CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206111Orig1s000

MEDICAL REVIEW(S)

Date	(electronic stamp)
From	Jean-Marc Guettier, MDCM
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	206111
Applicant Name	Boehringer Ingelheim
Date of Submission	August 4, 2014
PDUFA Goal Date	June 4, 2015
Proprietary Name / **Established (USAN) Name**	Synjardy Empagliflozin and Metformin hydrochloride
Dosage Forms / Strength	Tablet- 5/500 mg, 5/1000 mg, 12.5/500 mg, and 12.5 mg/1000 mg
Proposed Indication(s)	1. As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing empagliflozin or metformin, or in patients already being treated with both empagliflozin and metformin.
Action/Recommended Action:	Complete Response

Division Director Memorandum

Background:

On 4 August 2014 Boehringer Ingelheim Pharmaceuticals, Inc. submitted a new drug application for Synjardy, a fixed combination drug product (FCDP) containing empagliflozin and metformin hydrochloride, pursuant to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act. The NDA references NDA 204629 for Jardiance (empagliflozin) and NDA 20357 for Glucophage (metformin hydrochloride). The applicant does not have a right of reference to the data in NDA 20357 and relies, in part, upon the Agency's previous finding of safety and effectiveness for the listed drug Glucophage to establish the efficacy and safety of the FCDP.

The applicant seeks to indicate the FCDP as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus who are not adequately controlled on a regimen containing empagliflozin or metformin, or in patients already being treated with both empagliflozin and metformin. Dr. Chong has summarized, in detail, the data relied upon to establish the safety and effectiveness of the FCDP in his review and CDTL memorandum (refer to his review for details). All members of the review team agree that the applicant with these data has demonstrated that combining the two active ingredients in a FCDP does not decrease the purity, potency, safety or effectiveness of any of the individual components. In addition the

clinical reviewer agrees that the FCDP when used as directed provides rational concurrent treatment in that: the two products lower glucose through different mechanisms of action and can currently be independently co-administered in a significant proportion of the target population to improve glycemic control in patients not achieving glycemic control on maximally effective doses of either agent alone. I concur with the review team's assessments and note that the main benefit of this FCDP is convenience of administration.

To form the basis of the efficacy claim and establish the safety of Synjardy, the applicant relies on trials previously reviewed under NDA 204629. Two clinical trials (Trial numbers 1245.23_{met} and $1245.23_{met + SU}$) reviewed and summarized[1] previously, evaluated the efficacy and safety of empagliflozin 10 and 25 mg co-administered with maximally effective doses of metformin (≥ 1500 mg/day of metformin). These two trials are considered pivotal to support the efficacy claim for the FCDP but relied on independently administered products and on once daily empagliflozin administration. To bridge once to twice daily empagliflozin administration the applicant performed study number 1276.1, a 16 week study comparing HbA1c lowering achieved when empagliflozin is administered once vs. twice daily. To bridge differences between independently administered product versus combined administration in the FCDP dosage form the applicant performed two PK/PD bioequivalence studies (i.e., refer to study numbers: 1276.6 and 1276.8). Dr. Chong and the review team have summarized the trials and their findings in details. The Division concludes that the three studies adequately bridge differences between the FCDP and it's intended use and the pivotal trials relied upon to establish the safety and effectiveness of the FCDP.

Several other trials are included in this application and provide additional supportive data related to the safety of co-administering empagliflozin with metformin but are not necessary or are limited[2] in their ability to support the efficacy claim (refer to Section 5.1 of Dr. Chong's review for details).

Dr. Chong has reviewed the safety of empagliflozin and metformin co-administration, specifically, in great details in his review. Safety analyses include safety data previously reviewed under NDA 204629 and new data. Dr. Chong did not identify any new or concerning safety signal related to co-administration use that would warrant inclusion in product labeling and concludes that safety findings of co-administration use are consistent with findings made at the time of the empagliflozin NDA review.

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[1] Refer to my memorandum in DARRTS for NDA 204629 with a final date of 4 March, 2014

[2] For example in some trials included in this NDA, only non-randomized subgroups of patients within these trials were receiving both drugs in the FCDP

Summary of the Issues Leading to the Regulatory Action:

During labeling negotiations the Division was not able to reach agreement on the content of the full prescribing information for Synjardy.

I recommend a Complete Response of the application because labeling contains particulars that the Division consider false and misleading[3]. (b) (4) Trial 1245.28 was a randomized, double-blind, parallel group, active-controlled trial which compared the efficacy of empagliflozin (25mg) to glimepiride (1-4 mg) when added to maximally tolerated background metformin. The 52-week efficacy and safety data from this trial were previously reviewed under NDA 204629 and figure in Section 14.2 of the current Jardiance Full Prescribing Information[4]. We view the 52-week data (i.e., the data already in the Jardiance package insert) as supporting efficacy of the combination product.

In this submission, the applicant seeks (b) (4)

After reviewing these data, the Division concluded that (b) (4) would be unsubstantiated and would be otherwise misleading for the following reasons: (b) (4)

[3] See 21 CFR 314.125

[4] http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=faf3dd6a-9cd0-39c2-0d2e-232cb3f67565 accessed 4 June, 2015.

[5] (b) (4)

The Division communicated to the applicant that it regarded the 52-week efficacy data from this trial as sufficient to inform the safe and effective use of the FCDP. The applicant was given several opportunities to communicate their views on the matter during labeling negotiations. In addition, on 3 June 2015, a teleconference between the Division and applicant took place to discuss a potential path forward. On 3 June 2015 Michael White, project manager in the Division, received and email from Dr. Joachim Troost in Regulatory Affairs at Boehringer Ingelheim stating that they did not agree with the Division's assessment and could not agree to labeling at this time. The email response is copied below.

"We would again like to thank Dr. Guettier and the Division for the opportunity to discuss the status of the SYNJARDY NDA earlier today. After further internal discussions involving leadership, we hereby inform you that BI is not able to agree to the most recent FDA comments on the proposed labeling for SYNJARDY, (b) (4) *We understand, based on our discussions with you, that that this will likely result in a Complete Response Letter. Please note that BI intends to resubmit the NDA, and intends to address the FDA comments to the proposed labeling at that time."*

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/s/

JEAN-MARC P GUETTIER
06/04/2015

CLINICAL REVIEW/CROSS-DISCIPLINE MEMORANDUM

Application Type	New Combination NDA
Application Number(s)	NDA-206111
Priority or Standard	Standard
Submit Date(s)	August 4, 2014
PDUFA Goal Date	June 4, 2015
Division / Office	Division of Metabolism and Endocrinology Products
Reviewer Name(s)	William H. Chong, MD
Review Completion Date	
Established Name	Empagliflozin and metformin HCl
(Proposed) Trade Name	SYNJARDY (proposed)
Therapeutic Class	Fixed combination drug product of a sodium-glucose cotransporter-2 inhibitor and a biguanide
Applicant	Boehringer Ingelheim
Formulation(s)	Oral tablet
Dosing Regimen	Empagliflozin/Metformin hydrochloride 5/500 mg, (b) (4) 5/1000 mg, 12.5/500 mg, (b) (4) and 12.5/1000 mg
Indication(s)	Adjunct to diet and exercise to improve glycemic control in adult subjects with type 2 diabetes mellitus (b) (4)
Intended Population(s)	Adults with type 2 diabetes mellitus

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Abbreviations:

AE	Adverse event
Alk Phos	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	Twice daily
Bpm	Beats per minute
CI	Confidence interval
CMC	Chemistry, manufacturing, and controls
CMQ	Customized MedDRA query
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
eGFR	Estimated glomerular filtration rate
Empa	Empagliflozin
FCDP	Fixed combination drug product
HbA1c	Hemoglobin A1c
ICH	International Conference on Harmonization
LDL-C	Low density lipoprotein cholesterol
LLRR	Lower limit of reference range
LVOT	Last value on treatment
MedDRA	Medical Dictionary for Regulatory Affairs
mmHg	Millimeters of mercury
MRHD	Maximum recommended human dose
NDA	New drug application
NOAEL	No observed adverse effect limit
Per100	Per 100 patient-years
PT	Preferred term
Pt-yrs	Patient-years
Q1	First quartile
Q3	Third quartile
QDay	Once daily
RR	Reference range
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SGLT2	Sodium-glucose cotransporter-2
SMQ	Standard MedDRA query
SOC	System organ class
T. Bili.	Total bilirubin
T2DM	Type 2 diabetes mellitus
ULRR	Upper limit of reference range

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend an approval action for this New Drug Application (NDA), pending agreement on labeling.

