4	2	1.5
Pancreatitis acute	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Pancreatitis chronic	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8
Treatment naïve										
Number of patients	136		136		135		135		135	
Lipase increased[1]	2	1.5	4	2.9	1	0.7	0	0.0	1	0.7
Pancreatitis acute	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
Pancreatitis chronic	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
[1] not included in the prespecified terms for this adverse event of special interest
Source: Review of submitted datasets for study 1275.1

4-month Safety Update:

Three cases of pancreatitis were reported in the safety update. All of these cases occurred during open-label treatment with empagliflozin in study 1275.10. There were no cases of pancreatitis in patients on blinded treatment, or in study 1275.9. The information included in the safety update does not change the safety observations from the original NDA submission.

1.1.1.3 Cardiovascular Safety

The two individual components that make up the FDC were evaluated for an increased risk for cardiovascular events as outlined in the FDA's "Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes". Both satisfied the condition that the upper bound of the 95% confidence interval for the hazard ratio for MACE+[7] did not exceed 1.8. A separate analysis of cardiovascular risk to satisfy the Guidance for Industry for the FDC product was not performed. Cardiovascular events from study 1275.1 were adjudicated by an independent adjudication committee and analyzed by the Applicant.

Metformin patients:

A total of 18 events qualified for adjudication (Table 75). Ten of these events were confirmed as

[7] MACE = major cardiovascular event; MACE+ = cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and hospitalization for unstable angina

cardiovascular events. There was one fatal event. There was no clear imbalance between treatments to suggest increased cardiovascular risk with the FDC product.

Table 75: Cardiovascular events – treated set, metformin patients

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
	N	%	N	%	N	%	N	%	N	%
Number of patients	137		136		141		140		132	
Adjudicated	4	2.9	4	2.9	3	2.1	4	2.9	3	2.3
Confirmed	2	1.5	2	1.5	1	0.7	3	2.1	2	1.5
Fatal	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
- Sudden death	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
Nonfatal	2	1.5	1	0.7	1	0.7	3	2.1	2	1.5
- Acute MI	0	0.0	0	0.0	0	0.0	1	0.7	0	0.0
- Coronary revascularization	1	0.7	0	0.0	0	0.0	2	1.4	1	0.8
- Stent thrombosis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Hospitalization for heart failure	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Hospitalization for unstable angina	1	0.7	0	0.0	0	0.0	1	0.7	1	0.8
- Non-fatal neurologic event	1	0.7	1	0.7	0	0.0	1	0.7	1	0.8
- Ischemic stroke	0	0.0	1	0.7	0	0.0	0	0.0	1	0.8
- TIA	1	0.7	0	0.0	0	0.0	1	0.7	0	0.0

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; MI = myocardial infarction; TIA = transient ischemic attack
Source: Adapted from 15.5.3.2.2: 1 and 15.5.3.2.2: 2 of the study report for study 1275.1

Treatment naïve:

A total of 21 events qualified for adjudication (Table 76). Four of these events were confirmed as cardiovascular events. There was one fatal event. There was no clear imbalance between treatments to suggest increased risk for cardiovascular events with the FDC product.

Table 76: Cardiovascular events – treated set, treatment naive

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
	N	%	N	%	N	%	N	%	N	%
Number of patients	136		136		135		135		135	
Adjudicated	3	2.2	4	2.9	4	3.0	8	5.9	2	1.5
Confirmed	0	0.0	2	1.5	0	0.0	1	0.7	1	0.7
Fatal	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
- Not assessable	0	0.0	1	0.7	0	0.0	0	0.0	0	0.0
Nonfatal	0	0.0	2	1.5	0	0.0	1	0.7	1	0.7
- Acute MI	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Coronary revascularization	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Stent thrombosis	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Hospitalization for heart failure	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Hospitalization for unstable angina	0	0.0	2	1.5	0	0.0	0	0.0	0	0.0

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
	N	%	N	%	N	%	N	%	N	%
- Non-fatal neurologic event	0	0.0	0	0.0	0	0.0	1	0.7	0	0.0
- Ischemic stroke	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- TIA	0	0.0	0	0.0	0	0.0	1	0.7	0	0.0

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; MI = myocardial infarction; TIA = transient ischemic attack
Source: Adapted from 15.4.3.2.2: 1 and 15.4.3.2.2: 2 of the study report for study 1275.1

4-month Safety Update:

Two patients were reported to have cardiovascular events during blinded treatment in the safety update. Both came from study 1275.9. One patient was found to have an abnormal electrocardiogram after starting blinded treatment. The other reported chest pain related to coronary artery disease after starting blinded treatment. There was one patient from study 1275.10 with an event of atrial fibrillation which occurred during open-label treatment with empagliflozin. This case was included in the original NDA submission. The information included in the safety update does not change the safety observations from the original NDA submission.

7.5 Supportive Safety Results

7.5.1 Common Adverse Events

To assist in exploration of common AEs, the submitted AE.xpt, DM.xpt and SuppDM.xpt datasets were combined to generate treatment emergent adverse event incidence tables separated by background therapy. Each FDC dose was compared with the respective empagliflozin dose and with the linagliptin arm to identify adverse events that occurred at either an appreciably higher event-rate (i.e. events per 100 patient-years) or incidence (i.e. percent of subjects). The generated tables can be found in Appendix 9.5 (Table 97, Table 98, Table 99, Table 100, Table 101, and Table 102). The overall safety profile of the FDC was as expected given the drug products which form the combination.

Metformin patients:

The most frequent treatment emergent adverse events (TEAEs) came from the "Infections and infestations" SOC (Table 77). Within that SOC, the high level terms (HLTs) with the highest incidence were "Upper respiratory tract infections", and "Urinary tract infections". These were also the most commonly reported PTs in this SOC. Overall, the incidence of events in the HLT was not noticeably higher with the FDC, but at there were some at the PT level they were more common than in the linagliptin arm. The incidence of events in the "Urinary tract infections" HLT and "Urinary tract infection" PT was similar between arms. There were additional events reported within this SOC that were reported more commonly with the FDC. This included the

HLTs “Abdominal and gastrointestinal infections”, “Female reproductive tract infections”, “Fungal infections NEC”, and “Viral infections NEC”. The PTs “Gastroenteritis” and “Vaginal infection” was also more commonly reported in the FDC arms.

The next most common SOCs were “Gastrointestinal disorders” and “Musculoskeletal and connective tissue disorders”. Events in the “Gastrointestinal disorders” SOC were reported most commonly in the FDC 10/5 arm compared to the active comparators. This was due to a higher incidence/event-rate in the “Diarrhea (excl infective)”, “Gastrointestinal and abdominal pains (excl oral and throat)”, “Gastrointestinal atonic and hypomotility disorders NEC”, and “Nausea and vomiting symptoms” HLTs. Preferred terms reported more commonly with the FDC include “Abdominal pain”, “Abdominal pain upper”, “Constipation”, “Diarrhea”, “Gastroesophageal reflux disease”, and “Nausea”. In the “Musculoskeletal and connective tissue disorders” SOC, the majority of events came from the “Musculoskeletal and connective tissue pain and discomfort”, “Joint related signs and symptoms”, and “Muscle pains” HLTs. The PTs reported in these HLTs included “Arthralgia”, “Myalgia”, “Back pain”, and “Pain in extremity”.

The “Nervous system disorders” SOC was also among the SOCs reported at a relatively high incidence. These events came primarily from the “Headaches NEC” and the “Neurological signs and symptoms NEC” HLTs. Preferred terms that contributed to this were “Dizziness” and “Headache”. The “Metabolism and nutrition disorders” and “Investigations” SOCs were also reported at a relatively high incidence; however no single HLT or PT was predominant in these SOCs. Within the “Investigations” SOC, the preferred terms “Lipase increased” and “Weight decreased” were reported more commonly in the FDC arms.

Other TEAEs that were reported more commonly in the FDC arms (Table 78) included the following:

- **High level terms:** Asthenic conditions NEC, Anxiety symptoms, Urinary abnormalities, Coughing and associated symptoms, Nasal congestion and inflammations, Upper respiratory tract signs and symptoms, and Vascular hypertensive disorders NEC.

- **Preferred terms:** Fatigue, Microalbuminuria, Cough, Nasal congestion, and Hypertension.

Treatment naïve:

The most commonly reported TEAEs came from the “Infections and infestations” SOC (Table 79). Within this SOC, the HLTs of “Upper respiratory tract infections” and “Urinary tract infections” had the highest incidence, though neither was noticeably increased versus the comparators. As might be expected given empagliflozin’ s mechanism of action, the PT

"Urinary tract infection" was reported more commonly with the FDC than with linagliptin.

The "Metabolism and nutrition disorders" SOC was the next most common SOC. The events that comprised the TEAEs in this SOC were primarily glucose and lipid related. These were all more common with the FDC treatment than with comparators. There was a higher incidence of the PT "Hypokalemia", but the overall number of subjects with this event was small (6 in FDC vs. 1 in all comparators).

Treatment emergent adverse events from the "Gastrointestinal disorders" and "Musculoskeletal and connective tissue disorders" SOCs were also relatively common. In both of these SOCs, there was no notable difference between treatments for the incidence of individual HLTs or PTs.

Other SOCs reported with relatively high incidences were "Renal and urinary disorders", "Investigations", and "Skin and subcutaneous tissue disorders". There was a small imbalance in events coded to the PT "Hematuria" not favoring the FDC, but the overall number of patients reporting this event was small (9 in FDC vs. 2 in all comparators). The PT "Lipase increased" was more commonly reported for the FDC treatment arms than the comparators. Again, the overall number of patients was small (6 in FDC vs. 2 in all comparators). In the "Skin and subcutaneous tissue disorders" SOC, there was slight imbalance not favoring the FDC for the HLT "Dermatitis and eczema" (7 in FDC vs. 2 in all comparators). None of these differences raises concern for serious new safety issues with treatment using the FDC.

Other TEAEs that were reported more commonly in the FDC arms (Table 80) included the following:

- **High level terms:** Asthenic conditions, Feelings and sensations NEC, Limb injuries NEC (incl traumatic amputation), Muscle, tendon and ligament injuries, Non-site specific injuries NEC, Skin injuries NEC, Disturbances to consciousness, Headaches NEC, Neurological signs and symptoms NEC, Paresthesias and dysthesias, Sensory abnormalities NEC, Tremor (excl congenital), Cervix disorders NEC, Penile and scrotal infections and inflammations, Vulvovaginal signs and symptoms, Coughing and associated symptoms, Upper respiratory tract signs and symptoms, Dental and gingival therapeutic procedures, and Vascular hypertensive disorders.

- **Preferred terms:** Fatigue, Headache, Dizziness, Cervical dysplasia, Balanitis, Vulvovaginal pruritus, Cough, Tooth extraction, and Hypertension.

Reviewer Comment:
It is notable that the preferred term "Hypertension" was reported more frequently in the FDC treated patients. The SGLT2 inhibitors are associated with a mean decrease in blood pressure.

It is unclear whether this observed change in mean blood pressure is clinically meaningful, but it may be best to avoid labeling language which may be used to promote a blood pressure lowering effect.

Table 77: Treatment emergent adverse events occurring in ≥ 10% of patients by system organ class from either fixed dose combination arm by system organ class– treated set, metformin patients

- Includes high level terms and preferred terms reported in ≥ 2% and more commonly in either fixed dose combination arm

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				141				140				132			
Exposure (patient-years)	126.9				130.2				132.6				126.3				120.3			
System Organ Class - **High Level Term** • **Preferred Term**	**#**	**Per 100**	**N**	**%**	**#**	**Per 100**	**N**	**%**	**#**	**Per 100**	**N**	**%**	**#**	**Per 100**	**N**	**%**	**#**	**Per 100**	**N**	**%**
Gastrointestinal disorders	41	32.3	25	18.2	56	43.0	34	25.0	39	29.4	26	18.4	28	22.2	23	16.4	40	33.3	23	17.4
- Diarrhea (excl infective)	5	3.9	4	2.9	12	9.2	10	7.4	7	5.3	5	3.5	6	4.8	6	4.3	1	0.8	1	0.8
• Diarrhea	5	3.9	4	2.9	12	9.2	10	7.4	7	5.3	5	3.5	6	4.8	6	4.3	1	0.8	1	0.8
- Dyspeptic signs and symptoms	4	3.2	4	2.9	1	0.8	1	0.7	7	5.3	7	5.0	1	0.8	1	0.7	5	4.2	5	3.8
- Gastrointestinal and abdominal pains (excl oral and throat)	7	5.5	4	2.9	7	5.4	5	3.7	4	3.0	4	2.8	1	0.8	1	0.7	5	4.2	5	3.8
• Abdominal pain	5	3.9	3	2.2	2	1.5	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	2	1.7	2	1.5
• Abdominal pain upper	2	1.6	2	1.5	3	2.3	3	2.2	3	2.3	3	2.1	0	0.0	0	0.0	3	2.5	3	2.3
- Gastrointestinal atonic and hypomotility disorders NEC	10	7.9	9	6.6	10	7.7	9	6.6	4	3.0	4	2.8	7	5.5	5	3.6	3	2.5	3	2.3
• Constipation	9	7.1	8	5.8	7	5.4	7	5.1	4	3.0	4	2.8	5	4.0	4	2.9	3	2.5	3	2.3
• Gastroesophageal reflux disease	1	0.8	1	0.7	3	2.3	3	2.2	0	0.0	0	0.0	2	1.6	2	1.4	0	0.0	0	0.0
- Nausea and vomiting symptoms	6	4.7	5	3.6	8	6.1	6	4.4	9	6.8	7	5.0	3	2.4	2	1.4	6	5.0	5	3.8
• Nausea	5	3.9	5	3.6	6	4.6	5	3.7	6	4.5	5	3.5	2	1.6	2	1.4	4	3.3	4	3.0
Injury, poisoning and procedural complications	14	11.0	11	8.0	19	14.6	16	11.8	21	15.8	15	10.6	18	14.3	10	7.1	9	7.5	8	6.1
Infections and infestations	93	73.3	53	38.7	98	75.3	57	41.9	117	88.2	53	37.6	110	87.1	60	42.9	115	95.6	57	43.2
- Abdominal and gastrointestinal infections	9	7.1	8	5.8	4	3.1	4	2.9	4	3.0	3	2.1	3	2.4	2	1.4	5	4.2	4	3.0
• Gastroenteritis	9	7.1	8	5.8	4	3.1	4	2.9	4	3.0	3	2.1	3	2.4	2	1.4	5	4.2	4	3.0
- Female reproductive tract infections	1	0.8	1	0.7	6	4.6	4	2.9	2	1.5	2	1.4	2	1.6	1	0.7	1	0.8	1	0.8
• Vaginal infection	1	0.8	1	0.7	6	4.6	4	2.9	2	1.5	2	1.4	2	1.6	1	0.7	0	0.0	0	0.0
- Fungal infections NEC	1	0.8	1	0.7	8	6.1	7	5.1	10	7.5	8	5.7	5	4.0	4	2.9	4	3.3	4	3.0
- Infections NEC	4	3.2	3	2.2	2	1.5	2	1.5	3	2.3	3	2.1	1	0.8	1	0.7	1	0.8	1	0.8
- Lower respiratory tract and lung infections	5	3.9	4	2.9	5	3.8	5	3.7	8	6.0	7	5.0	9	7.1	8	5.7	7	5.8	6	4.5
- Skin structures and soft tissue infections	3	2.4	3	2.2	2	1.5	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.8
- Upper respiratory tract infections	31	24.4	23	16.8	40	30.7	32	23.5	26	19.6	21	14.9	33	26.1	27	19.3	39	32.4	24	18.2
• Nasopharyngitis	9	7.1	8	5.8	13	10.0	12	8.8	8	6.0	7	5.0	12	9.5	11	7.9	21	17.5	14	10.6

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	**137**				**136**				**141**				**140**				**132**			
Exposure (patient-years)	**126.9**				**130.2**				**132.6**				**126.3**				**120.3**			
System Organ Class **- High Level Term** **• Preferred Term**	**#**	**Per 100**	**N**	**%**	**#**	**Per 100**	**N**	**%**	**#**	**Per 100**	**N**	**%**	**#**	**Per 100**	**N**	**%**	**#**	**Per 100**	**N**	**%**
• Pharyngitis	3	2.4	3	2.2	2	1.5	2	1.5	2	1.5	2	1.4	2	1.6	2	1.4	6	5.0	5	3.8
• Sinusitis	4	3.2	2	1.5	4	3.1	3	2.2	3	2.3	3	2.1	2	1.6	2	1.4	1	0.8	1	0.8
• Upper respiratory tract infection	15	11.8	11	8.0	17	13.1	14	10.3	11	8.3	9	6.4	15	11.9	12	8.6	6	5.0	4	3.0
- Urinary tract infections	20	15.8	16	11.7	17	13.1	13	9.6	34	25.6	24	17.0	20	15.8	16	11.4	27	22.4	19	14.4
• Urinary tract infection	17	13.4	14	10.2	17	13.1	13	9.6	32	24.1	23	16.3	16	12.7	13	9.3	21	17.5	15	11.4
- Viral infections NEC	7	5.5	7	5.1	2	1.5	2	1.5	3	2.3	3	2.1	6	4.8	6	4.3	2	1.7	2	1.5
Investigations	17	13.4	14	10.2	10	7.7	8	5.9	23	17.3	18	12.8	15	11.9	11	7.9	18	15.0	15	11.4
- Digestive enzymes	6	4.7	5	3.6	0	0.0	0	0.0	1	0.8	1	0.7	2	1.6	2	1.4	2	1.7	2	1.5
• Lipase increased	6	4.7	5	3.6	0	0.0	0	0.0	1	0.8	1	0.7	2	1.6	2	1.4	2	1.7	2	1.5
- Physical examination procedures and organ system status	3	2.4	3	2.2	3	2.3	3	2.2	5	3.8	5	3.5	5	4.0	5	3.6	1	0.8	1	0.8
• Weight decreased	2	1.6	2	1.5	3	2.3	3	2.2	4	3.0	4	2.8	5	4.0	5	3.6	0	0.0	0	0.0
Metabolism and nutrition disorders	22	17.3	14	10.2	23	17.7	18	13.2	29	21.9	25	17.7	21	16.6	16	11.4	37	30.8	24	18.2
- Disorders of purine metabolism	0	0.0	0	0.0	3	2.3	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
- Hyperglycemic conditions NEC	3	2.4	1	0.7	8	6.1	5	3.7	10	7.5	8	5.7	6	4.8	4	2.9	11	9.1	10	7.6
• Hyperglycemia	3	2.4	1	0.7	8	6.1	5	3.7	10	7.5	8	5.7	6	4.8	4	2.9	11	9.1	10	7.6
- Hypoglycemic conditions NEC	9	7.1	5	3.6	6	4.6	5	3.7	6	4.5	6	4.3	5	4.0	4	2.9	15	12.5	4	3.0
• Hypoglycemia	9	7.1	5	3.6	6	4.6	5	3.7	6	4.5	6	4.3	5	4.0	4	2.9	15	12.5	4	3.0
- Lipid metabolism and deposit disorders NEC	4	3.2	4	2.9	2	1.5	2	1.5	4	3.0	4	2.8	3	2.4	2	1.4	3	2.5	3	2.3
• Dyslipidemia	4	3.2	4	2.9	1	0.8	1	0.7	3	2.3	3	2.1	3	2.4	2	1.4	3	2.5	3	2.3
Musculoskeletal and connective tissue disorders	24	18.9	18	13.1	43	33.0	26	19.1	36	27.1	24	17.0	34	26.9	23	16.4	38	31.6	27	20.5
- Joint related signs and symptoms	1	0.8	1	0.7	7	5.4	6	4.4	10	7.5	7	5.0	6	4.8	5	3.6	6	5.0	6	4.5
• Arthralgia	1	0.8	1	0.7	7	5.4	6	4.4	10	7.5	7	5.0	4	3.2	3	2.1	6	5.0	6	4.5
- Muscle pains	3	2.4	3	2.2	7	5.4	6	4.4	1	0.8	1	0.7	4	3.2	4	2.9	0	0.0	0	0.0
• Myalgia	3	2.4	3	2.2	6	4.6	5	3.7	1	0.8	1	0.7	4	3.2	4	2.9	0	0.0	0	0.0
- Musculoskeletal and connective tissue pain and discomfort	10	7.9	8	5.8	15	11.5	12	8.8	11	8.3	10	7.1	17	13.5	14	10.0	21	17.5	16	12.1
• Back pain	6	4.7	6	4.4	6	4.6	6	4.4	3	2.3	2	1.4	12	9.5	9	6.4	9	7.5	7	5.3
• Pain in extremity	1	0.8	1	0.7	3	2.3	3	2.2	5	3.8	5	3.5	2	1.6	2	1.4	3	2.5	3	2.3
- Osteoarthropathies	2	1.6	2	1.5	3	2.3	3	2.2	1	0.8	1	0.7	1	0.8	1	0.7	4	3.3	4	3.0

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				141				140				132			
Exposure (patient-years)	126.9				130.2				132.6				126.3				120.3			
System Organ Class – **High Level Term** • **Preferred Term**	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
Nervous system disorders	25	19.7	20	14.6	38	29.2	19	14.0	35	26.4	22	15.6	24	19.0	21	15.0	21	17.5	17	12.9
– Headaches NEC	8	6.3	7	5.1	16	12.3	7	5.1	12	9.0	7	5.0	11	8.7	10	7.1	9	7.5	8	6.1
• Headache	8	6.3	7	5.1	16	12.3	7	5.1	10	7.5	6	4.3	11	8.7	10	7.1	9	7.5	8	6.1
– Neurological signs and symptoms NEC	4	3.2	4	2.9	14	10.8	6	4.4	12	9.0	5	3.5	3	2.4	3	2.1	6	5.0	5	3.8
• Dizziness	4	3.2	4	2.9	14	10.8	6	4.4	12	9.0	5	3.5	3	2.4	3	2.1	6	5.0	5	3.8

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; # = number of events; per 100 = event rate per 100 patient-years; N = number of patients with event; % = percent of patients with event; NEC = not elsewhere classified; incl = including; excl = excluding
Source: Based on review up submitted datasets, information from the Applicant's Response to Information Request received on April 14, 2014, and information from Table 12.A.1: 2 of the study report for study 1275.1

Table 78: Treatment emergent adverse events reported in ≥ 2% of patients by preferred term and more commonly with the fixed dose combination that are not presented in Table 77 – treated set, metformin patients

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				141				140				132			
Exposure (patient-years)	126.9				130.2				132.6				126.3				120.3			
System Organ Class – **High Level Term** • **Preferred Term**	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
General disorders and administration site conditions																				
– Asthenic conditions	6	4.7	6	4.4	6	4.6	6	4.4	5	3.8	2	1.4	2	1.6	2	1.4	1	0.8	1	0.8
• Fatigue	4	3.2	4	2.9	3	2.3	3	2.2	1	0.8	1	0.7	2	1.6	2	1.4	1	0.8	1	0.8
Psychiatric disorders																				
– Anxiety symptoms	3	2.4	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	3	2.4	3	2.1	6	5.0	4	3.0
Renal and urinary disorders																				
– Urinary abnormalities	5	3.9	4	2.9	0	0.0	0	0.0	3	2.3	3	2 1	3	2.4	3	2.1	1	0.8	1	0.8
• Microalbuminuria	4	3.2	4	2.9	0	0.0	0	0.0	2	1.5	2	1.4	0	0.0	0	0.0	1	0.8	1	0.8
Respiratory, thoracic and mediastinal disorders																				
– Coughing and associated symptoms	6	4.7	6	4.4	6	4.6	6	4.4	4	3.0	4	2.8	3	2.4	2	1.4	4	3.3	3	2.3
• Cough	5	3.9	5	3.6	6	4.6	6	4.4	3	2.3	3	2 1	3	2.4	2	1.4	3	2.5	2	1.5
– Nasal congestion and inflammations	3	2.4	3	2.2	3	2.3	3	2.2	2	1.5	2	1.4	1	0.8	1	0.7	0	0.0	0	0.0
• Nasal congestion	1	0.8	1	0.7	2	1.5	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0
– Upper respiratory tract signs and symptoms	1	0.8	1	0.7	4	3.1	3	2.2	4	3.0	4	2.8	3	2.4	2	1.4	1	0.8	1	0.8

Vascular disorders																				
– Vascular hypertensive disorders NEC	7	5.5	6	4.4	1	0.8	1	0.7	3	2.3	3	2.1	6	4.8	6	4.3	7	5.8	7	5.3
• Hypertension	7	5.5	6	4.4	1	0.8	1	0.7	3	2.3	3	2.1	6	4.8	6	4.3	7	5.8	7	5.3

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; # = number of events; per 100 = event rate per 100 patient-years; N = number of patients with event; % = percent of patients with event; NEC = not elsewhere classified; incl = including; excl = excluding
Source: Based on review up submitted datasets, information from the Applicant's Response to Information Request received on April 14, 2014, and information from Table 12.A.1: 2 of the study report for study 1275.1

Table 79: Treatment emergent adverse events occurring in ≥ 10% of patients by system organ class from either fixed dose combination arm by system organ class – treated set, treatment naive

– Includes high level terms and preferred terms reported in ≥ 2% and more commonly in either fixed dose combination arm

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				141				140				132			
Exposure (patient-years)	126.9				130.2				132.6				126.3				120.3			
System Organ Class **– High Level Term** **• Preferred Term**	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
Gastrointestinal disorders	33	26.7	21	15.3	28	22.4	19	14.0	42	34.1	26	18.7	30	24.4	20	14.8	29	23.6	21	15.6
- Dental pain and sensation disorders	3	2.4	3	2.2	1	0.8	1	0.7	2	1.6	2	1.5	4	3.3	4	3.0	2	1.6	2	1.5
• Toothache	3	2.4	3	2.2	1	0.8	1	0.7	2	1.6	2	1.5	4	3.3	4	3.0	2	1.6	2	1.5
- Dyspeptic signs and symptoms	1	0.8	1	0.7	5	4.0	4	2.9	1	0.8	1	0.7	2	1.6	2	1.5	2	1.6	2	1.5
• Dyspepsia	1	0.8	1	0.7	5	4.0	4	2.9	1	0.8	1	0.7	2	1.6	2	1.5	2	1.6	2	1.5
- Gastritis (excl infective)	1	0.8	1	0.7	3	2.4	3	2.2	2	1.6	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7
• Gastritis	1	0.8	1	0.7	3	2.4	3	2.2	2	1.6	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7
- Gastrointestinal and abdominal pains (excl oral and throat)	4	3.2	4	2.9	5	4.0	5	3.7	5	4.1	3	2.2	2	1.6	2	1.5	4	3.3	4	3.0
• Abdominal pain upper	2	1.6	2	1.5	3	2.4	3	2.2	5	4.1	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0
- Hemorrhoids and gastrointestinal varices (excl esophageal)	4	3.2	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• Hemorrhoids	4	3.2	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Nausea and vomiting symptoms	6	4.9	4	2.9	3	2.4	3	2.2	8	6.5	4	3.0	5	4.1	4	3.0	4	3.3	3	2.2
• Nausea	6	4.9	4	2.9	3	2.4	3	2.2	5	4.1	4	3.0	5	4.1	4	3.0	2	1.6	2	1.5
Infections and infestations	105	85.0	57	41.6	102	81.7	51	37.5	91	74.0	49	35.3	108	87.8	65	48.1	82	66.7	53	39.3
- Abdominal and gastrointestinal infections	4	3.2	4	2.9	3	2.4	3	2.2	1	0.8	1	0.7	4	3.3	4	3.0	4	3.3	2	1.5
- Bacterial infections NEC	7	5.7	6	4.4	4	3.2	3	2.2	4	3.3	4	3.0	5	4.1	4	3.0	2	1.6	2	1.5
- Candida infections	4	3.2	4	2.9	2	1.6	2	1.5	8	6.5	6	4.4	0	0.0	0	0.0	0	0.0	0	0.0
- Ear infections	4	3.2	4	2.9	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0
- Female reproductive tract infections	5	4.0	3	2.2	3	2.4	1	0.7	0	0.0	0	0.0	4	3.3	3	2.2	2	1.6	2	1.5
- Fungal infections NEC	7	5.7	5	3.6	9	7.2	5	3.7	8	6.5	5	3.7	14	11.4	10	7.4	6	4.9	5	3.7
• Fungal infection	4	3.2	2	1.5	7	5.6	4	2.9	5	4.1	3	2.2	4	3.3	4	3.0	1	0.8	1	0.7

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				141				140				132			
Exposure (patient-years)	126.9				130.2				132.6				126.3				120.3			
System Organ Class - **High Level Term** • **Preferred Term**	**#**	**Per 100**	**N**	**%**	**#**	**Per 100**	**N**	**%**	**#**	**Per 100**	**N**	**%**	**#**	**Per 100**	**N**	**%**	**#**	**Per 100**	**N**	**%**
- Influenza viral infections	9	7.3	7	5.1	10	8.0	8	5.9	4	3.3	4	3.0	6	4.9	6	4.4	2	1.6	2	1.5
• Influenza	9	7.3	7	5.1	10	8.0	8	5.9	4	3.3	4	3.0	6	4.9	6	4.4	2	1.6	2	1.5
- Lower respiratory tract and lung infections	6	4.9	6	4.4	8	6.4	8	5.9	6	4.9	5	3.7	6	4.9	6	4.4	4	3.3	4	3.0
• Bronchitis	6	4.9	6	4.4	5	4.0	5	3.7	4	3.3	3	2.2	4	3.3	4	3.0	4	3.3	4	3.0
- Tinea infections	0	0.0	0	0.0	3	2.4	3	2.2	0	0.0	0	0.0	2	1.6	2	1.5	0	0.0	0	0.0
- Upper respiratory tract infections	28	22.7	26	19.0	21	16.8	17	12.5	27	22.0	19	14.1	25	20.3	23	17.0	33	26.8	24	17.8
• Nasopharyngitis	11	8.9	11	8.0	7	5.6	6	4.4	8	6.5	6	4.4	13	10.6	11	8.1	12	9.8	9	6.7
• Otitis externa	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• Sinusitis	4	3.2	4	2.9	3	2.4	3	2.2	1	0.8	1	0.7	5	4.1	5	3.7	1	0.8	1	0.7
• Upper respiratory tract infection	10	8.1	8	5.8	6	4.8	5	3.7	14	11.4	11	8.1	2	1.6	2	1.5	14	11.4	13	9.6
- Urinary tract infections	23	18.6	16	11.7	29	23.2	20	14.7	19	15.4	14	10.4	26	21.1	23	17.0	16	13.0	15	11.1
• Urinary tract infection	22	17.8	16	11.7	26	20.8	18	13.2	16	13.0	11	8.1	22	17.9	19	14.1	14	11.4	13	9.6
- Viral infections NEC	1	0.8	1	0.7	4	3.2	4	2.9	2	1.6	2	1.5	5	4.1	4	3.0	0	0.0	0	0.0
Investigations	14	1.3	9	6.6	21	16.8	18	13.2	23	18.7	15	10.8	14	11.4	12	8.9	20	16.3	11	8.1
- Bacteria identification and serology (excl mycobacteria)	0	0.0	0	0.0	3	2.4	3	2.2	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8	1	0.7
- Digestive enzymes	2	1.6	2	1.5	4	3.2	4	2.9	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.7
• Lipase increased	2	1.6	2	1.5	4	3.2	4	2.9	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.7
- Liver function analyses	4	3.2	2	1.5	4	3.2	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	6	4.9	4	3.0
Metabolism and nutrition disorders	40	32.4	32	23.4	36	28.8	24	17.6	24	19.5	18	12.9	37	30.1	31	23.0	38	30.9	30	22.2
- Potassium imbalance	4	3.2	4	2.9	2	1.6	2	1.5	1	0.8	1	0.7	2	1.6	2	1.5	1	0.8	1	0.7
• Hypokalemia	4	3.2	4	2.9	2	1.6	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0
- Hyperglycemic conditions NEC	10	8.1	10	7.3	9	7.2	5	3.7	8	6.5	5	3.7	12	9.8	11	8.1	18	14.6	14	10.4
• Hyperglycemia	10	8.1	10	7.3	9	7.2	5	3.7	8	6.5	5	3.7	12	9.8	11	8.1	18	14.6	14	10.4
- Hyperlipidemia NEC	3	2.4	3	2.2	2	1.6	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.7
• Hyperlipidemia	3	2.4	3	2.2	2	1.6	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.7
- Lipid metabolism and deposit disorders NEC	13	10.5	12	8.8	10	8.0	10	7.4	4	3.3	4	3.0	9	7.3	9	6.7	4	3.3	4	3.0
• Dyslipidemia	12	9.7	11	8.0	9	7.2	9	6.6	4	3.3	4	3.0	9	7.3	9	6.7	3	2.4	3	2.2
Musculoskeletal and connective tissue disorders	31	25.1	23	16.8	39	31.2	25	18.4	34	27.6	21	15.1	39	31.7	26	19.3	25	20.3	22	16.3
- Intervertebral disc disorders NEC	1	0.8	1	0.7	3	2.4	3	2.2	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.7
• Arthralgia	6	4.9	5	3.6	9	7.2	8	5.9	7	5.7	6	4.4	9	7.3	7	5.2	7	5.7	7	5.2
- Joint related signs and symptoms	8	6.5	7	5.1	11	8.8	9	6.6	7	5.7	6	4.4	10	8.1	7	5.2	7	5.7	7	5.2
- Muscle related signs and symptoms NEC	5	4.0	4	2.9	2	1.6	2	1.5	0	0.0	0	0.0	3	2.4	3	2.2	2	1.6	2	1.5
• Muscle spasms	5	4.0	4	2.9	2	1.6	2	1.5	0	0.0	0	0.0	2	1.6	2	1.5	2	1.6	2	1.5