1.2 Risk Benefit Assessment

The clinical studies submitted in support of the empagliflozin NDA and in support of this fixed combination drug product (FCDP) have demonstrated efficacy in improving glycemic control (as measured by HbA1c) of empagliflozin plus metformin when compared to placebo (i.e., metformin alone). Whether the combination yields greater glycemic control than empagliflozin alone was not studied and is not known, but I do not feel that this needs to be shown to conclude that this FCDP is efficacious. The studies to support this product were not done with the FCDP tablet but with separately administered drug, thus additional studies were needed to support the twice daily FCDP. Data from these additional studies support that splitting the dose of empagliflozin does not result in altered efficacy. This allows for the acceptance of the efficacy findings from the studies performed with the separately administered drugs for this FCDP.

The findings from the safety data submitted to support this FCDP is similar to what was seen in the empagliflozin NDA. This is not surprising given that the vast majority of the studies submitted were the same studies submitted in support of the monocomponent NDA. Safety findings include increased risk for urogenital infections, volume depletion/hypotension, and decreases in renal function. There were some concerning laboratory findings such as increases in low-density lipoprotein cholesterol, but the significance of these observations is not known. Notably, there was no evidence of new or more concerning safety signals with twice daily vs. once daily dosing. I believe that the identified risks are manageable with appropriate labeling, and that the risks associated with therapy do not outweigh the benefits.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I do not recommend a Risk Evaluation and Mitigation Strategy for this NDA.

1.4 Recommendations for Postmarket Requirements and Commitments

I have no recommendations for post-marketing requirements or commitments.

2 Introduction and Regulatory Background

2.1 Product Information

Empagliflozin is a sodium-glucose cotransporter-2 (SGLT2) inhibitor approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). By inhibiting glucose reabsorption in the kidney, empagliflozin increases the urinary excretion of glucose and thus reduces plasma glucose levels.

Metformin is a biguanide approved for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. By decreasing hepatic gluconeogenesis, and improving peripheral insulin sensitivity leading to increased peripheral glucose uptake and utilization, metformin lowers plasma glucose levels.

This fixed combination drug product (FCDP) combines these two products into a single tablet.

2.2 Tables of Currently Available Treatments for Proposed Indications

Several classes of drugs are currently approved for the treatment of T2DM, used either alone or in combination. These drug classes are:

- Biguanides (i.e. metformin)
- Sulfonylureas
- Thiazolidinediones
- Meglitinides
- Phenylalanine derivatives
- DPP-4 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 two active ingredients for the proposed FCDP are approved for use in the United States and available by prescription. The FCDP tablet is not available in the United States or elsewhere.

2.4 Important Safety Issues with Consideration to Related Drugs

Safety concerns with SGLT2 inhibitors 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 with metformin include:

- Lactic acidosis
- Diarrhea
- Nausea
- Vitamin B12 deficiency
- Hypoglycemia with concomitant insulin or insulin secretagogue therapy

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Date	Interaction
January 25, 2011	Written responses provided to the Applicant in response to questions submitted as a Type C meeting (submitted to IND-102145 [empagliflozin]). The main question discussed was the general design of a factorial study evaluating the combination of empagliflozin and metformin.
July 22, 2013	Initial pediatric study plan submitted requesting a full waiver.
November 22, 2013	Revised pediatric study plan submitted amending the plan to waive study of subjects < 10 years old and defer study of subjects 10 to < 18 years old.
January 10, 2014	Preliminary responses issued to the Applicant in response to questions submitted in preparation for a pre-NDA meeting (submitted to IND-117670). The pre-NDA meeting was ultimately cancelled by the Applicant.
August 4, 2014	Submission of NDA-206111

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The NDA submission is adequate for meaningful review. The clinical summaries and individual study reports have been submitted for review along with datasets.

3.2 Compliance with Good Clinical Practices

The Applicant reports that all of the clinical studies that support this NDA were performed in compliance with the protocol, in accordance with the Declaration of Helsinki, in accordance with the International Conference on Harmonization – Good Clinical Practice (ICH E6), and in accordance with applicable regulatory requirements.

3.3 Financial Disclosures

The Applicant has submitted an integrated financial disclosure form for all of the studies submitted in support of the NDA. While some investigators disclosed significant compensation or equity interest in the company, it is unlikely that the input of these few investigators substantially impacted the findings from the studies. See section 9.3 for the completed Financial Disclosure Review Template.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

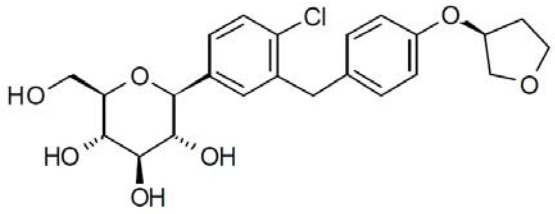
For detailed discussion of the Chemistry, Manufacturing, and Controls (CMC), see Dr. Joseph Leginus' CMC review. Based on review of the information submitted to the NDA, Dr. Leginus recommends approval.

The FCDP product will be an immediate-release, film-coated tablet for oral administration. The Applicant initially proposed manufacture of [redacted] (b) (4) empagliflozin/metformin hydrochloride 5/500 mg, [redacted] (b) (4) 5/1000 mg, 12.5/500 mg, [redacted] (b) (4) and 12.5/1000 mg. [redacted] (b) (4)

Empagliflozin:

Chemical formula: $C_{23}H_{27}ClO_7$
Molecular weight: 450.91 g/mol

Figure 1: Structural formula of empagliflozin

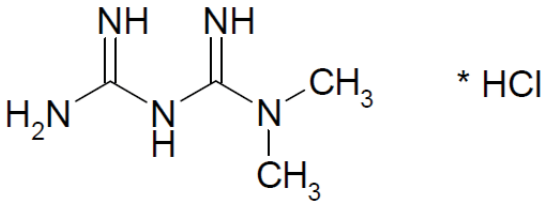


Source: Excerpted from Figure 1 of the Quality Overall Summary

Metformin hydrochloride:

Chemical formula: $C_4H_{11}N_5$•HCl
Molecular weight: 165.62 g/mol

Figure 2: Structural formula of metformin hydrochloride



Source: Excerpted from Figure 3 of the Quality Overall Summary

Compatibility testing of empagliflozin and metformin was investigated (b) (4) Thus, Dr. Leginus concludes that the drug substances are compatible.

The excipients used in the FCDP product are compendial. While the film-coat is not compendial, the components of the film-coat are compendial. Dr. Leginus has no concerns about the excipients or film-coat.

Manufacture of the FCDP tablet requires (b) (4) steps:

(b) (4)

(b) (4)

Stability batches were manufactured at production scale. The stability of the FCDP tablet was investigated under long-term and accelerated conditions. Stress stability studies included exposure of (b) (4) samples to light, temperature, and humidity. (b) (4)

(b) (4)

(b) (4) all tested attributes remained within specification limits (b) (4) no change in test parameters was observed.

Based on the stability studies, Dr. Leginus concludes that a shelf-life of 30 months for the tablets containing empagliflozin 5 mg and of 36 months for the tablets containing empagliflozin 12.5 mg can be granted when the product is maintained at 25^{o}C and 60% relative humidity in the proposed container closure system.

No concerns were raised in Dr. Leginus' review with regard to the manufacturing of the FCDP product.

4.2 Clinical Microbiology

No information on microbial enumeration was included in the NDA. A rationale for excluding this testing was included. This was reviewed by Dr. John W. Metcalfe who found the rationale suitable and agreed with the proposal to waive microbial limits testing. For detailed discussion, see Dr. Metcalfe's memorandum.

4.3 Preclinical Pharmacology/Toxicology

The primary Pharmacology/Toxicology review was completed by Dr. Mukesh Summan. Dr. Summan's review relies in part on prior findings of safety and efficacy for the components of

this FCDP. The current review focuses on the interactions between empagliflozin and metformin. For a detailed discussion of the pharmacology/toxicology data, see Dr. Summan's review. Based on these studies and on information from the individual components, Dr. Summan concludes that the nonclinical studies support safety and approval of the FCDP product.