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				141				140				132			
Exposure (patient-years)	126.9				130.2				132.6				126.3				120.3			
System Organ Class – High Level Term • Preferred Term	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
- Musculoskeletal and connective tissue pain and discomfort	14	11.3	11	8.0	11	8.8	9	6.6	15	12.2	15	11.1	8	6.5	8	5.9	12	9.8	10	7.4
• Back pain	9	7.3	6	4.4	5	4.0	4	2.9	10	8.1	10	7.4	4	3.3	4	3.0	3	2.4	3	2.2
- Osteoarthropathies	1	0.8	1	0.7	4	3.2	4	2.9	4	3.3	4	3.0	4	3.3	4	3.0	1	0.8	1	0.7
• Osteoarthropathies	1	0.8	1	0.7	4	3.2	4	2.9	4	3.3	4	3.0	4	3.3	4	3.0	1	0.8	1	0.7
Renal and urinary disorders	26	21.0	16	11.7	16	12.8	15	11.0	18	14.6	16	11.5	12	9.8	10	7.4	17	13.8	13	9.6
- Bladder and urethral symptoms	10	8.1	7	5.1	7	5.6	6	4.4	4	3.3	4	3.0	5	4.1	4	3.0	7	5.7	5	3.7
• Dysuria	1	0.8	1	0.7	4	3.2	3	2.2	0	0.0	0	0.0	2	1.6	2	1.5	3	2.4	2	1.5
• Pollakiuria	7	5.7	5	3.6	3	2.4	3	2.2	3	2.4	3	2.2	1	0.8	1	0.7	2	1.6	2	1.5
- Urinary abnormalities	9	7.3	8	5.8	6	4.8	6	4.4	5	4.1	5	3.7	3	2.4	3	2.2	7	5.7	7	5.2
• Hematuria	7	5.7	6	4.4	3	2.4	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.7
- Urinary tract signs and symptoms NEC	5	4.0	4	2.9	2	1.6	2	1.5	5	4.1	4	3.0	2	1.6	2	1.5	3	2.4	3	2.2
• Polyuria	4	3.2	3	2.2	0	0.0	0	0.0	4	3.3	3	2.2	0	0.0	0	0.0	2	1.6	2	1.5
Skin and subcutaneous tissue disorders	22	17.8	16	11.7	24	19.2	11	8.1	14	11.4	10	7.2	6	4.9	6	4.4	3	2.4	2	1.5
- Apocrine and eccrine gland disorders	3	2.4	3	2.2	12	9.6	2	1.5	2	1.6	1	0.7	2	1.6	2	1.5	0	0.0	0	0.0
- Dermal and epidermal conditions NEC	3	2.4	3	2.2	1	0.8	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
- Dermatitis and eczema	3	2.4	3	2.2	5	4.0	4	2.9	1	0.8	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; # = number of events; per 100 = event rate per 100 patient-years; N = number of patients with event; % = percent of patients with event; NEC = not elsewhere classified; incl = including; excl = excluding
Source: Based on review up submitted datasets, information from the Applicant's Response to Information Request received on April 14, 2014, and information from Table 12.A.1: 2 of the study report for study 1275.1

Table 80: Treatment emergent adverse events reported in ≥ 2% of patients by preferred term and more commonly with the fixed dose combination that are not presented in Table 79 – treated set, metformin patients

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				141				140				132			
Exposure (patient-years)	126.9				130.2				132.6				126.3				120.3			
System Organ Class – High Level Term • Preferred Term	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
General disorders and administration site conditions																				
- Asthenic conditions	3	2.4	3	2.2	21	16.8	7	5.1	2	1.6	2	1.5	6	4.9	5	3.7	5	4.1	5	3.7
• Fatigue	1	0.8	1	0.7	8	6.4	4	2.9	1	0.8	1	0.7	3	2.4	3	2 2	5	4.1	5	3.7
- Feelings and sensations NEC	4	3.2	3	2.2	2	1.6	2	1.5	1	0.8	1	0.7	3	2.4	3	2 2	1	0.8	1	0.7

Injury, poisoning and procedural complications																				
- Limb injuries NEC (incl traumatic amputation)	1	0.8	1	0.7	3	2.4	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
- Muscle, tendon and ligament injuries	5	4.0	4	2.9	3	2.4	3	2.2	0	0.0	0	0.0	2	1.6	1	0.7	4	3.3	4	3.0
- Non-site specific injuries NEC	3	2.4	3	2.2	2	1.6	2	1.5	5	4.1	5	3.7	1	0.8	1	0.7	3	2.4	3	2.2
- Skin injuries NEC	2	1.6	2	1.5	5	4.0	3	2.2	5	4.1	4	3.0	0	0.0	0	0.0	1	0.8	1	0.7
Nervous system disorders																				
- Disturbances in consciousness NEC	0	0.0	0	0.0	3	2.4	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
- Headaches NEC	11	8.9	10	7.3	17	13.6	8	5.9	11	8.9	9	6.7	14	11.4	9	6.7	22	17.9	16	11.9
• Headache	11	8.9	10	7.3	15	12.0	8	5.9	9	7.3	8	5.9	14	11.4	9	6.7	22	17.9	16	11.9
- Neurological signs and symptoms NEC	8	6.5	7	5.1	5	4.0	3	2.2	4	3.3	4	3.0	5	4.1	5	3.7	7	5.7	6	4.4
• Dizziness	8	6.5	7	5.1	5	4.0	3	2.2	4	3.3	4	3.0	5	4.1	5	3.7	7	5.7	6	4.4
- Paresthesias and dysesthesias	1	0.8	1	0.7	8	6.4	4	2.9	1	0.8	1	0.7	0	0.0	0	0.0	2	1.6	2	1.5
- Sensory abnormalities NEC	3	2.4	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0
- Tremor (excl congenital)	0	0.0	0	0.0	9	7.2	3	2.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Reproductive system and breast disorders																				
- Cervix disorders NEC	3	2.4	3	2.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• Cervical dysplasia	3	2.4	3	2.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Penile and scrotal infections and inflammations	5	4.0	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• Balanitis	5	4.0	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Vulvovaginal signs and symptoms	2	1.6	2	1.5	4	3.2	3	2.2	1	0.8	1	0.7	2	1.6	2	1.5	0	0.0	0	0.0
• Vulvovaginal pruritus	2	1.6	2	1.5	3	2.4	3	2.2	1	0.8	1	0.7	2	1.6	2	1 5	0	0.0	0	0.0
Respiratory, thoracic and mediastinal disorders																				
- Coughing and associated symptoms	4	3.2	4	2.9	2	1.6	2	1.5	2	1.6	2	1.5	4	3.3	4	3.0	4	3.3	4	3.0
• Cough	4	3.2	4	2.9	2	1.6	2	1.5	2	1.6	2	1.5	3	2.4	3	2 2	4	3.3	4	3.0
- Upper respiratory tract signs and symptoms	1	0.8	1	0.7	6	4.8	4	2.9	2	1.6	2	1.5	2	1.6	2	1.5	3	2.4	2	1.5
Surgical and medical procedures																				
- Dental and gingival therapeutic procedures	5	4.0	3	2.2	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.7
• Tooth extraction	5	4.0	3	2.2	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0

Vascular disorders																				
- Vascular hypertensive disorders NEC	6	4.9	6	4.4	4	3.2	4	2.9	5	4.1	5	3.7	6	4.9	6	4.4	5	4.1	5	3.7
• Hypertension	6	4.9	6	4.4	4	3.2	4	2.9	5	4.1	5	3.7	6	4.9	6	4.4	5	4.1	5	3.7

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; # = number of events; per 100 = event rate per 100 patient-years; N = number of patients with event; % = percent of patients with event; NEC = not elsewhere classified; incl = including; excl = excluding
Source: Based on review up submitted datasets, information from the Applicant's Response to Information Request received on April 14, 2014, and information from Table 12.A.1: 2 of the study report for study 1275.1

7.5.2 Laboratory Findings

Specific laboratory tests of concern for the individual components that make up the FDC product include changes in electrolytes, hematocrit, lipids, and lipase. These will be discussed in this section. Additional laboratory findings of interest discussed elsewhere include changes in renal function (see 1.1.1.1 above), and changes in liver enzymes (see 1.1.1.2 above).

7.5.2.1 Electrolytes

Given the diuretic action of empagliflozin, there is concern for shifts in electrolytes as a result of treatment. Review of electrolyte changes from baseline did not reveal any notable changes in mean or median values for serum sodium, potassium, chloride, magnesium, calcium, phosphate, or bicarbonate. Similarly, no notable differences in categorical shifts were seen for serum sodium, potassium, chloride, magnesium, calcium, or phosphate. Consistent with what was observed in the empagliflozin development program there were downward categorical shifts in serum bicarbonate in the FDC and empagliflozin arms compared with the linagliptin arm (Table 81 and Table 82). This was more apparent in the treatment naïve patients. In the metformin treated patients, the most notable difference was seen for the FDC 25/5 arm in the percentage that started within the reference range but ended below the reference range. No acid-base disorder adverse events were reported during the study.

Table 81: Categorical shifts in serum bicarbonate – 52 weeks, treated set, metformin patients

		LVOT					
At baseline	**N**	**< LLRR**	**%**	**In RR**	**%**	**> ULRR**	**%**
FDC 25/5							
< LLRR	35	20	57.1	15	42.9	0	0.0
In RR	98	39	39.8	59	60.2	0	0.0
> ULRR	0	0	0.0	0	0.0	0	0.0
FDC 10/5							
< LLRR	38	17	44.7	21	55.3	0	0.0
In RR	95	23	24.2	72	75.8	0	0.0
> ULRR	1	1	100.0	0	0.0	0	0.0
Empa 25							
- < LLRR	40	25	62.5	15	37.5	0	0.0
- In RR	97	25	25.8	72	74.2	0	0.0
- > ULRR	1	0	0.0	1	100.0	0	0.0
Empa 10							
< LLRR	43	25	58.1	18	41.9	0	0.0
In RR	88	19	21.6	69	78.4	0	0.0
> ULRR	0	0	0.0	0	0.0	0	0.0

		LVOT					
At baseline	**N**	**< LLRR**	**%**	**In RR**	**%**	**> ULRR**	**%**
Lina 5							
< LLRR	34	22	64.7	12	35.3	0	0.0
In RR	90	19	21.1	71	78.9	0	0.0
> ULRR	1	0	0.0	1	100.0	0	0.0

LVOT = last value on treatment; LLRR = lower limit of reference range; RR = reference range; ULRR = upper limit of reference range; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Table 15.5.3.3.1: 3 of the study report from study 1275.1

Table 82: Categorical shifts in serum bicarbonate – 52 weeks, treated set, treatment naïve

		LVOT					
At baseline	**N**	**< LLRR**	**%**	**In RR**	**%**	**> ULRR**	**%**
FDC 25/5							
< LLRR	39	23	59.0	16	41.0	0	0.0
In RR	90	40	44.4	50	55.6	0	0.0
> ULRR	1	0	0.0	1	100.0	0	0.0
FDC 10/5							
< LLRR	41	27	65.9	14	34.1	0	0.0
In RR	89	42	47.2	47	52..8	0	0.0
> ULRR	2	0	0.0	2	100.0	0	0.0
Empa 25							
< LLRR	36	26	72.2	10	27.8	0	0.0
In RR	92	43	46.7	48	52.2	1	1.1
> ULRR	2	1	50.0	0	0.0	1	50.0
Empa 10							
< LLRR	44	22	50.0	22	50.0	0	0.0
In RR	83	29	34.9	54	65.1	0	0.0
> ULRR	1	0	0.0	1	100.0	0	0.0
Lina 5							
< LLRR	48	26	54.2	22	45.8	0	0.0
In RR	81	22	27.2	59	72.8	0	0.0
> ULRR	1	0	0.0	1	100.0	0	0.0

LVOT = last value on treatment; LLRR = lower limit of reference range; RR = reference range; ULRR = upper limit of reference range; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Table 15.4.3.3.1: 3 of the study report from study 1275.1

7.5.2.2 Lipase

Pancreatitis is an AE of concern with linagliptin and the other DPP4 inhibitors. The diagnosis of pancreatitis can be suggested by an elevation in pancreatic enzymes (i.e. amylase and lipase). Lipase is the more specific of the two, and changes in lipase with treatment could be considered a predictor for the development of pancreatitis. As discussed in 1.1.1.1, treatment with the FDC did not result in an increased incidence of clinical pancreatitis. While the PT "lipase increased" was reported more frequently in the FDC treated patients, the clinical significance of this is unclear.

Metformin patients:

Patients treated with the FDC had a greater increase in serum lipase levels compared to the respective empagliflozin dose. The increases were similar to those observed in the linagliptin treated patients. The percentage of patients with an upward categorical shift was similarly greater in the FDC treated patients than the respective empagliflozin dose. Again, this observation was similar to that seen in the linagliptin treated patients. Treatment with the FDC does not appear to result in more frequent of a greater increase in serum lipase compared to linagliptin, the component associated with increased lipase. This observation does not appear to be clinically significant given the absence a difference in reported pancreatitis (see section 1.1.1.1)

Table 83: Change in median serum lipase – 52 weeks, treated set, metformin patients

	Baseline			LVOT			Difference		
	Median	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	**Median**	**Q1**	**Q3**
FDC 25/5									
N = 133	99	75	123	112	88	155	11	-3	35
FDC 10/5									
N = 134	101	75	141	117	85	155	11	-3	35
Empa 25									
N = 138	99	67	125	99	69	125	3	-11	19
Empa 10									
N = 131	93	75	128	96	77	123	0	-13	16
Lina 5									
N = 125	99	69	133	107	77	144	8	-5	29

LVOT = last value on treatment; Q1 = 1st quartile; Q3 = 3rd quartile; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Lipase values reported in units/liter (U/L)
Source: Adapted from Table 15.5.3.3.1: 1 of the study report for study 1275.1

Table 84: Categorical shifts in serum lipase – 52 weeks, treated set, metformin patients

		LVOT					
At baseline	**N**	**< LLRR**	**%**	**In RR**	**%**	**> ULRR**	**%**
FDC 25/5							
< LLRR	0	0	0.0	0	0.0	0	0.0
In RR	121	0	0.0	102	84.3	19	15.7
> ULRR	12	0	0.0	1	8.3	11	91.7
FDC 10/5							
< LLRR	0	0	0.0	0	0.0	0	0.0
In RR	113	0	0.0	99	87.6	14	12.4
> ULRR	21	0	0.0	8	38.1	13	61.9
Empa 25							
< LLRR	0	0	0.0	0	0.0	0	0.0
In RR	117	0	0.0	112	95.7	5	4.3
> ULRR	21	0	0.0	11	52.4	10	47.6
Empa 10							
< LLRR	0	0	0.0	0	0.0	0	0.0

		LVOT					
At baseline	**N**	**< LLRR**	**%**	**In RR**	**%**	**> ULRR**	**%**
In RR	113	0	0.0	105	92.9	8	7.1
> ULRR	18	0	0.0	9	50.0	9	50.0
Lina 5							
< LLRR	0	0	0.0	0	0.0	0	0.0
In RR	107	0	0.0	91	85.0	16	15.0
> ULRR	18	0	0.0	11	61.1	7	38.9

LVOT = last value on treatment; LLRR = lower limit of reference range; RR = reference range; ULRR = upper limit of reference range; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Table 15.5.3.3.1: 3 of the study report from study 1275.1

Treatment naïve:

Patients treated with the FDC had a greater increase in serum lipase levels compared to the respective empagliflozin dose. The increases were similar to those observed in the linagliptin treated patients. The percentage of patients with an upward categorical shift was similarly greater in the FDC treated patients than the respective empagliflozin dose. This also appeared to be the case for the FDC when compared to linagliptin. Treatment with the FDC appears to result in a slightly more frequent increase in serum lipase, but not a greater increase in serum lipase compared to linagliptin, the component associated with increased lipase. This observation does not appear to be clinically significant given the absence a difference in reported pancreatitis (see section 1.1.1.1)

Table 85: Change in serum lipase – 52 weeks, treated set, treatment naïve

	Baseline			LVOT			Difference		
	Median	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	**Median**	**Q1**	**Q3**
FDC 25/5									
N = 130	85	67	109	91	75	123	8	-5	21
FDC 10/5									
N = 133	99	75	123	104	80	149	11	-3	29
Empa 25									
N = 130	95	72	123	99	72	123	3	-11	13
Empa 10									
N = 130	93	69	125	101	77	123	3	-11	16
Lina 5									
N = 130	85	67	115	104	69	125	11	0	21

LVOT = last value on treatment; Q1 = 1st quartile; Q3 = 3rd quartile; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Lipase values reported in units/liter (U/L)
Source: Adapted from Table 15.4.3.3.1: 1 of the study report for study 1275.1

Table 86: Categorical shifts in serum lipase – 52 weeks, treated set, treatment naïve

		LVOT					
At baseline	**N**	**< LLRR**	**%**	**In RR**	**%**	**> ULRR**	**%**
FDC 25/5							
< LLRR	0	0	0.0	0	0.0	0	0.0

		LVOT					
At baseline	**N**	**< LLRR**	**%**	**In RR**	**%**	**> ULRR**	**%**
In RR	123	0	0.0	109	88.6	14	11.4
> ULRR	7	0	0.0	2	28.6	5	71.4
FDC 10/5							
< LLRR	0	0	0.0	0	0.0	0	0.0
In RR	123	0	0.0	105	85.4	18	14.6
> ULRR	10	0	0.0	1	10.0	9	90.0
Empa 25							
< LLRR	0	0	0.0	0	0.0	0	0.0
In RR	110	0	0.0	102	92.7	8	7.3
> ULRR	20	0	0.0	11	55.0	9	45.0
Empa 10							
< LLRR	0	0	0.0	0	0.0	0	0.0
In RR	116	0	0.0	114	98.3	2	1.7
> ULRR	14	0	0.0	9	64.3	5	35.7
Lina 5							
< LLRR	0	0	0.0	0	0.0	0	0.0
In RR	121	0	0.0	111	91.7	10	8.3
> ULRR	9	0	0.0	7	77.8	2	22.2

LVOT = last value on treatment; LLRR = lower limit of reference range; RR = reference range; ULRR = upper limit of reference range; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Table 15.4.3.3.1: 3 of the study report from study 1275.1

7.5.2.3 Hematocrit

In the empagliflozin development program, increases in hematocrit were noted compared to placebo. No increase in thrombotic events was noted. Examining the FDC compared to empaliflozin and to linagliptin produced findings consistent with this observation.