The safety of co-administration of empagliflozin was evaluated in a 2 week rat, 3 month rat, and embryo-fetal development studies. Additionally, a 2 week rat toxicology study and a rat embryo-fetal development study were performed with metformin alone.

The toxicology findings from the co-administration studies were consistent with the findings with the toxicology studies of the individual components.

The 2 week repeat dose rat toxicology study showed that doses of 500/1000 mg/kg of empagliflozin/metformin were not tolerated and resulted in mortality and moribund animals. There was failure to gain weight, kidney tubular degeneration, mineralization of pelvic calculi and hydronephrosis. From this study, the no observed adverse effect limit (NOAEL) was determined to be the 100/200 mg/kg dose. This translates to roughly 13x the maximum recommended human dose (MRHD) for empagliflozin and 3x the MRHD for metformin.

In the 3 month repeat dose rat toxicology study, doses of 200/400 mg/kg of empagliflozin/metformin resulted in reduced body weight. There was one unexplained death at this dose as well. There was minimal mineralization of the renal pelvic epithelium at the 200/400 mg/kg dose. From this study, the NOAEL was set determined to be 50/100 mg/kg. This translates to roughly 4-6x the MRHD for empagliflozin and 2x the MRHD for metformin.

In the embryo-fetal development studies, there was no evidence of teratogenicity at the 100/200 mg/kg dose. Higher exposure resulted in dose-dependent increases in skeletal malformations. These malformations were also seen in the animals treated with the individual components, though at a lower incidence. Based on reduced maternal body weight, body weight gain, and food consumption, the NOAEL for maternal toxicity was determined to be 30/60 mg/kg. This translates roughly to 3-4x the MRHD for empagliflozin and 1x the MRHD for metformin.

4.4 Clinical Pharmacology

For a detailed discussion of the clinical pharmacology information, see Dr. Suryanarayana Sista's review. For detailed discussion of biopharmaceutics, see Dr. Kelly Kitchens' review. The clinical bridging study was also reviewed as part of the statistical review by Dr. Shuxian Sinks. Based on the findings from the reviews of Drs. Kitchens, Sista, and Sinks, there appears to be an adequate bridge between once daily dosing of empagliflozin to twice daily dosing of

empagliflozin. All three reviewers recommend approval of the FCDP based on the submitted data.

4.4.1 Mechanism of Action and Pharmacodynamics

Empagliflozin is a member of the SGLT2 inhibitor class of drugs. The mechanism of action for this class is inhibition of the renal sodium-dependent glucose co-transporter-2. As a result of this, renal glucose reabsorption is blocked leading to increased urinary glucose losses. Administration of empagliflozin results in a dose-dependent increase in urinary glucose excretion. The urinary glucose excretion appears to plateau at around the 10 mg dose. Plasma glucose decreases after administration of empagliflozin.

Metformin is a biguanide. It is believed that metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves peripheral insulin sensitivity. As a result of these actions, it improves glucose tolerance and lowers fasting and postprandial glucose.

4.4.2 Pharmacokinetics

Empagliflozin:

- Absorption:

After single dose administration, empagliflozin is absorbed rapidly with a median time to peak plasma concentration of 1 hour. Plasma levels decline in a biphasic fashion. Exposure increases in proportion to the dose.

- Distribution:

The apparent steady-state volume of distribution ranged from 180-230 L.

- Metabolism:

The primary route of metabolism based on *in vitro* studies is glucuronidation by uridine 5`-diphospho-glucuronosyltransferases. No major metabolites are detected in human plasma.

- Elimination:

The apparent terminal elimination half-life of empagliflozin is 12.4 hours, and the apparent oral clearance is 10.6 L/hour. Approximately 54.4% of the dose is excreted in the urine and 41.2% of the dose is excreted in the feces.

Metformin:

- Absorption:

The bioavailability of metformin 500 mg is approximately 50 to 60%. There is a lack of dose proportionality with increasing dose, presumably due to decreased absorption. Food decreases and delays absorption of metformin, but the clinical relevance is unknown.

- Distribution:

The apparent volume of distribution after an 850 mg dose is 654 +/- 358 L.

- Metabolism:

No metabolites have been identified in humans.

- Elimination:

Metformin is excreted in the urine. Renal clearance is approximately 3.5x greater than creatinine clearance. This suggests that tubular secretion is the major route of metformin elimination.

Additional pharmacology studies submitted in support of this NDA include an empagliflozin-metformin drug-drug interaction (DDI) study, and a relative bioavailability/food effect study.

The DDI study was reviewed by Dr. Manoj Khurana during the review of the empagliflozin NDA (NDA-204629). Co-administration of multiple daily doses of empagliflozin and metformin did not demonstrate any drug-drug interactions.

Dr. Sista reviewed the relative bioavailability/food effect study (study 1276.5) in his review. Administration of the FCDP product was bioequivalent to separate administration of the individual components. Co-administration with a high-fat, high-calorie meal decreased the peak systemic exposure for empagliflozin and metformin, but the area under the curve was unaffected. This is consistent with previous findings of food effect for the individual components, and the observed effect is unlikely to be clinical importance.

4.4.3 Bridging/Bioequivalence

The FCDP tablet was not used in any of the clinical studies that support the evaluation of safety and efficacy. These studies used separate tablets of empagliflozin and metformin to evaluate safety and efficacy of the combination. To support the proposed FCDP tablet, the Applicant has performed dissolution testing as well as three phase 1/bioequivalence studies in healthy volunteers (studies 1276.6, (b) (4) and 1276.8).

There were differences between the FCDP product and metformin on dissolution testing. This was not seen when comparing the FCDP product with empagliflozin. However, the observed differences on dissolution testing with metformin were not felt to be meaningful due to the findings from the clinical bioequivalence studies. Based on bioequivalence studies, systemic exposures after administration of the FCDP product are bioequivalent to exposures seen with administration of the separate components under fasting and fed conditions. (b) (4) For detailed discussion of the findings from the dissolution testing and bioequivalence studies, see Dr. Kitchens' review.

As empagliflozin is approved for once daily use, support for the twice daily dosing of the FCDP product was needed. The Applicant has performed a 16 week phase 2 study looking at twice daily empagliflozin vs. once daily empagliflozin on a background of metformin (study 1276.10). This study was required by the European Medicines Agency to show comparable efficacy of twice daily vs. once daily dosing. In Dr. Sista's review of this study, he notes that trough concentrations were similar between each dose group on days 28 and 112 indicating that steady-state concentrations were maintained during the course of the study. Exposure increases were roughly proportional with an increase from 5 mg twice daily to 12.5 mg twice daily and with an increase from 10 mg once daily to 25 mg once daily. The primary endpoint of this study was change in HbA1c from baseline to week 16 with an objective of showing non-inferiority. This study was considered in Dr. Shuxian Sinks' statistical review, who concluded that the change in HbA1c was comparable with twice daily dosing and once daily dosing (Table 1).

Table 1: HbA1c results from Study 1276.10

	Empa 5 mg BID N=219	**Empa 10 mg QDay N=220**	**Placebo N=107**
Mean baseline HbA1c (SE)	7.79 (0.79)	7.83 (0.75)	7.69 (0.72)
Change from baseline to week 16	-0.74 (0.06)	-0.7 (0.06)	-0.28 (0.08)
Vs. Empa 10mg QDay			
– difference (97.5 % CI)	-0.04 (-0.20, 0.14)		
Vs. Placebo			
– difference (95% CI)	-0.47 (-0.66,-0.27)	-0.43 (-0.63, -0.23)	
	Empa 12.5 mg BID N=219	**Empa 25 mg QDay N=218**	**Placebo N=107**
Mean baseline HbA1c (SE)	7.78 (0.79)	7.73 (0.79)	7.69 (0.72)
Change from baseline to week 16	-0.9 (0.06)	-0.78 (0.05)	-0.28 (0.08)
Vs. Empa 10mg QDay			
– difference (97.5 % CI)	-0.13 (-0.27, 0.036)		
Vs. Placebo			
– difference (95% CI)	-0.63 (-0.83, -0.42)	-0.5 (-0.69, -0.37)	

BID = twice daily; QDay = once daily; SE = standard error; Empa = empagliflozin
Source: Adapted from Table 14 of Dr. Sinks' review

5 Sources of Clinical Data

The majority of the clinical data submitted to support this Application come from the empagliflozin NDA submission (NDA-204629) where the individual components of the FCDP product were administered separately.

Studies with the FCDP product are limited to studies used to support bioequivalence of the individual components and the FCDP product.

5.1 Tables of Studies/Clinical Trials

To support the safety and efficacy of this FCDP product, the Applicant is relying primarily on data previously submitted to the empagliflozin NDA. An additional study from the empagliflozin/linagliptin FCDP program (study 1275.1) is included, and a not previously reviewed study of empagliflozin on a background of multiple daily injections of insulin (study 1245.29) is also included. Updated 104 week data is included for the active-controlled study of empagliflozin vs. glimepiride (study 1245.28).

The pool of submitted studies is comprised of five phase 1 studies, three phase 2 studies (with one extension study), and seven phase 3 studies (with one extension). There were five studies (four phase 1, one phase 2) performed specifically to support the FCDP NDA (Table 2).

Table 2: Studies submitted in support of the New Drug Application

Study Number	Description
Phase 1	
1245.6	Drug-drug interaction of empagliflozin with metformin
1276.5[1]	Bioavailability of empagliflozin/metformin 12.5/1000 mg, and evaluation of food effect
1276.6[1]	Bioequivalence of empagliflozin/metformin 12.5 or 5/500 mg
	(b) (4)
1276.8	Bioequivalence of empagliflozin/metformin 12.5 or 5/1000 mg
Phase 2	
1245.10	12 week dose-finding with metformin background
1245.33	78 week study of empagliflozin with basal insulin, +/- metformin and/or sulfonylurea
1276.10[1]	16 week study of empagliflozin once daily vs. empagliflozin twice daily on background of metformin
Phase 3	
1245.23_{met}	24 week study of empagliflozin on a background of metformin
1245.23_{met+SU}	24 week study of empagliflozin on a background of metformin + sulfonylurea
$1245.19_{pio+met}$	24 week study of empagliflozin on a background of pioglitazone + metformin
1245.28	4 year study of empagliflozin vs. glimepiride on a background of metformin (includes updated data to 104 weeks)
1245.36	52 week study of empagliflozin in subjects with renal impairment on a background of various antidiabetics
1245.48	12 week study of empagliflozin in subjects with T2DM and hypertension on a background of various antidiabetics
1245.49	52 week study of empagliflozin on a background of multiple daily injection of insulin +/- metformin
1275.1_{met}	52 week study of empagliflozin/linagliptin FCDP vs. the individual components with metformin background

Study Number	Description
Extension studies	
1245.24	78 week extension of study 1245.10
1245.31	Long-term extension of studies 1245.23 and 1245.19

[1] studies performed specifically to support this fixed combination drug product
FCDP = fixed combination drug product
Source: Adapted from Table 1.1.1: 1 of the Summary of Clinical Safety

5.2 Review Strategy

For efficacy, my review focuses on the new clinical data submitted with this NDA (i.e., study 1245.28, study 1245.49, and study 1276.10). Discussion of the efficacy findings from previously submitted studies can be found in the review by Dr. Dongmei Liu and in my review for NDA-204629 (empagliflozin), and in the review by Dr. Jennifer Clark and my review for NDA-206073 (empagliflozin/linagliptin FCDP).

For safety, I will focus on the pool of placebo-controlled studies. In the pools used to support this NDA, the Applicant has presented only those subjects that were concomitantly treated with metformin. Safety findings from study 1276.10 will be separately discussed.

5.3 Discussion of Individual Studies/Clinical Trials

I will briefly discuss the general design of the clinical studies included to support the FCDP product. Details of each of the studies can be found in the respective study protocol.

Phase 1:

The phase 1 studies submitted in support of the FCDP product were all single-dose, cross-over studies in healthy volunteers.

Phase 2:

Study 1245.10 was a 12 week randomized, double-blind study which studied 5 different dosage strengths of empagliflozin once daily compared to placebo. There was also an open-label sitagliptin arm. The subject population was subjects with T2DM already treated with metformin (≥ 1500 mg/day). The primary endpoint was change in HbA1c from baseline. Change in fasting plasma glucose from baseline was also assessed. This study was used to select the dosage strengths to evaluate in phase 3.

Study 1245.33 was a 78 week randomized double-blind study of empagliflozin vs. placebo on a background of basal insulin. The subject population was subjects with T2DM already treated

with basal insulin, with or without metformin and/or sulfonylurea. The basal insulin could be insulin glargine, insulin detemir, or NPH insulin. Insulin dose was to be kept stable during the first 18 weeks. The primary endpoint was change in HbA1c at 18 weeks. Only information from subjects with a background of metformin therapy is included in the evaluation of efficacy and safety of the proposed FCDP.

Study 1276.10 was a 16 week randomized, double-blind study of empagliflozin administered once daily vs. empagliflozin administered twice daily on a background of metformin. The subject population was subjects with T2DM already treated with metformin. The total daily dose of empagliflozin was the same for once daily and twice daily dosing. The primary endpoint was change in HbA1c at 16 weeks. The purpose of this study was to show non-inferiority between a divided dose of empagliflozin and a once daily dose of empagliflozin to support the twice daily dosing of the proposed FCDP product.

Phase 3:

Study 1245.23 was a 24 week randomized double-blind study of empagliflozin vs. placebo. The subject population was subjects with T2DM already treated with metformin +/- a sulfonylurea. Due to the possible sulfonylurea background therapy, the study was designed and analyzed as two separate study populations (metformin only background and metformin + sulfonylurea background). In addition to the blinded treatment arms, there was an open-label empagliflozin arm. The primary endpoint was change in HbA1 at 24 weeks. This study was a "pivotal" phase 3 study supporting the empagliflozin NDA.

Study 1245.19 was a 24 week randomized double-blind study of empagliflozin vs. placebo. The subject population was subjects with T2DM already treated with pioglitazone +/- metformin. The primary endpoint was change in HbA1c at 24 weeks. This study was a "pivotal" phase 3 study supporting the empagliflozin NDA. Only information from subjects with a background of metformin therapy is included in the evaluation of efficacy and safety of the proposed FCDP. The statistical testing included separate testing of the pioglitazone + metformin background subjects (assuming preceding hypothesis testing was successful).

Study 1245.28 is a 208 week randomized double-blind study of empagliflozin vs. glimepiride. The subject population is subjects with T2DM already treated with metformin. The primary endpoint is change in HbA1c at 52 and 104 weeks. There is an ongoing 104 week extension. The available 104 week data from this study is included for evaluation of efficacy and safety of the proposed FCDP.

Study 1245.36 was a 52 week randomized double-blind study of empagliflozin vs. placebo. The subject population was subjects with T2DM and varying degrees of renal impairment. Any anti-diabetic therapy was allowed as background. The primary endpoint was change in HbA1c at 24 weeks. Only the information from subjects with a background of metformin therapy is included in the evaluation of efficacy and safety of the proposed FCDP.

Study 1245.48 was a 12 week randomized double-blind study of empagliflozin vs. placebo. The subject population was subjects with T2DM and hypertension. Any anti-diabetic therapy was allowed as background. The primary endpoint was change in HbA1c at 12 weeks with a co-primary endpoint of change in mean 24 hour systolic blood pressure. Only the information from subjects with a background of metformin therapy is included in the evaluation of efficacy and safety of the proposed FCDP.

Study 1245.49 was a 52 week randomized double-blind study of empagliflozin vs. placebo. The subject population was subjects with T2DM already treated with multiple daily injections of insulin, with or without metformin. Insulin dose was to remain stable for the first 18 weeks. The primary endpoint was change in HbA1c at 18 weeks. Only information from subjects with a background of metformin therapy is included in the evaluation of efficacy and safety of the proposed FCDP.

Study 1275.1_{met} was a 52 week randomized double-blind study of an FCDP of empagliflozin and linagliptin vs. the individual components. The subject population was subjects with T2DM, with or without metformin background. The primary endpoint was change in HbA1c at 24 weeks. Only the information from subjects with a background of metformin therapy is included in the evaluation of efficacy and safety of the proposed FCDP. This study was designed to analyze the treatment naïve and the metformin treated subjects separately. Only the metformin treated subjects are considered for this FCDP.

Extensions:

Study 1245.24 was a 78 week open-label extension of two phase 2 studies. The phase 2 study included in to support the efficacy and safety of the FCDP was study 1245.10 (see summary of this study above). The other phase 2 study did not include metformin therapy as background. The main objective of this extension was to collect additional safety information. Only information from the extension of study 1245.10 is included in the evaluation of efficacy and safety of the proposed FCDP.