Metformin patients:

Increases in median hematocrit were noted in the FDC treated patients (Table 87). This increase was similar in magnitude to that seen with empagliflozin treatment. The change in hematocrit was not seen in the linagliptin treated patients. This observation is further supported by the greater number of patients with upward categorical shifts in hematocrit from the FDC and empagliflozin arms (Table 88). As was seen in the empagliflozin development program, this was not accompanied by an increase in thrombotic complications. There was only one treatment emergent thrombotic event which was a pulmonary embolism in a patient treated with Empa 10. The clinical significance of this laboratory test observation is unknown.

Table 87: Change in hematocrit – 52 weeks, treated set, metformin patients

	Baseline			LVOT			Difference		
	Median	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	**Median**	**Q1**	**Q3**
FDC 25/5									
N = 133	41.7	38.8	44.5	47.3	43.8	50.2	5.7	2.8	7.1

	Baseline			LVOT			Difference		
	Median	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	**Median**	**Q1**	**Q3**
FDC 10/5									
N = 134	41.4	37.4	44.5	45.9	43.1	48.8	5.4	2.6	7.1
Empa 25									
N = 137	41.7	38.8	45.2	46.5	43.8	48.8	4.3	2.8	7.1
Empa 10									
N = 131	41.7	37.4	44.5	45.9	42.5	48.8	4.3	2.6	7.1
Lina 5									
N = 124	41.7	38.8	44.5	42.5	39.9	45.2	1.4	0.0	2.8

LVOT = last value on treatment; Q1 = 1st quartile; Q3 = 3rd quartile; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Hematocrit reported as %
Source: Adapted from Table 15.5.3.3.1: 1 of the study report for study 1275.1

Table 88: Categorical shifts in hematocrit – 52 weeks, treated set, metformin patient

		LVOT					
At baseline	**N**	**< LLRR**	**%**	**In RR**	**%**	**> ULRR**	**%**
FDC 25/5							
< LLRR	8	2	25.0	6	75.0	0	0.0
In RR	123	0	0.0	112	91.1	11	8.9
> ULRR	2	0	0.0	0	0.0	2	100.0
FDC 10/5							
< LLRR	16	3	18.8	12	75.0	1	6.3
In RR	117	2	1.7	110	94.0	5	4.3
> ULRR	1	0	0.0	0	0.0	1	100.0
Empa 25							
< LLRR	8	2	25.0	6	75.0	0	0.0
In RR	128	3	2.3	119	93.0	6	4.7
> ULRR	1	0	0.0	0	0.0	1	100.0
Empa 10							
< LLRR	11	1	9.1	10	90.9	0	0.0
In RR	120	1	0.8	112	93.3	7	5.8
> ULRR	0	0	0.0	0	0.0	0	0.0
Lina 5							
< LLRR	8	2	25.0	6	75.0	0	0.0
In RR	115	1	0.9	112	97.4	2	1.7
> ULRR	1	0	0.0	1	100.0	0	0.0

LVOT = last value on treatment; LLRR = lower limit of reference range; RR = reference range; ULRR = upper limit of reference range; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Table 15.5.3.3.1: 3 of the study report from study 1275.1

Treatment naïve:

Increases in median hematocrit were noted in the FDC treated patients (Table 89). This increase was similar in magnitude to that seen with empagliflozin treatment. The change in hematocrit was not seen in the linagliptin treated patients. This observation is further supported by the greater number of patients with upward categorical shifts in hematocrit from the FDC and empagliflozin arms (Table 90). As was seen in the empagliflozin development program, this was

not accompanied by an increase in thrombotic complications. There was only one treatment emergent thrombotic event which was a left knee thrombosis in a patient treated with FDC 25/5. The clinical significance of this laboratory test observation is unknown.

Table 89: Change in hematocrit – 52 weeks, treated set, treatment naïve

	Baseline			LVOT			Difference		
	Median	**Q1**	**Q3**	**Median**	**Q1**	**Q3**	**Median**	**Q1**	**Q3**
FDC 25/5									
N = 130	43.1	40.3	45.9	47.3	43.1	51.6	4.3	1.4	7.1
FDC 10/5									
N = 133	44.5	41.2	47.3	47.8	44.5	51.6	4.3	2.8	7.1
Empa 25									
N = 130	43.1	39.9	45.9	48.8	45.2	51.6	5.7	2.7	7.1
Empa 10									
N = 127	44.5	40.3	47.8	48.8	44.5	51.7	4.3	2.8	7.1
Lina 5									
N = 130	43.1	40.3	45.9	44.5	41.7	47.8	1.4	0.0	2.8

LVOT = last value on treatment; Q1 = 1st quartile; Q3 = 3rd quartile; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Hematocrit reported as %
Source: Adapted from Table 15.4.3.3.1: 1 of the study report for study 1275.1

Table 90: Categorical shifts in hematocrit – 52 weeks, treated set, treatment naïve

		LVOT					
At baseline	**N**	**< LLRR**	**%**	**In RR**	**%**	**> ULRR**	**%**
FDC 25/5							
< LLRR	8	1	12.5	6	7.0	1	12.5
In RR	120	0	0.0	107	89.2	13	10.8
> ULRR	2	0	0.0	0	0.0	2	100.0
FDC 10/5							
< LLRR	6	1	16.7	5	83.3	0	0.0
In RR	124	0	0.0	112	90.3	12	9.7
> ULRR	3	0	0.0	1	33.3	2	66.7
Empa 25							
< LLRR	7	2	28.6	5	71.4	0	0.0
In RR	119	0	0.0	107	89.9	12	10.1
> ULRR	4	0	0.0	1	25.0	3	75.0
Empa 10							
< LLRR	4	0	0.0	4	100.0	0	0.0
In RR	119	0	0.0	101	84.9	18	15.1
> ULRR	4	0	0.0	2	50.0	2	50.0
Lina 5							
< LLRR	7	1	14.3	5	71.4	1	14.3
In RR	120	2	1.7	117	97.5	1	0.8
> ULRR	3	0	0.0	1	33.3	2	66.7

LVOT = last value on treatment; LLRR = lower limit of reference range; RR = reference range; ULRR = upper limit of reference range; FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin
Source: Adapted from Table 15.4.3.3.1: 3 of the study report from study 1275.1

7.5.2.4 Lipids

Dyslipidemia is often seen in conjunction with diabetes mellitus, and is a risk factor for cardiovascular disease. Additionally, changes in lipid parameters were observed with the SGLT2 inhibitors.

Metformin patients:

Compared to linagliptin, treatment with the FDC led to slight increases in total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C) (Table 91). Only one comparison met nominal statistical significance. That was the comparison between FDC 25/5 and Lina 5 for HDL. The clinical significance of this is not known.

Treatment naïve:

Compared to linagliptin, treatment with the FDC led to slight increases in TC, HDL-C, and LDL-C (Table 92). There were three between treatment comparisons with nominal statistical significant. These were in change in TC for FDC 25/5 versus Lina 5, and change in HDL-C for both doses of the FDC versus Lina 5. The clinical significance of this is not known.

Table 91: Change in lipid parameters – 52 weeks, treated set, metformin patients

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	135		133		141		139		131	
	mg/dL	SE	mg/dL	SE	mg/dL	SE	mg/dL	SE	mg/dL	SE
Total cholesterol										
Mean baseline	177.71	3.34	175.7	3.41	185.54	3.78	185.73	3.53	184.36	3.93
Adj mean at 52 weeks	187.98	2.89	185.56	2.91	186.97	2.83	188.46	2.85	183.37	2.93
Adj mean change from baseline	6.11	2.89	3.7	2.91	5.1	2.83	6.59	2.85	1.5	2.93
Vs. empagliflozin[1]										
– Adj mean difference	1.01	4.05	-2.9	4.08						
– p-value	0.8029		0.4778							
Vs. linagliptin										
– Adj mean difference	4.61	4.12	2.19	4.14						
– p-value	0.2637		0.5962							
HDL-C										
Mean baseline	47.82	1.07	45.78	0.93	47.56	1.1	46.57	1.07	46.77	0.98
Adj mean at 52 weeks	50.73	0.61	49.87	0.61	51.22	0.59	49.99	0.6	48.19	0.61
Adj mean change from baseline	3.82	0.61	2.97	0.61	4.31	0.59	30.9	0.6	1.28	0.61
Vs. empagliflozin[1]										
– Adj mean difference	-0.49	0.85	-0.12	0.85						
– p-value	0.5639		0.8902							
Vs. linagliptin										
– Adj mean difference	2.54	0.86	1.69	0.87						
– p-value	0.0033		0.0517							
LDL-C										
Mean baseline	99.5	2.85	97.49	3.12	101.04	2.85	104.41	3.16	104.2	3.55
Adj mean at 52 weeks	104.55	2.47	102.84	2.48	104.4	2.41	104.9	2.43	101.54	2.5
Adj mean change from baseline	3.22	2.47	1.51	2.48	3.07	2.41	3.56	2.43	0.2	2.5
Vs. empagliflozin[1]										
– Adj mean difference	0.15	3.45	-2.05	3.48						
– p-value	0.9653		0.5550							
Vs. linagliptin										
– Adj mean difference	3.01	3.52	1.31	3.53						
– p-value	0.3914		0.7116							

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	135		133		141		139		131	
	mg/dL	**SE**	**mg/dL**	**SE**	**mg/dL**	**SE**	**mg/dL**	**SE**	**mg/dL**	**SE**
Triglycerides										
Mean baseline	154.5	6.51	163.28	6.86	189.87	14.43	178.38	8.1	170.21	7.61
Adj mean at 52 weeks	161.51	6.84	170.96	6.88	161.91	6.7	176.07	6.73	172.23	6.93
Adj mean change from baseline	-9.98	6.84	-0.52	6.88	-9.58	6.7	4.58	6.73	0.74	6.93
Vs. empagliflozin[1]										
– Adj mean difference	-0.4	9.6	-5.11	9.63						
– p-value	0.9668		0.5959							
Vs. linagliptin										
– Adj mean difference	-10.72	9.74	-1.26	9.76						
– p-value	0.2713		0.8970							

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; SE = standard error; Adj = adjusted; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol
[1] compared with the respective dose of empagliflozin
Source: Adapted from Tables 15.5.3.3.4.1: 1, 15.5.3.3.4.2: 1, 15.5.3.3.4.3: 1, and 15.5.3.3.4.6: 1 of the study report for study 1275.1

Table 92: Change in lipid parameters – 52 weeks, treated set, treatment naïve

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	132		134		134		130		133	
	mg/dL	**SE**	**mg/dL**	**SE**	**mg/dL**	**SE**	**mg/dL**	**SE**	**mg/dL**	**SE**
Total cholesterol										
Mean baseline	191.36	4.17	195.22	4.07	190.13	3.56	197.47	3.74	193.91	5.12
Adj mean at 52 weeks	197.04	2.65	194.78	2.63	199.90	2.63	200.00	2.67	189.21	2.64
Adj mean change from baseline	3.44	2.65	1.18	2.63	6.30	2.63	6.40	2.67	-4.39	2.64
Vs. empagliflozin[1]										
– Adj mean difference	-2.87	3.73	-5.22	3.74						
– p-value	0.4425		0.1636							
Vs. linagliptin										
– Adj mean difference	7.83	3.74	5.57	3.72						
– p-value	0.0364		0.1350							
HDL-C										
Mean baseline	45.51	1.04	43.10	0.91	45.59	1.16	45.33	0.93	45.15	1.00
Adj mean at 52 weeks	48.45	0.60	48.89	0.59	49.73	0.59	48.33	0.60	46.01	0.59
Adj mean change from baseline	3.52	0.60	3.95	0.59	4.80	0.59	3.40	0.60	1.08	0.59

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	132		134		134		130		133	
	mg/dL	**SE**	**mg/dL**	**SE**	**mg/dL**	**SE**	**mg/dL**	**SE**	**mg/dL**	**SE**
Vs. empagliflozin[1]										
– Adj mean difference	-1.28	0.84	0.56	0.84						
– p-value	0.1261		0.5072							
Vs. linagliptin										
– Adj mean difference	2.44	0.84	2.88	0.84						
– p-value	0.0039		0.0006							
LDL-C										
Mean baseline	112.31	3.65	116.57	3.50	111.28	2.95	114.60	2.83	112.64	3.21
Adj mean at 52 weeks	114.36	2.16	111.45	2.15	115.30	2.14	114.28	2.18	110.03	2.15
Adj mean change from baseline	0.88	2.16	-2.03	2.15	1.82	2.14	0.80	2.18	-3.45	2.15
Vs. empagliflozin[1]										
– Adj mean difference	-0.93	3.04	-2.83	3.05						
– p-value	0.7587		0.3548							
Vs. linagliptin										
– Adj mean difference	4.34	3.05	1.43	3.04						
– p-value	0.1554		0.6386							
Triglycerides										
Mean baseline	173.39	9.85	184.37	9.64	176.15	9.93	200.44	12.78	187.32	26.45
Adj mean at 52 weeks	178.24	8.34	183.28	8.28	176.83	8.27	197.54	8.41	170.91	8.31
Adj mean change from baseline	-6.03	8.34	-0.99	8.28	-7.44	8.27	13.27	8.41	-13.36	8.31
Vs. empagliflozin[1]										
– Adj mean difference	1.41	11.74	-14.26	11.80						
– p-value	0.9045		0.2273							
Vs. linagliptin										
– Adj mean difference	7.33	11.77	12.37	11.72						
– p-value	0.5336		0.2917							

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; SE = standard error; Adj = adjusted; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol

[1] compared with the respective dose of empagliflozin

Source: Adapted from Tables 15.4.3.3.4.1: 1, 15.4.3.3.4.2: 1, 15.4.3.3.4.3: 1, and 15.4.3.3.4.6: 1 of the study report for study 1275.1

7.5.3 Vital Signs

Vitals signs measured as part of this study included heart rate (HR), BP, and weight. Changes in BP and weight were considered as secondary efficacy endpoints. These are discussed in 6.2.6.1 and 6.2.5.2, respectively.

Metformin patients:

Changes in HR (Table 93) were small in all of the treatment arms at 24 weeks, with all arms showing a < 1 beat per minute (bpm) changes. There was no consistency in the direction of change. At 52 weeks, similar observations were seen, though the Empa 25and Lina 5 arms had changes in HR > 1 bpm but < 2 bpm. These changes are unlikely to be clinically significant.

Table 93: Changes in heart rate – treated set, metformin patients

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	**137**		**136**		**141**		**140**		**132**	
	bpm	**SE**	**bpm**	**SE**	**bpm**	**SE**	**bpm**	**SE**	**bpm**	**SE**
Mean baseline	**73.2**	**0.83**	**72.28**	**0.77**	**73.87**	**0.8**	**73.57**	**0.87**	**73.76**	**0.91**
24 weeks										
Mean at week 24	73.6	0.84	71.36	0.76	74.47	0.83	74.4	0.87	73.55	0.78
Change in mean	0.66	0.76	-0.73	0.65	0.64	0.73	0.44	0.84	-0.13	0.82
52 weeks										
Mean at week 52	72.47	0.97	71.93	0.79	75.02	0.99	74.19	0.94	74.22	0.95
Change in mean	-0.45	0.84	-0.11	0.70	1.24	0.81	0.24	0.89	1.41	0.79

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; bpm = beats per minute; SE = standard error
Source: Adapted from Tables 15.2.3.4: 1 and 15.5.3.4: 1 of the study report for study 1275.1

Treatment naïve:

Changes in HR (Table 94) were small in all of the treatment arms at 24 weeks, with all arms showing a < 2 bpm change. There was no consistency in the direction of change. At 52 weeks, similar observations were seen.

These changes are unlikely to be clinically significant.

Table 94: Changes in heart rate – treated set, treatment naïve

	FDC 25/5		FDC 10/5		Empa 25		Empa 10		Lina 5	
Number of patients	**136**		**136**		**135**		**135**		**135**	
	bpm	**SE**	**bpm**	**SE**	**bpm**	**SE**	**bpm**	**SE**	**bpm**	**SE**
Mean baseline	**72.25**	**0.77**	**70.91**	**0.85**	**72.75**	**0.87**	**73.84**	**0.75**	**71.47**	**0.86**
24 weeks										
Mean at week 24	73.11	0.78	72.00	0.89	72.74	0.97	71.95	0.75	72.80	0.82
Change in mean	1.12	0.75	1.01	0.84	-0.28	0.76	-1.85	0.81	1.46	0.94
52 weeks										
Mean at week 52	72.27	0.91	70.97	0.96	72.59	1.01	72.00	0.87	72.04	0.96
Change in mean	0.15	0.83	0.24	0.88	-0.38	0.80	-1.33	0.79	1.28	0.87

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; bpm = beats per minute; SE = standard error
Source: Adapted from Tables 15.1.3.4: 1 and 15.4.3.4: 1 of the study report for study 1275.1

7.5.4 Electrocardiograms

See the previously completed reviews of the individual components for discussion of electrocardiogram changes. A thorough QT study was not performed as part of this NDA.

7.5.5 Special Safety Studies/Clinical Trials

No special safety studies were performed to support this NDA. There are ongoing cardiovascular outcomes trials for both on the components of the FDC.

7.5.6 Immunogenicity

Not applicable.

7.6 Other Safety Explorations

7.6.1 Dose Dependency for Adverse Events

There was no evident dose dependency for adverse events based on review of the data from study 1275.1. See the previously completed reviews for the individual components for additional discussion of dose dependency for adverse events.

7.6.2 Time Dependency for Adverse Events

Time to onset of the first urinary tract infection and first genital infection are discussed in 7.4.5.2 above and 7.4.5.3 above. The Applicant also examined the time to the first confirmed hypoglycemic event. This is discussed in 7.4.5.1 above. No other exploration for time dependency was performed.

7.6.3 Drug-Demographic Interactions

No assessment of drug-demographic interaction was performed by the Applicant. As discussed in 6.2.7 above, the overall small numbers for subpopulations limits the value of subpopulation

analyses. See the previously completed reviews for the individual components for additional discussion of drug-demographic interactions for adverse events.

7.6.4 Drug-Disease Interactions

No specific exploration for drug-disease interaction was performed as part of this NDA submission. See the previously completed reviews for the individual components for additional discussion of drug-disease interactions for adverse events.

7.6.5 Drug-Drug Interactions

As discussed in 4.4.2 above, addition of empagliflozin did not affect the DPP4 inhibitory activity of linagliptin, but the addition of linagliptin resulted in a decrease in renal glucose excretion. See the dedicated Clinical Pharmacology review for this NDA as well as the previously completed reviews for the individual components for detailed discussion of drug-drug interaction.

7.7 Additional Safety Evaluations

7.7.1 Human Carcinogenicity

See 1.1.1.1 for discussion of malignancies.

7.7.2 Human Reproduction and Pregnancy Data

There was one patient with a reported pregnancy after exposure to study drug in the study. This patient came from the treatment naïve population, and was treated with FDC 25/5. This 26 year old was treated with FDC 25/5 for 90 days before discontinuation of study drug. She had a negative urine pregnancy test on day (b) (6) days after discontinuation of study drug), she delivered a normal male infant at 39 weeks gestation.

There is no other information on use of the FDC product during pregnancy.

7.7.3 Pediatrics and Assessment of Effects on Growth

Not applicable. No pediatric patients were enrolled in this study. Neither of the components has completed any trials in pediatric patients or assessed the effect on growth.

7.7.4 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

There is little concern for overdose, drug abuse, withdrawal, or rebound.

7.8 Additional Submission/Safety Issues

8. Post marketing Experience

The FDC of empagliflozin/linagliptin is not approved. There is no post marketing experience with the FDC product. While linagliptin is approved, empagliflozin was not approved at the time of NDA submission. Use of the combination of the two components is not known to have occurred outside of the setting of clinical trials.

9. Appendices

9.1 Labeling Recommendations

Given the equivocal efficacy findings for the treatment naïve population, (b) (4) and that there remains some uncertainty whether using the FDC offers any benefit over the use of empagliflozin alone in this setting. Other recommendations include (b) (4)

9.2 Advisory Committee Meeting

Not applicable. No Advisory Committee Meeting was held prior to completion of this review.

9.3 Financial Disclosures Template(s)

Clinical Investigator Financial Disclosure
Review Template

Application Number: NDA-206073

Submission Date(s): January 30, 2014

Applicant: Boehringer Ingelheim

Product: Empagliflozin/Linagliptin Fixed Dose Combination

Reviewer: William H. Chong

Date of Review: February 28, 2014

Covered Clinical Study (Name and/or Number):
Study 1275.1: A phase 3 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 and insufficient glycemic control

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 940		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		

If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

The Applicant has submitted a list of 940 investigators that participated in study 1275.1. There were 40 investigators for whom the Applicant is unable to provide certification of an absence of financial arrangements. None of these investigators enrolled any patients, and none were in contact with any patients.

This information is not likely to influence the outcome of the study or affect the review of the NDA.

There has been adequate disclosure of financial arrangements and interests for the investigators that participated in study 1275.1.

9.4 Lists of preferred terms

Table 95: List of preferred terms used in the urinary tract infection CMQ

Genitourinary tract infection	Tuberculosis of genitourinary system	Emphysematous cystitis
Urogenital infection fungal	Tuberculosis ureter	Asymptomatic bacteriuria
Urogenital infection bacterial	Urethral abscess	Adenoviral hemorrhagic cystitis
Bacteriuria	Urethral papilloma	Bladder candidiasis
Bacteriuria in pregnancy	Urethral stricture post infection	Renal cyst infection
Cystitis	Urethritis	Viral hemorrhagic cystitis
Cystitis escherichia	Urethritis chlamydial	Bacterial pyelonephritis
Cystitis gonococcal	Urethritis gonococcal	Genitourinary tract gonococcal infection
Cystitis hemorrhagic	Urethritis trichomonal	Ureter abscess
Cystitis klebsiella	Urethritis ureaplasmal	Urinary tract infection pseudomonal
Cystitis pseudomonal	Urinary tract infection	Urinary tract infection staphylococcal
Fungal cystitis	Urinary tract infection enterococcal	Urinary tract infection viral
Genitourinary chlamydia infection	Urinary tract infection neonatal	Cystitis viral
Kidney infection	Urogenital trichomoniasis	Cystitis bacterial
Perinephric abscess	Urosepsis	Cystitis helminthic
Pyelonephritis	Urinary tract infection fungal	Pyelonephritis viral
Pyelonephritis acute	Pyelocystitis	Pyelonephritis fungal
Pyelonephritis chronic	Candiduria	Urinary tract abscess
Pyelonephritis mycoplasmal	Ureteritis	Emphysematous pyelonephritis
Pyonephrosis	Cytomegalovirus urinary tract infection	Streptococcal urinary tract infection
Renal abscess	Urinary bladder abscess	Acute focal bacterial nephritis
Renal syphilis	Escherichia urinary tract infection	Perinephritis
Renal tuberculosis	Urethral carbuncle	
Tuberculosis bladder	Urinary tract infection bacterial	

Table 96: List of preferred terms used in the genital infections CMQ

Balanitis	Vulval abscess	Genitourinary tract infection
Balanitis candida	Vulval cellulitis	Penile infection
Balanoposthitis	Vulvitis	Genital infection female
Bartholin’s abscess	Vulvovaginal candidiasis	Scrotal infection
Bartholinitis	Vulvovaginitis	Vaginitis bacterial
Cervicitis	Genital infection	Uterine infection
Cervicitis cystic	Clitoris abscess	Genital abscess
Endometritis	Scrotal abscess	Genital infection male
Epididymitis	Vaginal abscess	Parametric abscess
Genital candidiasis	Salpingo−oophoritis	Uterine abscess
Hydrocele male infected	Fallopian tube abscess	Spermatic cord funiculitis
Oophoritis	Prostate infection	Testicular abscess
Orchitis	Erosive balanitis	Vulvovaginal mycotic infection
Ovarian abscess	Myometritis	Cellulitis of male external genital organ
Parametritis	Prostatovesiculitis	Genital infection viral

Pelvic abscess	Vaginal cellulitis	Urogenital infection fungal
Pelvic inflammatory disease	Perineal abscess	Urogenital infection bacterial
Pelvic inflammatory disease mycoplasmal	Escherichia vaginitis	Vulvovaginal human papilloma virus infection
Penile abscess	Tubo−ovarian abscess	Perineal infection
Posthitis	Ovarian infection	Vulvovaginitis streptococcal
Prostatic abscess	Intrauterine infection	Cervicitis streptococcal
Prostatitis	Rectovaginal septum abscess	Prostatitis Escherichia coli
Pyometra	Ovarian bacterial infection	Cytolytic vaginosis
Salpingitis	Epididymal infection	Balanoposthitis infective
Scrotal gangrene	Seminal vesicular infection	Gangrenous balanitis
Seminal vesiculitis	Pelvic infection	Bacterial prostatitis
Toxic shock syndrome staphylococcal	Vaginitis viral	Candida cervicitis
Toxic shock syndrome streptococcal	Pelvic sepsis	Pyospermia
Vaginal infection	Genital infection bacterial	Genital herpes zoster
Vaginitis gardnerella	Genital infection fungal	

9.5 Reviewer generated adverse event tables

Table 97: Incidence of treatment emergent adverse events by system organ class – treated set, metformin patients

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	**137**				**136**				**141**				**140**				**132**			
Exposure (patient-years)	**126.9**				**130.2**				**132.6**				**126.3**				**120.3**			
System Organ Class	**#**	**Per 100**	**N**	**%**	**#**	**Per 100**	**N**	**%**	**#**	**Per 100**	**N**	**%**	**#**	**Per 100**	**N**	**%**	**#**	**Per 100**	**N**	**%**
Blood and lymphatic system disorders	3	2.4	3	2.2	3	2.3	3	2.2	3	2.3	3	2.1	2	1.6	2	1.4	4	3.3	4	3.0
Cardiac disorders	8	6.3	5	3.6	5	3.8	5	3.7	2	1.5	2	1.4	5	4.0	3	2.1	7	5.8	6	4.5
Congenital, familial and genetic disorders	1	0.8	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0
Ear and labyrinth disorders	2	1.6	2	1.5	1	0.8	1	0.7	7	5.3	4	2.8	2	1.6	2	1.4	4	3.3	4	3.0
Endocrine disorders	0	0.0	0	0.0	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.7	2	1.7	2	1.5
Eye disorders	6	4.7	6	4.4	12	9.2	5	3.7	8	6.0	8	5.7	4	3.2	4	2.9	5	4.2	4	3.0
Gastrointestinal disorders	41	32.3	25	18.2	56	43.0	34	25.0	39	29.4	26	18.4	28	22.2	23	16.4	40	33.3	23	17.4
General disorders and administration site conditions	14	11.0	12	8.8	11	8.4	9	6.6	16	12.1	11	7.8	6	4.8	6	4.3	14	11.6	11	8.3
Hepatobiliary disorders	2	1.6	2	1.5	2	1.5	2	1.5	0	0.0	0	0.0	3	2.4	3	2.1	4	3.3	3	2.3
Immune system disorders	1	0.8	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0	3	2.4	3	2.1	1	0.8	1	0.8
Infections and infestations	93	73.3	53	38.7	98	75.3	57	41.9	117	88.2	53	37.6	110	87.1	60	42.9	115	95.6	57	43.2
Injury, poisoning and procedural complications	14	11.0	11	8.0	19	14.6	16	11.8	21	15.8	15	10.6	18	14.3	10	7.1	9	7.5	8	6.1
Investigations	17	13.4	14	10.2	10	7.7	8	5.9	23	17.3	18	12.8	15	11.9	11	7.9	18	15.0	15	11.4
Metabolism and nutrition disorders	22	17.3	14	10.2	23	17.7	18	13.2	29	21.9	25	17.7	21	16.6	16	11.4	37	30.8	24	18.2
Musculoskeletal and connective tissue disorders	24	18.9	18	13.1	43	33.0	26	19.1	36	27.1	24	17.0	34	26.9	23	16.4	38	31.6	27	20.5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6	4.7	6	4.4	1	0.8	1	0.7	6	4.5	5	3.5	5	4.0	4	2.9	4	3.3	2	1.5
Nervous system disorders	25	19.7	20	14.6	38	29.2	19	14.0	35	26.4	22	15.6	24	19.0	21	15.0	21	17.5	17	12.9
Psychiatric disorders	8	6.3	6	4.4	8	6.1	6	4.4	3	2.3	2	1.4	10	7.9	8	5.7	10	8.3	7	5.3
Renal and urinary disorders	13	10.2	10	7.3	7	5.4	5	3.7	17	12.8	14	9.9	11	8.7	9	6.4	12	10.0	8	6.1
Reproductive system and breast disorders	7	5.5	5	3.6	8	6.1	6	4.4	13	9.8	11	7.8	8	6.3	6	4.3	2	1.7	2	1.5
Respiratory, thoracic and mediastinal disorders	12	9.5	11	8.0	17	13.1	12	8.8	14	10.6	12	8.5	12	9.5	8	5.7	8	6.7	6	4.5

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				141				140				132			
Exposure (patient-years)	126.9				130.2				132.6				126.3				120.3			
System Organ Class	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
Skin and subcutaneous tissue disorders	12	9.5	8	5.8	13	10.0	12	8.8	10	7.5	9	6.4	11	8.7	11	7.9	9	7.5	9	6.8
Surgical and medical procedures	2	1.6	2	1.5	1	0.8	1	0.7	2	1.5	2	1.4	1	0.8	1	0.7	1	0.8	1	0.8
Vascular disorders	10	7.9	9	6.6	6	4.6	4	2.9	5	3.8	5	3.5	8	6.3	8	5.7	11	9.1	11	8.3

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; # = number of events; per 100 = event rate per 100 patient-years; N = number of patients with event; % = percent of patients with event
Source: Based on review up submitted datasets, information from the Applicant's Response to Information Request received on April 14, 2014, and information from Table 12.A.1: 2 of the study report for study 1275.1

Table 98: Incidence of treatment emergent adverse events by high level term reported by > 1 patient in either fixed dose combination arm – treated set, metformin patients

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				141				140				132			
Exposure (patient-years)	126.9				130.2				132.6				126.3				120.3			
System Organ Class - High Level Term	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
Blood and lymphatic system disorders																				
– Thrombocytopenias	0	0.0	0	0.0	2	1.5	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Cardiac disorders																				
– Cardiac signs and symptoms NEC	0	0.0	0	0.0	2	1.5	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8	1	0.8
– Ischemic coronary artery disorders	3	2.4	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	2	1.6	2	1.4	1	0.8	1	0.8
– Myocardial disorders NEC	3	2.4	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
– Supraventricular arrhythmias	2	1.6	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0	2	1.7	2	1.5
Eye disorders																				
– Conjunctival infections, irritations and inflammations	2	1.6	2	1.5	2	1.5	2	1.5	3	2.3	3	2.1	3	2.4	3	2.1	2	1.7	2	1.5
– Iris and ciliary body structural change, deposit and degeneration	0	0.0	0	0.0	2	1.5	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
– Visual disorders NEC	1	0.8	1	0.7	3	2.3	1	0.7	2	1.5	2	1.4	0	0.0	0	0.0	0	0.0	0	0.0
Gastrointestinal disorders																				
– Colitis (excl infective)	1	0.8	1	0.7	3	2.3	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0
– Dental pain and sensation disorders	0	0.0	0	0.0	3	2.3	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.8
– Diarrhea (excl infective)	5	3.9	4	2.9	12	9.2	10	7.4	7	5.3	5	3.5	6	4.8	6	4.3	1	0.8	1	0.8
– Dyspeptic signs and symptoms	4	3.2	4	2.9	1	0.8	1	0.7	7	5.3	7	5.0	1	0.8	1	0.7	5	4.2	5	3.8
– Gastrointestinal and abdominal pains (excl oral and throat)	7	5.5	4	2.9	7	5.4	5	3.7	4	3.0	4	2.8	1	0.8	1	0.7	5	4.2	5	3.8