Study 1245.31 was a 78 week open-label extension of three phase 3 studies. Two of those studies (study 1245.23 and study 1245.19) included subjects with metformin therapy as

background. The main objective of this extension was to collect additional safety information. Only information from the subjects with a background of metformin therapy is included in the evaluation of efficacy and safety of the proposed FCDP.

6 Review of Efficacy

Efficacy Summary

The efficacy of empagliflozin in a variety of background therapies was reviewed in the empagliflozin NDA. Many of those studies included (at least in part) a background of metformin, and are thus relevant to this NDA. Additionally, a factorial study previously submitted to support the empagliflozin/linagliptin NDA was submitted as well. Findings from previously reviewed studies will not be discussed here, but the results support additional efficacy with adding empagliflozin to metformin.

New efficacy data from three studies were submitted to support the fixed combination product NDA. These were additional data from an active comparator study (study 1245.28), a new clinical study of empagliflozin vs. placebo on a background of multiple daily injections of insulin with or without metformin (study 1245.49), and a clinical bridging study to support splitting the dose of empagliflozin (study 1276.10).

At 104 weeks, empagliflozin 25 mg on a background of metformin was shown to be non-inferior to glimepiride (mean dose of 2.7 mg) for reducing HbA1c. This finding was robust in all of the sensitivity analyses. (b) (4) These issues taken in combination with the absence of a second study showing the same outcome lead me to conclude that a conclusion of non-inferiority seems appropriate (b) (4)

(b) (4)

Study 1276.10 showed that the split dosing (i.e., twice daily) of empagliflozin produces similar efficacy as once daily dosing. Given that empagliflozin is approved as a once daily drug, an obvious question in considering a twice daily formulation is whether this alters the efficacy. From the findings of this study, it is reasonable to conclude splitting the dose does not impact glycemic lowering.

Based on the efficacy findings in previously reviewed studies, and from the new clinical data submitted it is reasonable to conclude that combining empagliflozin with metformin results in improved glycemic control.

6.1 Indication

The proposed indication for this FCDP product is "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (b) (4) ".

6.1.1 Methods

The primary review for efficacy was performed by Dr. Shuxian Sinks. Many of the studies submitted in support of this NDA were previously reviewed during the review of the empagliflozin NDA (NDA-204629) or during review of the empagliflozin/linagliptin FCDP NDA (NDA-206073). The focus of the discussion of efficacy will be on the additional efficacy data included in this submission. The focus of the efficacy discussion in Dr. Sinks' review is on the 104 week data from the active comparator study of empagliflozin 25 mg vs. glimepiride (study 1245.28), the add-on to multiple daily injections of insulin with or without metformin (study 1245.49), and the clinical bridging study to support twice daily dosing of empagliflozin (study 1276.10).

In this review, I will focus on the new efficacy data included in this submission. Discussion of the previously reviewed studies can be found in the reviews for empagliflozin (NDA-204629) and empagliflozin/linagliptin (NDA-206073).

6.1.2 Demographics

In general, the baseline demographics were balance between treatment arms in study 1245.28, study 1245.49, and study 1276.10 (Table 3, Table 4, and Table 5). Baseline demographics were also generally balanced between treatment groups in the previously reviewed studies. The majority of subjects in these studies were Non-Hispanic and White. This is similar to what was

seen in previous studies reviewed for the empagliflozin NDA. Though the population may not be an accurate representation of the United States population with T2DM, I do not believe this to have a meaningful effect on the interpretation of efficacy.

Table 3: Baseline demographics for Study 1245.28

	Empa 25 N=765	Glimepiride N=780
Age (years)		
– Mean (SD)	56.2 (10.3)	55.7 (10.44)
Age (years), N (%)		
– 50 to <65	395 (51.6)	417 (53.5)
– 65 to <75	145 (19.0)	125 (16.0)
– <50	197 (25.8)	212 (27.2)
– ≥75	28 (3.7)	26 (3.3)
Ethnic, N (%)		
– Hispanic	153 (20.0)	159 (20.4)
– Non-Hispanic	612 (80.0)	621 (79.6)
Race, N (%)		
– Asian	254 (33.2)	253 (32.4)
– Black	12 (1.6)	8 (1.0)
– Native Hawaiian	1 (0.1)	0 (0.0)
– White	498 (65.1)	519 (66.5)
Region, N (%)		
– Asia	215 (28.1)	219 (28.1)
– Europe	317 (41.4)	322 (41.3)
– Latin America	136 (17.8)	140 (17.9)
– North America	97 (12.7)	99 (12.7)
Sex, N (%)		
– Male	432 (56.5)	421 (54.0)
eGFR, N (%)		
– 30 to <60	13 (1.7)	22 (2.8)
– 60 to <90	439 (57.4)	440 (56.4)
– ≥90	313 (40.9)	318 (40.8)
HbA1c		
– Mean (SD)	7.9 (0.81)	7.9 (0.86)
HbA1c, N (%)		
– <8.5	584 (76.3)	589 (75.5)
– ≥8.5	181 (23.7)	191 (24.5)

Empa = empagliflozin; eGFR = estimated glomerular filtration rate as calculated by modification of diet in renal disease equation and expressed in ml/min/1.73 m^2
Source: Adapted from Table 3, Table 6 and Table 7 of Dr. Sinks' review

Table 4: Baseline demographics for Study 1245.49

	Empa 10 N=187	Empa 25 N=189	Placebo N=188
Age (years)			
– Mean (SD)	56.7 (8.68)	58 (9.39)	55.3 (10.1)
Age (years), N (%)			
– 50 to <65	113 (60.8)	108 (57.1)	104 (55.3)
– 65 to <75	32 (17.2)	41 (21.7)	35 (18.6)
– <50	38 (20.4)	33 (17.5)	49 (26.1)
– ≥75	3 (1.6)	7 (3.7)	0 (0.0)
Ethnic, N (%)			
– Hispanic	65 (34.9)	74 (39.2)	67 (35.6)
– Non-Hispanic	121 (65.1)	115 (60.8)	121 (64.4)
Race, N (%)			
– American Indian	3 (1.6)	2 (1.1)	4 (2.1)
– Asian	0 (0.0)	1 (0.5)	2 (1.1)
– Black	7 (3.8)	4 (2.1)	8 (4.3)
– Native Hawaiian	1 (0.5)	0 (0.0)	0 (0.0)
– White	175 (94.1)	182 (96.3)	174 (92.6)
Region, N (%)			
– Europe	101 (54.3)	105 (55.6)	106 (56.4)
– Latin America	59 (31.7)	61 (32.3)	58 (30.9)
– North America	26 (14.0)	23 (12.2)	24 (12.8)
Sex, N (%)			
– Male	97 (52.2)	84 (44.4)	75 (39.9)
eGFR, N (%)			
– 30 to <60	13 (7.0)	7 (3.7)	8 (4.3)
– 60 to <90	108 (58.1)	112 (59.3)	120 (63.8)
– ≥90	65 (34.9)	70 (37.0)	60 (31.9)
HbA1c			
– Mean (SD)	8.4 (0.74)	8.3 (0.72)	8.3 (0.72)
HbA1c, N (%)			
– <8.5	101 (54.3)	112 (59.3)	105 (55.9)
– ≥8.5	85 (45.7)	77 (40.7)	83 (44.1)

Empa = empagliflozin; SD =standard deviation; eGFR = estimated glomerular filtration rate as calculated by modification of diet in renal disease equation and expressed in ml/min/1.73 m^2
Source: Adapted from Table 4, Table 8 and Table 9 of Dr. Sinks' review

Table 5: Baseline demographics for Study 1276.10

	Empa 5 BID N=219	Empa 10 QDay N=220	Empa 12.5 BID N=219	Empa 25 QDay N=218	Placebo N=107
Age					
– Mean (SD)	58.9 (10.1)	58.4 (10.9)	57.6 (9.9)	58.1 (10.3)	57.9 (11.2)
Age, N (%)					
– 50 to <65	106 (48.4)	112 (50.9)	118 (53.9)	111 (50.9)	54 (50.5)
– 65 to <75	57 (26.0)	53 (24.1)	52 (23.7)	49 (22.5)	25 (23.4)
– <50	44 (20.1)	45 (20.5)	44 (20.1)	47 (21.6)	23 (21.5)
– ≥75	12 (5.5)	10 (4.5)	5 (2.3)	11 (5.0)	5 (4.7)