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				141				140				132			
Exposure (patient-years)	126.9				130.2				132.6				126.3				120.3			
System Organ Class - High Level Term	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
– Gastrointestinal atonic and hypomotility disorders NEC	10	7.9	9	6.6	10	7.7	9	6.6	4	3.0	4	2.8	7	5.5	5	3.6	3	2.5	3	2.3
– Gastrointestinal disorders NEC	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
– Hemorrhoids and gastrointestinal varices (excl esophageal)	1	0.8	1	0.7	3	2.3	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
– Nausea and vomiting symptoms	6	4.7	5	3.6	8	6.1	6	4.4	9	6.8	7	5.0	3	2.4	2	1.4	6	5.0	5	3.8
General disorders and administration site conditions																				
– Asthenic conditions	6	4.7	6	4.4	6	4.6	6	4.4	5	3.8	2	1.4	2	1.6	2	1.4	1	0.8	1	0.8
– Edema NEC	2	1.6	2	1.5	0	0.0	0	0.0	6	4.5	6	4.3	2	1.6	2	1.4	2	1.7	2	1.5
– Pain and discomfort NEC	4	3.2	4	2.9	3	2.3	3	2.2	3	2.3	3	2.1	2	1.6	2	1.4	6	5.0	6	4.5
Hepatobiliary disorders																				
– Hepatocellular damage and hepatitis NEC	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	3	2.4	3	2.1	1	0.8	1	0.8
Infections and infestations																				
– Abdominal and gastrointestinal infections	9	7.1	8	5.8	4	3.1	4	2.9	4	3.0	3	2.1	3	2.4	2	1.4	5	4.2	4	3.0
– Bacterial infections NEC	2	1.6	2	1.5	3	2.3	2	1.5	3	2.3	3	2.1	2	1.6	2	1.4	3	2.5	3	2.3
– Dental and oral soft tissue infections	6	4.7	5	3.6	2	1.5	2	1.5	8	6.0	5	3.5	3	2.4	3	2.1	6	5.0	6	4.5
– Female reproductive tract infections	1	0.8	1	0.7	6	4.6	4	2.9	2	1.5	2	1.4	2	1.6	1	0.7	1	0.8	1	0.8
– Fungal infections NEC	1	0.8	1	0.7	8	6.1	7	5.1	10	7.5	8	5.7	5	4.0	4	2.9	4	3.3	4	3.0
– Giardia infections	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
– Infections NEC	4	3.2	3	2.2	2	1.5	2	1.5	3	2.3	3	2.1	1	0.8	1	0.7	1	0.8	1	0.8
– Influenza viral infections	1	0.8	1	0.7	2	1.5	2	1.5	6	4.5	5	3.5	10	7.9	9	6.4	9	7.5	7	5.3
– Lower respiratory tract and lung infections	5	3.9	4	2.9	5	3.8	5	3.7	8	6.0	7	5.0	9	7.1	8	5.7	7	5.8	6	4.5
– Skin structures and soft tissue infections	3	2.4	3	2.2	2	1.5	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.8
– Tinea infections	0	0.0	0	0.0	2	1.5	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8	1	0.8
– Upper respiratory tract infections	31	24.4	23	16.8	40	30.7	32	23.5	26	19.6	21	14.9	33	26.1	27	19.3	39	32.4	24	18.2
– Urinary tract infections	20	15.8	16	11.7	17	13.1	13	9.6	34	25.6	24	17.0	20	15.8	16	11.4	27	22.4	19	14.4
– Viral infections NEC	7	5.5	7	5.1	2	1.5	2	1.5	3	2.3	3	2.1	6	4.8	6	4.3	2	1.7	2	1.5
Injury, poisoning and procedural complications																				
– Fractures and dislocations NEC	0	0.0	0	0.0	2	1.5	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
– Lower limb fractures and dislocations	1	0.8	1	0.7	2	1.5	2	1.5	3	2.3	2	1.4	0	0.0	0	0.0	0	0.0	0	0.0

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				141				140				132			
Exposure (patient-years)	126.9				130.2				132.6				126.3				120.3			
System Organ Class - High Level Term	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
– Muscle, tendon and ligament injuries	4	3.2	3	2.2	4	3.1	4	2.9	3	2.3	2	1.4	0	0.0	0	0.0	2	1.7	2	1.5
– Non-site specific injuries NEC	3	2.4	3	2.2	5	3.8	5	3.7	5	3.8	5	3.5	7	5.5	6	4.3	2	1.7	2	1.5
– Skin injuries NEC	4	3.2	3	2.2	1	0.8	1	0.7	2	1.5	2	1.4	5	4.0	3	2.1	4	3.3	3	2.3
– Upper limb fractures and dislocations	0	0.0	0	0.0	3	2.3	2	1.5	2	1.5	2	1.4	0	0.0	0	0.0	0	0.0	0	0.0
Investigations																				
– Digestive enzymes	6	4.7	5	3.6	0	0.0	0	0.0	1	0.8	1	0.7	2	1.6	2	1.4	2	1.7	2	1.5
– Physical examination procedures and organ system status	3	2.4	3	2.2	3	2.3	3	2.2	5	3.8	5	3.5	5	4.0	5	3.6	1	0.8	1	0.8
– Renal function analyses	3	2.4	2	1.5	1	0.8	1	0.7	3	2.3	3	2.1	2	1.6	2	1.4	3	2.5	3	2.3
– Skeletal and cardiac muscle analyses	2	1.6	2	1.5	1	0.8	1	0.7	3	2.3	3	2.1	0	0.0	0	0.0	1	0.8	1	0.8
Metabolism and nutrition disorders																				
– Disorders of purine metabolism	0	0.0	0	0.0	3	2.3	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
– Hyperglycemic conditions NEC	3	2.4	1	0.7	8	6.1	5	3.7	10	7.5	8	5.7	6	4.8	4	2.9	11	9.1	10	7.6
– Hyperlipidemia NEC	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8	1	0.8
– Hypoglycemic conditions NEC	9	7.1	5	3.6	6	4.6	5	3.7	6	4.5	6	4.3	5	4.0	4	2.9	15	12.5	4	3.0
– Lipid metabolism and deposit disorders NEC	4	3.2	4	2.9	2	1.5	2	1.5	4	3.0	4	2.8	3	2.4	2	1.4	3	2.5	3	2.3
Musculoskeletal and connective tissue disorders																				
– Intervertebral disc disorders NEC	0	0.0	0	0.0	2	1.5	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
– Joint related disorders NEC	0	0.0	0	0.0	3	2.3	2	1.5	2	1.5	2	1.4	0	0.0	0	0.0	0	0.0	0	0.0
– Joint related signs and symptoms	1	0.8	1	0.7	7	5.4	6	4.4	10	7.5	7	5.0	6	4.8	5	3.6	6	5.0	6	4.5
– Muscle pains	3	2.4	3	2.2	7	5.4	6	4.4	1	0.8	1	0.7	4	3.2	4	2.9	0	0.0	0	0.0
– Musculoskeletal and connective tissue pain and discomfort	10	7.9	8	5.8	15	11.5	12	8.8	11	8.3	10	7.1	17	13.5	14	10.0	21	17.5	16	12.1
– Osteoarthropathies	2	1.6	2	1.5	3	2.3	3	2.2	1	0.8	1	0.7	1	0.8	1	0.7	4	3.3	4	3.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)																				
– Uterine neoplasms benign	2	1.6	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
Nervous system disorders																				
– Cervical spinal cord and nerve root disorders	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
– Chronic polyneuropathies	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
– Headaches NEC	8	6.3	7	5.1	16	12.3	7	5.1	12	9.0	7	5.0	11	8.7	10	7.1	9	7.5	8	6.1
– Neurological signs and symptoms NEC	4	3.2	4	2.9	14	10.8	6	4.4	12	9.0	5	3.5	3	2.4	3	2.1	6	5.0	5	3.8

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				141				140				132			
Exposure (patient-years)	126.9				130.2				132.6				126.3				120.3			
System Organ Class - High Level Term	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
– Paresthesias and dysesthesias	2	1.6	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	2	1.6	2	1.4	1	0.8	1	0.8
Psychiatric disorders																				
– Anxiety symptoms	3	2.4	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	3	2.4	3	2.1	6	5.0	4	3.0
– Depressive disorders	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0
– Disturbances in initiating and maintaining sleep	1	0.8	1	0.7	2	1.5	2	1.5	2	1.5	1	0.7	3	2.4	3	2.1	3	2.5	3	2.3
Renal and urinary disorders																				
– Bladder and urethral symptoms	2	1.6	2	1.5	3	2.3	3	2.2	7	5.3	7	5.0	4	3.2	4	2.9	6	5.0	5	3.8
– Urinary abnormalities	5	3.9	4	2.9	0	0.0	0	0.0	3	2.3	3	2.1	3	2.4	3	2.1	1	0.8	1	0.8
– Urinary tract signs and symptoms NEC	2	1.6	2	1.5	2	1.5	2	1.5	2	1.5	2	1.4	1	0.8	1	0.7	1	0.8	1	0.8
Reproductive system and breast disorders																				
– Menstruation and uterine bleeding NEC	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
– Penile and scrotal infections and inflammations	1	0.8	1	0.7	2	1.5	2	1.5	2	1.5	2	1.4	2	1.6	2	1.4	0	0.0	0	0.0
– Reproductive tract signs and symptoms NEC	1	0.8	1	0.7	2	1.5	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0
– Vulvovaginal signs and symptoms	0	0.0	0	0.0	4	3.1	3	2.2	4	3.0	3	2.1	2	1.6	1	0.7	0	0.0	0	0.0
Respiratory, thoracic and mediastinal disorders																				
– Coughing and associated symptoms	6	4.7	6	4.4	6	4.6	6	4.4	4	3.0	4	2.8	3	2.4	2	1.4	4	3.3	3	2.3
– Nasal congestion and inflammations	3	2.4	3	2.2	3	2.3	3	2.2	2	1.5	2	1.4	1	0.8	1	0.7	0	0.0	0	0.0
– Nasal disorders NEC	1	0.8	1	0.7	3	2.3	2	1.5	2	1.5	2	1.4	0	0.0	0	0.0	0	0.0	0	0.0
– Upper respiratory tract signs and symptoms	1	0.8	1	0.7	4	3.1	3	2.2	4	3.0	4	2.8	3	2.4	2	1.4	1	0.8	1	0.8
Skin and subcutaneous tissue disorders																				
– Apocrine and eccrine gland disorders	1	0.8	1	0.7	2	1.5	2	1.5	3	2.3	3	2.1	2	1.6	2	1.4	0	0.0	0	0.0
– Dermal and epidermal conditions NEC	1	0.8	1	0.7	3	2.3	3	2.2	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0
– Pruritus NEC	3	2.4	2	1.5	2	1.5	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	2	1.7	2	1.5
– Rashes, eruptions and exanthems NEC	1	0.8	1	0.7	2	1.5	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
Surgical and medical procedures																				
– Dental and gingival therapeutic procedures	2	1.6	2	1.5	0	0.0	0	0.0	2	1.5	2	1.4	1	0.8	1	0.7	1	0.8	1	0.8
Vascular disorders																				

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				141				140				132			
Exposure (patient-years)	126.9				130.2				132.6				126.3				120.3			
System Organ Class - High Level Term	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
– Vascular hypertensive disorders NEC	7	5.5	6	4.4	1	0.8	1	0.7	3	2.3	3	2.1	6	4.8	6	4.3	7	5.8	7	5.3

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; # = number of events; per 100 = event rate per 100 patient-years; N = number of patients with event; % = percent of patients with event; NEC = not elsewhere classified; incl = including; excl = excluding
Source: Based on review up submitted datasets, information from the Applicant's Response to Information Request received on April 14, 2014, and information from Table 12.A.1: 2 of the study report for study 1275.1

Table 99: Incidence of treatment emergent adverse events with preferred terms occurring in > 1% of either fixed dose combination arm – treated set, metformin patients

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				141				140				132			
Exposure (patient-years)	126.9				130.2				132.6				126.3				120.3			
System Organ Class • Preferred Term	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
Eye disorders																				
• Conjunctivitis	2	1.6	2	1.5	2	1.5	2	1.5	3	2.3	3	2.1	3	2.4	3	2.1	2	1.7	2	1.5
Gastrointestinal disorders																				
• Abdominal pain	5	3.9	3	2.2	2	1.5	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	2	1.7	2	1.5
• Abdominal pain upper	2	1.6	2	1.5	3	2.3	3	2.2	3	2.3	3	2.1	0	0.0	0	0.0	3	2.5	3	2.3
• Constipation	9	7.1	8	5.8	7	5.4	7	5.1	4	3.0	4	2.8	5	4.0	4	2.9	3	2.5	3	2.3
• Diarrhea	5	3.9	4	2.9	12	9.2	10	7.4	7	5.3	5	3.5	6	4.8	6	4.3	1	0.8	1	0.8
• Dyspepsia	4	3.2	4	2.9	1	0.8	1	0.7	6	4.5	6	4.3	1	0.8	1	0.7	5	4.2	5	3.8
• Food poisoning	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• Gastroesophageal reflux disease	1	0.8	1	0.7	3	2.3	3	2.2	0	0.0	0	0.0	2	1.6	2	1.4	0	0.0	0	0.0
• Hemorrhoids	1	0.8	1	0.7	3	2.3	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
• Nausea	5	3.9	5	3.6	6	4.6	5	3.7	6	4.5	5	3.5	2	1.6	2	1.4	4	3.3	4	3.0
• Vomiting	1	0.8	1	0.7	2	1.5	2	1.5	3	2.3	2	1.4	1	0.8	1	0.7	2	1.7	1	0.8
General disorders and administration site conditions																				
• Asthenia	1	0.8	1	0.7	2	1.5	2	1.5	3	2.3	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
• Fatigue	4	3.2	4	2.9	3	2.3	3	2.2	1	0.8	1	0.7	2	1.6	2	1.4	1	0.8	1	0.8
• Edema peripheral	2	1.6	2	1.5	0	0.0	0	0.0	4	3.0	4	2.8	2	1.6	2	1.4	2	1.7	2	1.5
Hepatobiliary disorders																				
• Hepatic steatosis	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	2	1.6	2	1.4	0	0.0	0	0.0
Infections and infestations																				
• Bronchitis	4	3.2	3	2.2	5	3.8	5	3.7	7	5.3	6	4.3	7	5.5	6	4.3	7	5.8	6	4.5
• Cystitis	3	2.4	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	2	1.6	2	1.4	5	4.2	4	3.0
• Gastroenteritis	9	7.1	8	5.8	4	3.1	4	2.9	4	3.0	3	2.1	3	2.4	2	1.4	5	4.2	4	3.0

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				141				140				132			
Exposure (patient-years)	126.9				130.2				132.6				126.3				120.3			
System Organ Class • **Preferred Term**	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
• Gastroenteritis viral	2	1.6	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	3	2.4	3	2.1	1	0.8	1	0.8
• Giardiasis	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• Influenza	1	0.8	1	0.7	2	1.5	2	1.5	6	4.5	5	3.5	10	7.9	9	6.4	9	7.5	7	5.3
• Nasopharyngitis	9	7.1	8	5.8	13	10.0	12	8.8	8	6.0	7	5.0	12	9.5	11	7.9	21	17.5	14	10.6
• Pharyngitis	3	2.4	3	2.2	2	1.5	2	1.5	2	1.5	2	1.4	2	1.6	2	1.4	6	5.0	5	3.8
• Sinusitis	4	3.2	2	1.5	4	3.1	3	2.2	3	2.3	3	2.1	2	1.6	2	1.4	1	0.8	1	0.8
• Tooth abscess	4	3.2	3	2.2	1	0.8	1	0.7	4	3.0	2	1.4	1	0.8	1	0.7	2	1.7	2	1.5
• Upper respiratory tract infection	15	11.8	11	8.0	17	13.1	14	10.3	11	8.3	9	6.4	15	11.9	12	8.6	6	5.0	4	3.0
• Urinary tract infection	17	13.4	14	10.2	17	13.1	13	9.6	32	24.1	23	16.3	16	12.7	13	9.3	21	17.5	15	11.4
• Vaginal infection	1	0.8	1	0.7	6	4.6	4	2.9	2	1.5	2	1.4	2	1.6	1	0.7	0	0.0	0	0.0
Injury, poisoning and procedural complications																				
• Ligament sprain	3	2.4	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.8
Investigations																				
• Blood creatine phosphokinase increased	2	1.6	2	1.5	1	0.8	1	0.7	3	2.3	3	2.1	0	0.0	0	0.0	1	0.8	1	0.8
• Blood creatinine increased	2	1.6	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.8
• Lipase increased	6	4.7	5	3.6	0	0.0	0	0.0	1	0.8	1	0.7	2	1.6	2	1.4	2	1.7	2	1.5
• Weight decreased	2	1.6	2	1.5	3	2.3	3	2.2	4	3.0	4	2.8	5	4.0	5	3.6	0	0.0	0	0.0
Metabolism and nutrition disorders																				
• Dyslipidemia	4	3.2	4	2.9	1	0.8	1	0.7	3	2.3	3	2.1	3	2.4	2	1.4	3	2.5	3	2.3
• Hyperglycemia	3	2.4	1	0.7	8	6.1	5	3.7	10	7.5	8	5.7	6	4.8	4	2.9	11	9.1	10	7.6
• Hyperlipidemia	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8	1	0.8
• Hypoglycemia	9	7.1	5	3.6	6	4.6	5	3.7	6	4.5	6	4.3	5	4.0	4	2.9	15	12.5	4	3.0
Musculoskeletal and connective tissue disorders																				
• Arthralgia	1	0.8	1	0.7	7	5.4	6	4.4	10	7.5	7	5.0	4	3.2	3	2.1	6	5.0	6	4.5
• Back pain	6	4.7	6	4.4	6	4.6	6	4.4	3	2.3	2	1.4	12	9.5	9	6.4	9	7.5	7	5.3
• Myalgia	3	2.4	3	2.2	6	4.6	5	3.7	1	0.8	1	0.7	4	3.2	4	2.9	0	0.0	0	0.0
• Osteoarthritis	2	1.6	2	1.5	2	1.5	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	3	2.5	3	2.3
• Pain in extremity	1	0.8	1	0.7	3	2.3	3	2.2	5	3.8	5	3.5	2	1.6	2	1.4	3	2.5	3	2.3
Nervous system disorders																				
• Diabetic neuropathy	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• Dizziness	4	3.2	4	2.9	14	10.8	6	4.4	12	9.0	5	3.5	3	2.4	3	2.1	6	5.0	5	3.8
• Headache	8	6.3	7	5.1	16	12.3	7	5.1	10	7.5	6	4.3	11	8.7	10	7.1	9	7.5	8	6.1
• Paresthesia	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	2	1.6	2	1.4	1	0.8	1	0.8
Psychiatric disorders																				
• Anxiety	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	3	2.4	3	2.1	6	5.0	4	3.0
• Depression	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0
• Insomnia	1	0.8	1	0.7	2	1.5	2	1.5	2	1.5	1	0.7	3	2.4	3	2.1	3	2.5	3	2.3