	Empa 5 BID N=219	Empa 10 QDay N=220	Empa 12.5 BID N=219	Empa 25 QDay N=218	Placebo N=107
Ethnic, N (%)					
– Hispanic	42 (19.2)	42 (19.1)	36 (16.4)	43 (19.7)	23 (21.5)
– Non-Hispanic	177 (80.8)	178 (80.9)	183 (83.6)	175 (80.3)	84 (78.5)
Race, N (%)					
– American Indian	3 (1.4)	10 (4.5)	6 (2.7)	3 (1.4)	4 (3.7)
– Asian	7 (3.2)	10 (4.5)	16 (7.3)	10 (4.6)	2 (1.9)
– Black	18 (8.2)	14 (6.4)	17 (7.8)	10 (4.6)	8 (7.5)
– Native Hawaiian	0 (0.0)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)
– White	191 (87.2)	186 (84.5)	179 (81.7)	194 (89.0)	93 (86.9)
Region, N (%)					
– Europe	131 (59.8)	134 (60.9)	135 (61.6)	130 (59.6)	66 (61.7)
– Latin America	18 (8.2)	19 (8.6)	18 (8.2)	17 (7.8)	9 (8.4)
– North America	70 (32.0)	67 (30.5)	66 (30.1)	71 (32.6)	32 (29.9)
Sex, N (%)					
– Male	123 (56.2)	111 (50.5)	126 (57.5)	118 (54.1)	55 (51.4)
eGFR, N (%)					
– 30 to <60	15 (6.8)	16 (7.3)	11 (5.0)	12 (5.5)	3 (2.8)
– 60 to <90	110 (50.2)	103 (46.8)	111 (50.7)	102 (46.8)	55 (51.4)
– ≥90	94 (42.9)	101 (45.9)	97 (44.3)	104 (47.7)	49 (45.8)
HbA1c					
– Mean (SD)	7.8 (0.88)	7.8 (0.75)	7.8 (0.79)	7.7 (0.79)	7.7 (0.72)
HbA1c, N (%)					
– <8.5	173 (79.0)	175 (79.5)	180 (82.2)	176 (80.7)	89 (83.2)
– >=8.5	46 (21.0)	45 (20.5)	39 (17.8)	42 (19.3)	18 (16.8)

Empa = empagliflozin; BID = twice daily; QDay = once daily; SD =standard deviation; eGFR = estimated glomerular filtration rate as calculated by modification of diet in renal disease equation and expressed in ml/min/1.73 m^2
Source: Adapted from Table 5, Table 10 and Table 11 of Dr. Sinks' review

6.1.3 Subject Disposition

In study 1245.28, there were 765 subjects exposed to empagliflozin 25 mg and 780 subjects exposed to glimepiride (Table 6). At 104 weeks, there were 545 (71.2%) still receiving empagliflozin and 510 (65.4%) still receiving glimepiride.

Table 6: Disposition of subjects in Study 1245.28 at 104 weeks

	Empa 25		Glimepiride	
	N	%	N	%
Treated	765	100	780	100
– Still on study medication	545	71.2	510	65.4
– Did not continue to extension period	95	12.4	128	16.4
Prematurely discontinued study medication				
– AE-Unexpected worsening of pre-existing disease	2	0.3	4	0.5
– AE-Unexpected worsening of disease under study	3	0.4	8	1.0
– Other AE	33	4.3	22	2.8
– Lack of efficacy	3	0.4	3	0.4

	Empa 25		Glimepiride	
	N	%	N	%
– Non-complaint with protocol	6	0.8	13	1.7
– Lost to follow-up	16	2.1	15	1.9
– Withdrawal by subject	37	4.8	31	4.0
– Other	25	3.3	46	5.9

Empa = empagliflozin; AE = adverse event
Source: Reproduced from Table 3 of Dr. Sinks' review

In study 1245.49, there were 187 subjects exposed to empagliflozin 10 mg, 189 subjects exposed to empagliflozin 25 mg, and 188 subjects treated with placebo. More than 80% of subjects remained on study drug through the end of the study in all treatment arms.

Table 7: Disposition of subjects in Study 1245.49 at 52 weeks

	Empa 10		Empa 25		Placebo	
	N	%	N	%	N	%
Treated	187	100	189	100	188	100
– Not prematurely discontinued (study medication)	155	83.3	163	86.2	157	83.5
Prematurely discontinued study medication						
– AE- Unexpected worsening of pre-existing disease	1	0.5	0	0	0	0
– AE- Unexpected worsening of disease under study	0	0	0	0	1	0.5
– Other AE	9	4.8	9	4.8	8	4.3
– Non-complaint with protocol	4	2.2	4	2.1	7	3.7
– Lost to follow-up	5	2.7	2	1.1	2	1.1
– Withdrawal by subject	9	4.8	8	4.2	9	4.8
– Other	3	1.6	3	1.6	4	2.1

Empa = empagliflozin; AE = adverse event
Source: Reproduced from Table 4 of Dr. Sinks' review

In study 1276.10, there were 219 subjects exposed to empagliflozin 5 mg BID, 220 subjects exposed to empagliflozin 10 mg QDay, 219 subjects exposed to empagliflozin 12.5 mg BID, 218 subjects exposed to empagliflozin 25 mg QDay and 107 subjects exposed to placebo. More than 90% of subjects remained on study drug through the end of the study in all treatment arms.

Table 8: Disposition of subjects in Study 1276.10 at 16 weeks

	Empa 5 BID		Empa 10 QDay		Empa 12.5 BID		Empa 25 QDay		Placebo	
	N	%	N	%	N	%	N	%	N	%
Treated	219	100	220	100	219	100	218	100	107	100
– Not prematurely discontinued study medication	202	92.2	201	91.4	205	93.6	205	94.0	103	96.3
Prematurely discontinued study medication										
– AE-Unexpected worsening of disease under study	0	0	1	0.5	1	0.5	1	0.5	0	0
– Other AE	4	1.8	12	5.5	4	1.8	4	1.8	1	0.9

	Empa 5 BID		Empa 10 QDay		Empa 12.5 BID		Empa 25 QDay		Placebo	
	N	%	N	%	N	%	N	%	N	%
– Lack of efficacy	0	0	0	0	0	0	0	0	1	0.9
– Non-complaint with protocol	3	1.4	2	0.9	1	0.5	0	0	1	0.9
– Lost to follow-up	4	1.8	3	1.4	1	0.5	1	0.5	0	0
– Withdrawal by subject	4	1.8	1	0.5	3	1.4	6	2.8	1	0.9

Empa = empagliflozin; BID = twice daily; QDay = once daily; AE = adverse event
Source: Reproduced from Table 5 of Dr. Sinks' review

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint in all three studies (study 1245.28, 1245.49, and 1276.10) was change from baseline in HbA1c. The timepoint was different in these three studies. For study 1245.28, the change from baseline in HbA1c was assessed at 104 weeks with the primary endpoint being non-inferiority to glimepiride. For study 1245.49, the change from baseline in HbA1c was assessed at 18 weeks with the primary endpoint being superiority to placebo. For study 1276.10 the change from baseline in HbA1c was assessed at 16 weeks with the primary endpoint being non-inferiority of twice daily dosing to once daily dosing. The primary analysis was based on the Full Analysis Set using an analysis of covariance model for all three studies. Missing data was imputed using last observation carried forward. The results for the primary analysis of the primary endpoint are shown in Table 9 and Table 10.

Table 9: Change from baseline in HbA1c for Study 1245.28 and Study 1245.49

	N	Baseline Mean (SE)	Change from Baseline (SE)	Difference	97.5% CI	p-value[1]	p-value[2]
Study 1245.28 (104 weeks)							
Glimepiride	780	(b) (4)					
Empa 25	765						
Study 1245.49 (18 weeks)							
Placebo	188	(b) (4)					
Empa 10	186						
Empa 25	189						

[1] for non-inferiority; [2] for superiority
SE = standard error; CI = confidence interval; Empa = empagliflozin
Source: Adapted from Table 12 and Table 13 of Dr. Sinks' review

Table 10: Change from baseline in HbA1c at 16 weeks in Study 1276.10

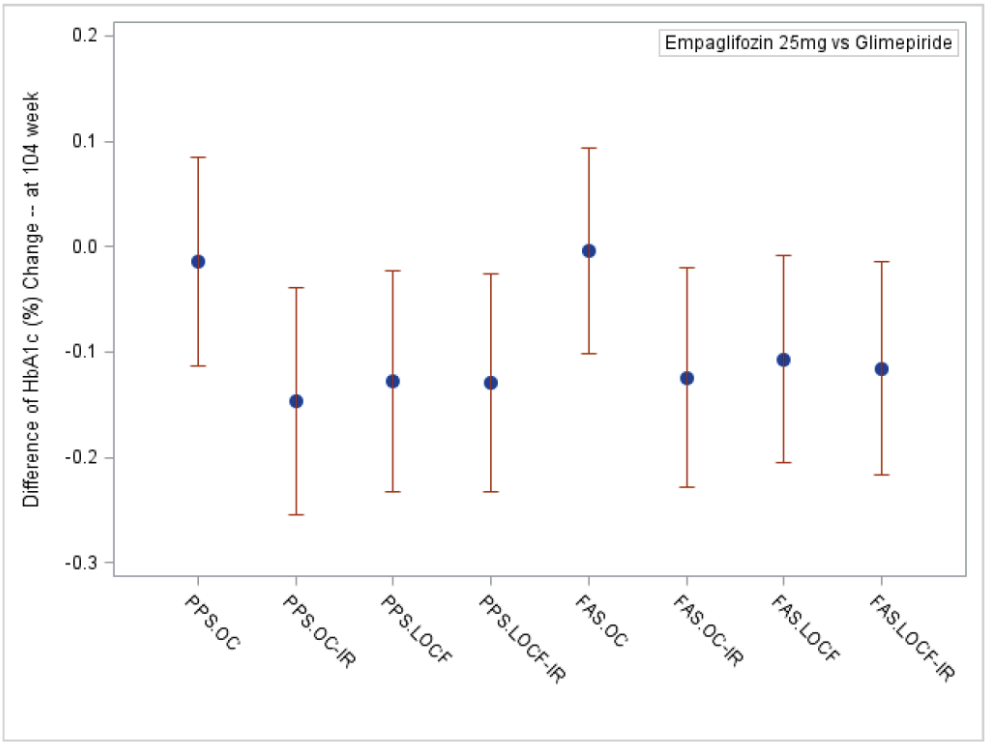
	Empa 5 BID N=219	**Empa 10 QDay N=220**	**Placebo N=107**
Mean baseline HbA1c (SE)	7.79 (0.79)	7.83 (0.75)	7.69 (0.72)
Change from baseline	-0.74 (0.06)	-0.7 (0.06)	-0.28 (0.08)
Comparison vs Empa 10mg QDay			
Difference (97.5 % CI)	-0.04 (-0.20, 0.14)		
Comparison vs placebo			
Difference (95% CI)	-0.47 (-0.66,-0.27)	-0.43 (-0.63, -0.23)	
	Empa 12.5 BID N=219	**Empa 25 QDay N=218**	**Placebo N=107**
Mean baseline HbA1c (SE)	7.78 (0.79)	7.73 (0.79)	7.69 (0.72)
Change from baseline	-0.9 (0.06)	-0.78 (0.05)	-0.28 (0.08)
Comparison vs Empa 25mg QDay			
Difference (97.5% CI)	-0.13 (-0.27, 0.036)		
Comparison vs placebo			
Difference (95% CI)	-0.63 (-0.83, -0.42)	-0.5 (-0.69, -0.37)	

Empa = empagliflozin; BID = twice daily; QDay = once daily; SE = standard error; CI = confidence interval
Source: Reproduced from Table 14 of Dr. Sinks' Review

The non-inferiority margin used in study 1245.28 was 0.3%. This margin was used for the analysis at 52 weeks (which is currently in the label) and for the analysis at 104 weeks. No justification for the selection of this margin was provided. Additional sensitivity analyses were performed by Dr. Sinks to assess the robustness of this finding. The non-inferiority finding was robust as none of the sensitivity analyses resulted in the upper bound of the confidence interval exceeding 0.3% (see Figure 1 of Dr. Sinks' review, excerpted below). (b) (4)

The current labeling language with regard to this study includes a statement about the mean dose of glimepiride (2.7 mg), the maximal approved dose in the United States, and concludes non-inferiority at 52 weeks. (b) (4)

Figure 1 Summary of Sensitivity Analysis on Change in HbA1c (ANCOVA) for Study 1245.28



Source: Excerpted from Dr. Sinks' Review

(b) (4)

For Study, 1276.10, the primary objective was to compare efficacy of once daily and twice daily dosing in combination with metformin. Efficacy was assessed using change in HbA1c from baseline after 16 weeks of treatment. The reduction in HbA1c from baseline was comparable between once daily and twice daily dosing with the upper bound of the confidence interval excluding the pre-specified non-inferiority margin on 0.35% (Table 10). Consistent with efficacy findings from other studies, all of the empagliflozin arms demonstrated superior efficacy than placebo.

6.1.5 Analysis of Secondary Endpoints(s)

Secondary endpoints that were tested in a hierarchical fashion for study 1245.28 and study 1245.49 are presented in Table 2 of Dr. Sinks' review (excerpted below).

Table 2 Summary of Key Secondary Endpoints for Reviewed Phase III studies

Hierarchical Testing Order	Study 1245.28	Study 1245.49
1	Change from baseline in Body weight at 52 and 104 weeks	Change from baseline in insulin at 52 weeks
2	Occurrence of Confirmed symptomatic hypoglycaemic events during 52 and 104 weeks	Change from baseline in body weight at 52 weeks
3	Change in blood pressure (SBP and DBP) from baseline at 52 and 104 weeks	Change from baseline in HbA1c at 52 weeks

Secondary endpoints in study 1276.10 included change from baseline in fasting plasma glucose and change from baseline in HbA1c over time. I will not discuss these endpoints, as I consider this is a supportive study.

(b) (4)

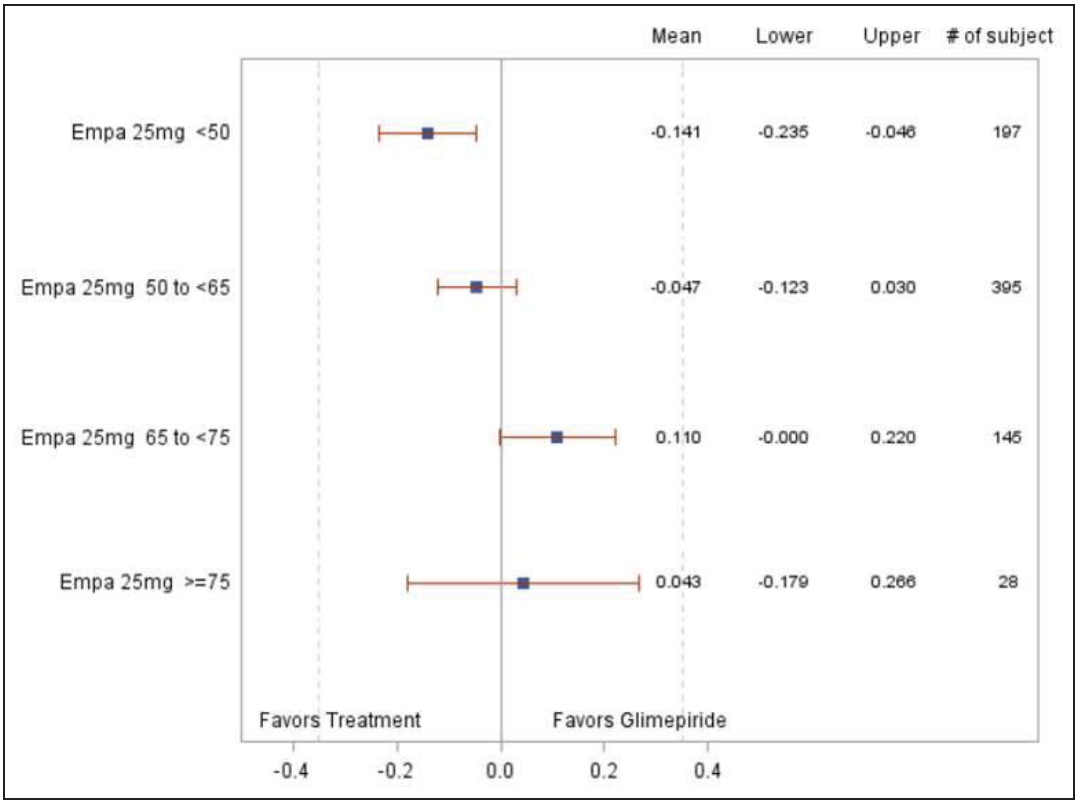
(b) (4)

6.1.6 Subpopulations

Sub-groups analyzed by Dr. Sinks included groups based on intrinsic factors (i.e., age, race, gender, geographic region) and disease-related factors (i.e., duration of diabetes, baseline HbA1c, renal function). If a sub-group contained < 20 subjects, that sub-group was excluded from analysis.