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				141				140				132			
Exposure (patient-years)	126.9				130.2				132.6				126.3				120.3			
System Organ Class • Preferred Term	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
Renal and urinary disorders																				
• Microalbuminuria	4	3.2	4	2.9	0	0.0	0	0.0	2	1.5	2	1.4	0	0.0	0	0.0	1	0.8	1	0.8
Reproductive system and breast disorders																				
• Balanitis	1	0.8	1	0.7	2	1.5	2	1.5	2	1.5	2	1.4	1	0.8	1	0.7	0	0.0	0	0.0
Respiratory, thoracic and mediastinal disorders																				
• Cough	5	3.9	5	3.6	6	4.6	6	4.4	3	2.3	3	2.1	3	2.4	2	1.4	3	2.5	2	1.5
• Nasal congestion	1	0.8	1	0.7	2	1.5	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0
• Rhinitis allergic	2	1.6	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
Skin and subcutaneous tissue disorders																				
• Dry skin	1	0.8	1	0.7	2	1.5	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• Pruritus	3	2.4	2	1.5	2	1.5	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	2	1.7	2	1.5
• Rash	1	0.8	1	0.7	2	1.5	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
Surgical and medical procedures																				
• Tooth extraction	2	1.6	2	1.5	0	0.0	0	0.0	2	1.5	2	1.4	1	0.8	1	0.7	1	0.8	1	0.8
Vascular disorders																				
• Hypertension	7	5.5	6	4.4	1	0.8	1	0.7	3	2.3	3	2.1	6	4.8	6	4.3	7	5.8	7	5.3

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; # = number of events; per 100 = event rate per 100 patient-years; N = number of patients with event; % = percent of patients with event
Source: Based on review up submitted datasets, information from the Applicant's Response to Information Request received on April 14, 2014, and information from Table 12.A.1: 2 of the study report for study 1275.1

Table 100: Incidence of treatment emergent adverse events by system organ class – treated set, treatment naïve

	FDC25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				135				135				135			
Exposure (patient-years	123.6				124.9				123				123				123			
System Organ Class	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
Blood and lymphatic system disorders	0	0.0	0	0.0	3	2.4	3	2.2	3	2.4	3	2.2	3	2.4	3	2.2	1	0.8	1	0.7
Cardiac disorders	4	3.2	3	2.2	9	7.2	7	5.1	3	2.4	3	2.2	9	7.3	9	6.7	4	3.3	4	3.0
Congenital, familial and genetic disorders	1	0.8	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0	2	1.6	2	1.5	3	2.4	3	2.2
Ear and labyrinth disorders	1	0.8	1	0.7	2	1.6	1	0.7	2	1.6	2	1.4	3	2.4	3	2.2	4	3.3	4	3.0
Endocrine disorders	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	2	1.6	2	1.5	1	0.8	1	0.7
Eye disorders	9	7.3	7	5.1	11	8.8	7	5.1	6	4.9	5	3.6	2	1.6	2	1.5	8	6.5	8	5.9
Gastrointestinal disorders	33	26.7	21	15.3	28	22.4	19	14.0	42	34.1	26	18.7	30	24.4	20	14.8	29	23.6	21	15.6
General disorders and administration site conditions	13	10.5	11	8.0	30	24.0	13	9.6	6	4.9	6	4.3	18	14.6	14	10.4	14	11.4	11	8.1
Hepatobiliary disorders	1	0.8	1	0.7	4	3.2	3	2.2	8	6.5	6	4.3	1	0.8	1	0.7	0	0.0	0	0.0

	FDC25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				135				135				135			
Exposure (patient-years	123.6				124.9				123				123				123			
System Organ Class	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
Immune system disorders	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	3	2.4	3	2.2	1	0.8	1	0.7
Infections and infestations	105	85.0	57	41.6	102	81.7	51	37.5	91	74.0	49	35.3	108	87.8	65	48.1	82	66.7	53	39.3
Injury, poisoning and procedural complications	19	15.4	13	9.5	20	16.0	11	8.1	15	12.2	10	7.2	6	4.9	5	3.7	9	7.3	8	5.9
Investigations	14	1.3	9	6.6	21	16.8	18	13.2	23	18.7	15	10.8	14	11.4	12	8.9	20	16.3	11	8.1
Metabolism and nutrition disorders	40	32.4	32	23.4	36	28.8	24	17.6	24	19.5	18	12.9	37	30.1	31	23.0	38	30.9	30	22.2
Musculoskeletal and connective tissue disorders	31	25.1	23	16.8	39	31.2	25	18.4	34	27.6	21	15.1	39	31.7	26	19.3	25	20.3	22	16.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	4.0	5	3.6	1	0.8	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0	2	1.6	2	1.5
Nervous system disorders	25	20.2	18	13.1	51	40.8	20	14.7	29	23.6	19	13.7	30	24.4	20	14.8	37	30.1	27	20.0
Psychiatric disorders	3	2.4	2	1.5	5	4.0	5	3.7	8	6.5	5	3.6	10	8.1	9	6.7	9	7.3	7	5.2
Renal and urinary disorders	26	21.0	16	11.7	16	12.8	15	11.0	18	14.6	16	11.5	12	9.8	10	7.4	17	13.8	13	9.6
Reproductive system and breast disorders	17	13.8	10	7.3	9	7.2	7	5.1	6	4.9	6	4.3	6	4.9	5	3.7	8	6.5	6	4.4
Respiratory, thoracic and mediastinal disorders	11	8.9	9	6.6	17	13.6	11	8.1	11	8.9	9	6.5	11	8.9	9	6.7	13	10.6	10	7.4
Skin and subcutaneous tissue disorders	22	17.8	16	11.7	24	19.2	11	8.1	14	11.4	10	7.2	6	4.9	6	4.4	3	2.4	2	1.5
Surgical and medical procedures	5	4.0	3	2.2	4	3.2	3	2.2	3	2.4	3	2.2	2	1.6	2	1.5	1	0.8	1	0.7
Vascular disorders	8	6.4	8	5.8	7	5.6	7	5.1	13	10.6	9	6.5	9	7.3	7	5.2	6	4.9	6	4.4

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; # = number of events; per 100 = event rate per 100 patient-years; N = number of patients with event; % = percent of patients with event
Source: Based on review up submitted datasets, information from the Applicant's Response to Information Request received on April 14, 2014, and information from Table 12.B.1: 2 of the study report for study 1275.1

Table 101: Incidence of treatment emergent adverse events by high level term reported by > 1 patient in either fixed dose combination arm – treated set, treatment naïve

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				135				135				135			
Exposure (patient-years)	123.6				124.9				123				123				123			
System Organ Class - High Level Term	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
Cardiac disorders																				
- Ischemic coronary artery disorders	1	0.8	1	0.7	3	2.4	2	1.5	1	0.8	1	0.7	2	1.6	2	1.5	1	0.8	1	0.7
- Myocardial disorders NEC	0	0.0	0	0.0	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8	1	0.7
Eye disorders																				
- Cataract conditions	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Conjunctival infections, irritations and inflammations	2	1.6	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	1	0.8	1	0.7	5	4.1	5	3.7

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				135				135				135			
Exposure (patient-years)	123.6				124.9				123				123				123			
System Organ Class - High Level Term	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
- Lacrimation disorders	3	2.4	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Visual disorders NEC	0	0.0	0	0.0	7	5.6	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	3	2.4	3	2.2
Gastrointestinal disorders																				
- Dental pain and sensation disorders	3	2.4	3	2.2	1	0.8	1	0.7	2	1.6	2	1.5	4	3.3	4	3.0	2	1.6	2	1.5
- Diarrhea (excl infective)	4	3.2	4	2.9	1	0.8	1	0.7	4	3.3	4	3.0	7	5.7	7	5.2	4	3.3	4	3.0
- Dyspeptic signs and symptoms	1	0.8	1	0.7	5	4.0	4	2.9	1	0.8	1	0.7	2	1.6	2	1.5	2	1.6	2	1.5
- Gastritis (excl infective)	1	0.8	1	0.7	3	2.4	3	2.2	2	1.6	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7
- Gastrointestinal and abdominal pains (excl oral and throat)	4	3.2	4	2.9	5	4.0	5	3.7	5	4.1	3	2.2	2	1.6	2	1.5	4	3.3	4	3.0
- Gastrointestinal atonic and hypomotility disorders NEC	2	1.6	2	1.5	4	3.2	3	2.2	12	9.8	11	8.1	5	4.1	5	3.7	3	2.4	3	2.2
- Gastrointestinal signs and symptoms NEC	2	1.6	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0	3	2.4	3	2.2
- Hemorrhoids and gastrointestinal varices (excl esophageal)	4	3.2	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Nausea and vomiting symptoms	6	4.9	4	2.9	3	2.4	3	2.2	8	6.5	4	3.0	5	4.1	4	3.0	4	3.3	3	2.2
- Oral dryness and saliva altered	1	0.8	1	0.7	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8	1	0.7
General disorders and administration site conditions																				
- Asthenic conditions	3	2.4	3	2.2	21	16.8	7	5.1	2	1.6	2	1.5	6	4.9	5	3.7	5	4.1	5	3.7
- Febrile disorders	1	0.8	1	0.7	2	1.6	2	1.5	0	0.0	0	0.0	3	2.4	3	2.2	2	1.6	1	0.7
- Feelings and sensations NEC	4	3.2	3	2.2	2	1.6	2	1.5	1	0.8	1	0.7	3	2.4	3	2.2	1	0.8	1	0.7
- General signs and symptoms NEC	2	1.6	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0	2	1.6	2	1.5
- Edema NEC	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.7	1	0.8	1	0.7
- Pain and discomfort NEC	1	0.8	1	0.7	4	3.2	4	2.9	2	1.6	2	1.5	4	3.3	3	2.2	3	2.4	3	2.2
Hepatobiliary disorders																				
- Cholecystitis and cholelithiasis	0	0.0	0	0.0	2	1.6	2	1.5	3	2.4	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0
Infections and infestations																				
- Abdominal and gastrointestinal infections	4	3.2	4	2.9	3	2.4	3	2.2	1	0.8	1	0.7	4	3.3	4	3.0	4	3.3	2	1.5
- Bacterial infections NEC	7	5.7	6	4.4	4	3.2	3	2.2	4	3.3	4	3.0	5	4.1	4	3.0	2	1.6	2	1.5
- Candida infections	4	3.2	4	2.9	2	1.6	2	1.5	8	6.5	6	4.4	0	0.0	0	0.0	0	0.0	0	0.0
- Dental and oral soft tissue infections	3	2.4	3	2.2	1	0.8	1	0.7	3	2.4	3	2.2	1	0.8	1	0.7	3	2.4	3	2.2
- Ear infections	4	3.2	4	2.9	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0
- Female reproductive tract infections	5	4.0	3	2.2	3	2.4	1	0.7	0	0.0	0	0.0	4	3.3	3	2.2	2	1.6	2	1.5
- Fungal infections NEC	7	5.7	5	3.6	9	7.2	5	3.7	8	6.5	5	3.7	14	11.4	10	7.4	6	4.9	5	3.7
- Influenza viral infections	9	7.3	7	5.1	10	8.0	8	5.9	4	3.3	4	3.0	6	4.9	6	4.4	2	1.6	2	1.5

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				135				135				135			
Exposure (patient-years)	123.6				124.9				123				123				123			
System Organ Class - **High Level Term**	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
- Lower respiratory tract and lung infections	6	4.9	6	4.4	8	6.4	8	5.9	6	4.9	5	3.7	6	4.9	6	4.4	4	3.3	4	3.0
- Tinea infections	0	0.0	0	0.0	3	2.4	3	2.2	0	0.0	0	0.0	2	1.6	2	1.5	0	0.0	0	0.0
- Upper respiratory tract infections	28	22.7	26	19.0	21	16.8	17	12.5	27	22.0	19	14.1	25	20.3	23	17.0	33	26.8	24	17.8
- Urinary tract infections	23	18.6	16	11.7	29	23.2	20	14.7	19	15.4	14	10.4	26	21.1	23	17.0	16	13.0	15	11.1
- Viral infections NEC	1	0.8	1	0.7	4	3.2	4	2.9	2	1.6	2	1.5	5	4.1	4	3.0	0	0.0	0	0.0
Injury, poisoning and procedural complications																				
- Exposures to agents or circumstances NEC	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Limb injuries NEC (incl traumatic amputation)	1	0.8	1	0.7	3	2.4	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
- Lower limb fractures and dislocations	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Muscle, tendon and ligament injuries	5	4.0	4	2.9	3	2.4	3	2.2	0	0.0	0	0.0	2	1.6	1	0.7	4	3.3	4	3.0
- Non-site specific injuries NEC	3	2.4	3	2.2	2	1.6	2	1.5	5	4.1	5	3.7	1	0.8	1	0.7	3	2.4	3	2.2
- Non-site specific procedural complications	1	0.8	1	0.7	4	3.2	2	1.5	0	0.0	0	0.0	2	1.6	2	1.5	0	0.0	0	0.0
- Skin injuries NEC	2	1.6	2	1.5	5	4.0	3	2.2	5	4.1	4	3.0	0	0.0	0	0.0	1	0.8	1	0.7
Investigations																				
- Bacteria identification and serology (excl mycobacteria)	0	0.0	0	0.0	3	2.4	3	2.2	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8	1	0.7
- Digestive enzymes	2	1.6	2	1.5	4	3.2	4	2.9	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.7
- Liver function analyses	4	3.2	2	1.5	4	3.2	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	6	4.9	4	3.0
- Mineral and electrolyte analyses	0	0.0	0	0.0	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
- Physical examination procedures and organ system status	2	1.6	2	1.5	1	0.8	1	0.7	8	6.5	8	5.9	2	1.6	2	1.5	2	1.6	2	1.5
- Skeletal and cardiac muscle analyses	3	2.4	2	1.5	3	2.4	3	2.2	3	2.4	3	2.2	6	4.9	4	3.0	2	1.6	1	0.7
Metabolism and nutrition disorders																				
- Elevated cholesterol	1	0.8	1	0.7	2	1.6	2	1.5	3	2.4	3	2.2	2	1.6	2	1.5	2	1.6	2	1.5
- Elevated triglycerides	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	3	2.4	3	2.2	0	0.0	0	0.0
- Hyperglycemic conditions NEC	10	8.1	10	7.3	9	7.2	5	3.7	8	6.5	5	3.7	12	9.8	11	8.1	18	14.6	14	10.4
- Hyperlipidemia NEC	3	2.4	3	2.2	2	1.6	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.7
- Hypoglycemic conditions NEC	0	0.0	0	0.0	8	6.4	2	1.5	1	0.8	1	0.7	4	3.3	4	3.0	2	1.6	2	1.5
- Lipid metabolism and deposit disorders NEC	13	10.5	12	8.8	10	8.0	10	7.4	4	3.3	4	3.0	9	7.3	9	6.7	4	3.3	4	3.0
- Potassium imbalance	4	3.2	4	2.9	2	1.6	2	1.5	1	0.8	1	0.7	2	1.6	2	1.5	1	0.8	1	0.7
Musculoskeletal and connective tissue disorders																				
- Intervertebral disc disorders NEC	1	0.8	1	0.7	3	2.4	3	2.2	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.7

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				135				135				135			
Exposure (patient-years)	123.6				124.9				123				123				123			
System Organ Class - High Level Term	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
- Joint related signs and symptoms	8	6.5	7	5.1	11	8.8	9	6.6	7	5.7	6	4.4	10	8.1	7	5.2	7	5.7	7	5.2
- Muscle pains	1	0.8	1	0.7	2	1.6	2	1.5	3	2.4	2	1.5	5	4.1	5	3.7	0	0.0	0	0.0
- Muscle related signs and symptoms NEC	5	4.0	4	2.9	2	1.6	2	1.5	0	0.0	0	0.0	3	2.4	3	2.2	2	1.6	2	1.5
- Musculoskeletal and connective tissue pain and discomfort	14	11.3	11	8.0	11	8.8	9	6.6	15	12.2	15	11.1	8	6.5	8	5.9	12	9.8	10	7.4
- Osteoarthropathies	1	0.8	1	0.7	4	3.2	4	2.9	4	3.3	4	3.0	4	3.3	4	3.0	1	0.8	1	0.7
Nervous system disorders																				
- Disturbances in consciousness NEC	0	0.0	0	0.0	3	2.4	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
- Headaches NEC	11	8.9	10	7.3	17	13.6	8	5.9	11	8.9	9	6.7	14	11.4	9	6.7	22	17.9	16	11.9
- Lumbar spinal cord and nerve root disorders	0	0.0	0	0.0	2	1.6	2	1.5	2	1.6	1	0.7	1	0.8	1	0.7	1	0.8	1	0.7
- Neurological signs and symptoms NEC	8	6.5	7	5.1	5	4.0	3	2.2	4	3.3	4	3.0	5	4.1	5	3.7	7	5.7	6	4.4
- Paresthesias and dysesthesias	1	0.8	1	0.7	8	6.4	4	2.9	1	0.8	1	0.7	0	0.0	0	0.0	2	1.6	2	1.5
- Peripheral neuropathies NEC	0	0.0	0	0.0	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	2	1.6	2	1.5
- Sensory abnormalities NEC	3	2.4	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0
- Tremor (excl congenital)	0	0.0	0	0.0	9	7.2	3	2.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Psychiatric disorders																				
- Disturbances in initiating and maintaining sleep	1	0.8	1	0.7	2	1.6	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.7
Renal and urinary disorders																				
- Bladder and urethral symptoms	10	8.1	7	5.1	7	5.6	6	4.4	4	3.3	4	3.0	5	4.1	4	3.0	7	5.7	5	3.7
- Urinary abnormalities	9	7.3	8	5.8	6	4.8	6	4.4	5	4.1	5	3.7	3	2.4	3	2.2	7	5.7	7	5.2
- Urinary tract signs and symptoms NEC	5	4.0	4	2.9	2	1.6	2	1.5	5	4.1	4	3.0	2	1.6	2	1.5	3	2.4	3	2.2
Reproductive system and breast disorders																				
- Cervix disorders NEC	3	2.4	3	2.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Penile and scrotal infections and inflammations	5	4.0	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Vulvovaginal signs and symptoms	2	1.6	2	1.5	4	3.2	3	2.2	1	0.8	1	0.7	2	1.6	2	1.5	0	0.0	0	0.0
Respiratory, thoracic and mediastinal disorders																				
- Bronchospasm and obstruction	1	0.8	1	0.7	3	2.4	2	1.5	0	0.0	0	0.0	3	2.4	2	1.5	0	0.0	0	0.0
- Coughing and associated symptoms	4	3.2	4	2.9	2	1.6	2	1.5	2	1.6	2	1.5	4	3.3	4	3.0	4	3.3	4	3.0
- Nasal congestion and inflammations	2	1.6	2	1.5	2	1.6	2	1.5	2	1.6	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7
- Nasal disorders NEC	2	1.6	2	1.5	2	1.6	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0

	FDC 25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				135				135				135			
Exposure (patient-years)	123.6				124.9				123				123				123			
System Organ Class - High Level Term	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
- Upper respiratory tract signs and symptoms	1	0.8	1	0.7	6	4.8	4	2.9	2	1.6	2	1.5	2	1.6	2	1.5	3	2.4	2	1.5
Skin and subcutaneous tissue disorders																				
- Alopecias	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8	1	0.7
- Apocrine and eccrine gland disorders	3	2.4	3	2.2	12	9.6	2	1.5	2	1.6	1	0.7	2	1.6	2	1.5	0	0.0	0	0.0
- Dermal and epidermal conditions NEC	3	2.4	3	2.2	1	0.8	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
- Dermatitis and eczema	3	2.4	3	2.2	5	4.0	4	2.9	1	0.8	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0
- Rashes, eruptions and exanthems NEC	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.7	1	0.8	1	0.7
Surgical and medical procedures																				
- Dental and gingival therapeutic procedures	5	4.0	3	2.2	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.7
Vascular disorders																				
- Hemorrhages NEC	0	0.0	0	0.0	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Vascular hypertensive disorders NEC	6	4.9	6	4.4	4	3.2	4	2.9	5	4.1	5	3.7	6	4.9	6	4.4	5	4.1	5	3.7

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; # = number of events; per 100 = event rate per 100 patient-years; N = number of patients with event; % = percent of patients with event; NEC = not elsewhere classified; incl = including; excl = excluding
Source: Based on review up submitted datasets, information from the Applicant's Response to Information Request received on April 14, 2014, and information from Table 12.B.1: 2 of the study report for study 1275.1

Table 102: Incidence of treatment emergent adverse events with preferred terms occurring in > 1% of either fixed dose combination arm – treated set, treatment naïve

	FDC25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				135				135				135			
Exposure (patient-years	123.6				124.9				123				123				123			
System Organ Class • Preferred Term	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
Eye disorders																				
• Cataract	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• Dry eye	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Gastrointestinal disorders																				
• Abdominal discomfort	2	1.6	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0	3	2.4	3	2.2
• Abdominal pain	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.7	3	2.4	3	2.2
• Abdominal pain upper	2	1.6	2	1.5	3	2.4	3	2.2	5	4.1	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0
• Constipation	2	1.6	2	1.5	2	1.6	2	1.5	9	7.3	8	5.9	4	3.3	4	3.0	3	2.4	3	2.2
• Diarrhea	4	3 2	4	2.9	1	0.8	1	0.7	4	3.3	4	3.0	7	5.7	7	5.2	4	3.3	4	3.0

	FDC25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				135				135				135			
Exposure (patient-years	123.6				124.9				123				123				123			
System Organ Class • **Preferred Term**	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
• Dry mouth	1	0.8	1	0.7	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8	1	0.7
• Dyspepsia	1	0.8	1	0.7	5	4.0	4	2.9	1	0.8	1	0.7	2	1.6	2	1.5	2	1.6	2	1.5
• Gastritis	1	0.8	1	0.7	3	2.4	3	2.2	2	1.6	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7
• Hemorrhoids	4	3 2	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• Nausea	6	4 9	4	2.9	3	2.4	3	2.2	5	4.1	4	3.0	5	4.1	4	3.0	2	1.6	2	1.5
• Toothache	3	2.4	3	2.2	1	0.8	1	0.7	2	1.6	2	1.5	4	3.3	4	3.0	2	1.6	2	1.5
General disorders and administration site conditions																				
• Fatigue	1	0.8	1	0.7	8	6.4	4	2.9	1	0.8	1	0.7	3	2.4	3	2.2	5	4.1	5	3.7
• Malaise	1	0.8	1	0.7	4	3.2	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• Edema peripheral	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0
• Pyrexia	1	0.8	1	0.7	2	1.6	2	1.5	0	0.0	0	0.0	3	2.4	3	2.2	2	1.6	1	0.7
• Thirst	2	1.6	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	3	2.4	3	2.2	0	0.0	0	0.0
Infections and infestations																				
• Asymptomatic bacteriuria	2	1.6	2	1.5	3	2.4	2	1.5	1	0.8	1	0.7	2	1.6	2	1.5	0	0.0	0	0.0
• Bronchitis	6	4 9	6	4.4	5	4.0	5	3.7	4	3.3	3	2.2	4	3.3	4	3.0	4	3.3	4	3.0
• Candidiasis	2	1.6	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
• Cellulitis	3	2.4	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8	1	0.7	1	0.8	1	0.7
• Cystitis	1	0.8	1	0.7	2	1.6	2	1.5	3	2.4	3	2.2	3	2.4	3	2.2	2	1.6	2	1.5
• Fungal infection	4	3 2	2	1.5	7	5.6	4	2.9	5	4.1	3	2.2	4	3.3	4	3.0	1	0.8	1	0.7
• Gastroenteritis	1	0.8	1	0.7	2	1.6	2	1.5	1	0.8	1	0.7	2	1.6	2	1.5	4	3.3	2	1.5
• Influenza	9	7 3	7	5.1	10	8.0	8	5.9	4	3.3	4	3.0	6	4.9	6	4.4	2	1.6	2	1.5
• Nasopharyngitis	11	8 9	11	8.0	7	5.6	6	4.4	8	6.5	6	4.4	13	10.6	11	8.1	12	9.8	9	6.7
• Otitis externa	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• Pharyngitis	1	0.8	1	0.7	4	3.2	4	2.9	2	1.6	2	1.5	4	3.3	4	3.0	4	3.3	3	2.2
• Sinusitis	4	3 2	4	2.9	3	2.4	3	2.2	1	0.8	1	0.7	5	4.1	5	3.7	1	0.8	1	0.7
• Tooth abscess	2	1.6	2	1.5	1	0.8	1	0.7	2	1.6	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7
• Upper respiratory tract infection	10	8 1	8	5.8	6	4.8	5	3.7	14	11.4	11	8.1	2	1.6	2	1.5	14	11.4	13	9.6
• Urinary tract infection	22	17.8	16	11.7	26	20.8	18	13.2	16	13.0	11	8.1	22	17.9	19	14.1	14	11.4	13	9.6
• Vaginal infection	2	1.6	2	1.5	3	2.4	1	0.7	0	0.0	0	0.0	4	3.3	3	2.2	1	0.8	1	0.7
• Vulvovaginitis	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Injury, poisoning and procedural complications																				
• Contusion	2	1.6	2	1.5	2	1.6	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
• Fall	2	1.6	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
• Ligament sprain	3	2.4	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• Muscle strain	2	1.6	2	1.5	1	0.8	1	0.7	0	0.0	0	0.0	2	1.6	1	0.7	1	0.8	1	0.7
Investigations																				

	FDC25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				135				135				135			
Exposure (patient-years	123.6				124.9				123				123				123			
System Organ Class • Preferred Term	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
• Alanine aminotransferase increased	2	1.6	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0	2	1.6	2	1.5
• Aspartate aminotransferase increased	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	2	1.6	2	1.5
• Blood creatine phosphokinase increased	2	1.6	2	1.5	3	2.4	3	2.2	3	2.4	3	2.2	4	3.3	3	2.2	2	1.6	1	0.7
• Lipase increased	2	1.6	2	1.5	4	3.2	4	2.9	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.7
Metabolism and nutrition disorders																				
• Dyslipidemia	12	9.7	11	8.0	9	7.2	9	6.6	4	3.3	4	3.0	9	7.3	9	6.7	3	2.4	3	2.2
• Hypercholesterolemia	1	0.8	1	0.7	2	1.6	2	1.5	3	2.4	3	2.2	2	1.6	2	1.5	2	1.6	2	1.5
• Hyperglycemia	10	8 1	10	7.3	9	7.2	5	3.7	8	6.5	5	3.7	12	9.8	11	8.1	18	14.6	14	10.4
• Hyperlipidemia	3	2.4	3	2.2	2	1.6	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.7
• Hypertriglyceridemia	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	3	2.4	3	2.2	0	0.0	0	0.0
• Hypokalemia	4	3 2	4	2.9	2	1.6	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0
Musculoskeletal and connective tissue disorders																				
• Arthralgia	6	4 9	5	3.6	9	7.2	8	5.9	7	5.7	6	4.4	9	7.3	7	5.2	7	5.7	7	5.2
• Back pain	9	7 3	6	4.4	5	4.0	4	2.9	10	8.1	10	7.4	4	3.3	4	3.0	3	2.4	3	2.2
• Joint swelling	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0
• Muscle spasms	5	4.0	4	2.9	2	1.6	2	1.5	0	0.0	0	0.0	2	1.6	2	1.5	2	1.6	2	1.5
• Musculoskeletal pain	2	1.6	2	1.5	2	1.6	2	1.5	0	0.0	0	0.0	3	2.4	3	2.2	1	0.8	1	0.7
• Myalgia	1	0.8	1	0.7	2	1.6	2	1.5	3	2.4	2	1.5	5	4.1	5	3.7	0	0.0	0	0.0
• Pain in extremity	2	1.6	2	1.5	2	1.6	2	1.5	4	3.3	4	3.0	0	0.0	0	0.0	6	4.9	6	4.4
Nervous system disorders																				
• Dizziness	8	6 5	7	5.1	5	4.0	3	2.2	4	3.3	4	3.0	5	4.1	5	3.7	7	5.7	6	4.4
• Headache	11	8 9	10	7.3	15	12.0	8	5.9	9	7.3	8	5.9	14	11.4	9	6.7	22	17.9	16	11.9
• Paresthesia	1	0.8	1	0.7	5	4.0	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8	1	0.7
Psychiatric disorders																				
• Insomnia	1	0.8	1	0.7	2	1.6	2	1.5	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.7
Renal and urinary disorders																				
• Dysuria	1	0.8	1	0.7	4	3.2	3	2.2	0	0.0	0	0.0	2	1.6	2	1.5	3	2.4	2	1.5
• Hematuria	7	5.7	6	4.4	3	2.4	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	1	0.8	1	0.7
• Microalbuminuria	2	1.6	2	1.5	1	0.8	1	0.7	4	3.3	4	3.0	3	2.4	3	2.2	3	2.4	3	2.2
• Pollakiuria	7	5.7	5	3.6	3	2.4	3	2.2	3	2.4	3	2.2	1	0.8	1	0.7	2	1.6	2	1.5
• Polyuria	4	3 2	3	2.2	0	0.0	0	0.0	4	3.3	3	2.2	0	0.0	0	0.0	2	1.6	2	1.5
Reproductive system and breast disorders																				
• Balanitis	5	4.0	3	2.2	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• Cervical dysplasia	3	2.4	3	2.2	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
• Vulvovaginal pruritus	2	1.6	2	1.5	3	2.4	3	2.2	1	0.8	1	0.7	2	1.6	2	1.5	0	0.0	0	0.0

	FDC25/5				FDC 10/5				Empa 25				Empa 10				Lina 5			
Patients	137				136				135				135				135			
Exposure (patient-years	123.6				124.9				123				123				123			
System Organ Class • Preferred Term	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%	#	Per 100	N	%
Respiratory, thoracic and mediastinal disorders																				
• Cough	4	3 2	4	2.9	2	1.6	2	1.5	2	1.6	2	1.5	3	2.4	3	2.2	4	3.3	4	3.0
Skin and subcutaneous tissue disorders																				
• Alopecia	2	1.6	2	1.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.8	1	0.7
• Dry skin	2	1.6	2	1.5	0	0.0	0	0.0	1	0.8	1	0.7	0	0.0	0	0.0	0	0.0	0	0.0
• Hyperhidrosis	1	0.8	1	0.7	12	9.6	2	1.5	0	0.0	0	0.0	2	1.6	2	1.5	0	0.0	0	0.0
Surgical and medical procedures																				
• Tooth extraction	5	4.0	3	2.2	1	0.8	1	0.7	1	0.8	1	0.7	1	0.8	1	0.7	0	0.0	0	0.0
Vascular disorders																				
• Hypertension	6	4 9	6	4.4	4	3.2	4	2.9	5	4.1	5	3.7	6	4.9	6	4.4	5	4.1	5	3.7

FDC = fixed dose combination; Empa = empagliflozin; Lina = linagliptin; # = number of events; per 100 = event rate per 100 patient-years; N = number of patients with event; % = percent of patients with event

Source: Based on review up submitted datasets, information from the Applicant's Response to Information Request received on April 14, 2014, and information from Table 12.B.1: 2 of the study report for study 1275.1

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/s/

WILLIAM H CHONG
01/29/2015

JEAN-MARC P GUETTIER
01/29/2015

I concur with Dr. Chong's benefit risk assessment and recommend approval of the NDA. The applicant has demonstrated that both drugs in the FDC contribute to the claimed effect in a factorial study. One comparison, for one clinical use setting did not show superiority and I agree with Dr. Chong's interpretation of this finding. The safety of the individual actives did not appear to be decreased when products were co-administered. The FDC meets the definition of rational concurrent therapy. The two products are marketed and lower glucose through different mechanisms of action. In the current care setting these individual products could be co-administered as second and third line agents in patients with diabetes not adequately controlled on maximally effective doses of metformin. This type of use for the FDC would be most consistent with treatment guidelines set by professional guidelines.