In study 1245.28, there was no evidence for significant heterogeneity of treatment effect by gender, race, or region. There did appear to be an age interaction with treatment effect with a greater reduction in HbA1c seen in younger subjects compared to older subjects (Figure 3). Similar findings were seen in the empagliflozin review.

Figure 3: Change in HbA1c from baseline by age sub-groups for Study 1245.28 at 104 weeks



Source: Adapted from Figure 6 of Dr. Sinks' Review

(b) (4)

There was no evidence of sub-group heterogeneity for any of the sub-groups examined in Study 1276.10.

6.1.7 Analysis of Clinical Information Relevant to Dosing Recommendations

Formal comparison of doses was not performed. In general, the higher dose (25 mg/day) resulted in a numerically greater reduction in HbA1c compared to the lower dose (10 mg/day), though there was substantial overlap in the confidence intervals. In the empagliflozin NDA, the percentage of subjects that achieved a target HbA1c of < 7% was considered to be supportive for additional efficacy with the higher dose. This also applies here.

6.1.8 Discussion of Persistence of Efficacy and/or Tolerance Effects

The efficacy of empagliflozin was shown to persist for at least one year based on the 52 week data in the phase 3 studies. Study 1245.28 followed subjects for 104 weeks, and in that study it remained non-inferior to glimepiride at a mean dose of 2.7 mg.

7 Review of Safety

Safety Summary

The pooled safety data for the use of empagliflozin in combination with metformin does not present any evidence of dramatically increased risk with the use of these drugs in combination. The safety findings are in line with what was observed as part of the empagliflozin NDA review,

and do not appear to be exaggerated over what was seen with use of the individual agent. Importantly, use of a divided dosing regimen rather than the approved once daily regimen does not appear to negatively impact the safety profile of empagliflozin. This should be caveated with the fact that the study that explored twice daily dosing was relatively small and of relatively short duration.

7.1 Methods

To evaluate the safety of the combination of empagliflozin and metformin, the Applicant has submitted all studies where subjects were exposed to the combination of the two. Subjects were allowed to be on other antidiabetic agents as background with or without metformin in many of those studies. For the evaluation of safety, only subjects treated with metformin were included by the Applicant in the safety pools. I agree with this approach as otherwise the sample for review is much smaller. Study 1276.10 will again be discussed separately to assess if there are any unique safety concerns due to twice daily dosing versus once daily dosing.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The evaluation of safety is based on the phase 2 and phase 3 studies submitted to support the NDA. See section 5.1 for a summary of the studies included in the NDA submission.

In the 120-Day Safety Update, additional safety information collected up to August 4, 2014 from three ongoing studies in subjects with type 2 diabetes (Table 13). Some of this data comes from open-label periods and some from double-blind periods.

Table 13: Studies included in the 120-Day Safety Update

Study Number	Description
1275.9	Addition of empagliflozin to subjects that required additional glycemic control after 16 weeks of linagliptin on a background of metformin. Includes a 16 week open-label period and a 24 week double-blind period
1275.10	Addition of linagliptin to subjects that required additional glycemic control after 16 weeks of empagliflozin on a background of metformin. Includes a 16 week open-label period and a 24 week double-blind period.
1276.1	Comparison of empagliflozin + metformin with the individual components in drug naïve subjects. Includes a 24 week double-blind period.

As blinded data is of limited utility in assessing safety, the safety update focuses on data from the open-label period of Study 1275.10. While there is no comparator during this period, it does provide an estimate of incidence which could be compared to the findings from the initially

submitted safety database. Data from the blinded period of Study 1275.10 will also be considered as the design of this study has all subjects exposed to metformin + empagliflozin.

7.1.2 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activity (MedDRA) version 16.1. Analyses were generally performed based on the number of subjects with adverse events, not the number of events. The Applicant has also presented analyses adjusted for exposure (i.e. incidence rate per 100 patient-years). Events analyzed include fatal events, serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, all adverse events, other significant adverse events (based on ICH E3), and adverse events of special interest (AESIs). Other significant adverse events included marked hematological and laboratory abnormalities (if not meeting criteria for an SAE), and any event that led to an intervention (if not meeting criteria for an SAE). The AESIs were changes in renal function, hepatic injury, urinary tract infection, genital infection, hypoglycemia, fractures, volume depletion, and malignancy.

The analysis of adverse events was focused on treatment-emergent adverse events. This was defined by the Applicant as an event that occurred after the first dose of study drug and up to seven days after that last dose of study drug. The population generally used was the treated set, defined as all subjects that were treated with at least one dose of randomized study drug.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

To perform the integrated safety analysis, the Applicant utilized five groupings of studies (Table 14). Note that though not all of the studies were specifically designed to study empagliflozin on a background of metformin (i.e., some studies were designed as with or without metformin), only those subjects treated with metformin are considered in these safety pools.

Table 14: Safety pools

Safety pool	Description	Studies included
SAF-C1	Pool of placebo-controlled studies (metformin background only)	1245.10, 1245.23_{met}, 1245.31_{met}, 1276.10
SAF-C2	Pool of all placebo-controlled studies (metformin background plus other antidiabetic agents)	1245.10, 1245.23_{met}, 1245.31_{met}, 1276.10, 1245.23_{met+SU}, 1245.31_{met+SU}, $1245.19_{pio+met}$, $1245.31_{pio+met}$, 1245.33, 1245.49, 1245.36, 1245.48
SAF-C3	Pool of all studies of subjects with T2DM (metformin background plus other antidiabetic agents)	1245.10, 1245.23_{met}, 1245.31_{met}, 1276.10, 1245.23_{met+SU}, 1245.31_{met+SU}, $1245.19_{pio+met}$, $1245.31_{pio+met}$, 1245.33, 1245.49, 1245.36, 1245.48, 1245.24_{met}, 1245.28, 1275.1_{met}

Safety pool	Description	Studies included
SAF-C4	Pool of placebo-controlled studies (metformin background plus other antidiabetic agents; up to 16-24 weeks)	1276.10, 1245.23_{met}, 1245.31_{met}, 1245.23_{met+SU}, 1245.31_{met+SU}, $1245.19_{pio+met}$, $1245.31_{pio+met}$, 1245.33, 1245.49
SAF-C5	Pool of phase 1 studies in healthy volunteers	1245.6, 1276.5, 1276.6, 1276.7, 1276.8

Adapted from Figure 1.1.2.1: 1 of the Summary of Clinical Safety

The Applicant has primarily presented the data for SAF-C3and SAF-C4. As the clearest assessment of the safety profile is from placebo-controlled data, I will focus my discussion on safety pools SAF-C2 and SAF-C4.

The approved label for empagliflozin recommends once daily dosing. The FCDP product is designed for twice daily dosing. To support this change, the Applicant performed a clinical bridging study (Study 1276.10). Safety findings from this study will be separately evaluated and discussed to identify any unique safety issues that may result from this change in dosing.

7.2 Adequacy of Safety Assessments

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

A summary of the number of subjects and exposure to study drug are presented in Table 15 and

Table 16.

Table 15: Summary of number of subjects and exposure to study drug for the safety pools

	Placebo		Empa 10		Empa 25		All Empa		Active Comp	
Pool	**N**	**Pt-yrs**	**N**	**Pt-yrs**	**N**	**Pt-yrs**	**N**	**Pt-yrs**	**N**	**Pt-yrs**
SAF-C1	384	323.7	727	487.0	720	454.9	1447	941.9		
SAF-C2	1400	1261.7	1670	1408.2	1751	1497.2	3421	2875.4		
SAF-C3[1]	1532	1382.1	1946	1905.1	2794	3614.0	4740	5519.1	780	1651.6
SAF-C4	926	469.2	1271	479.5	1259	367.6	2530	948.7		

[1] The placebo arm includes subjects treated with linagliptin 5 mg from study 1275.1

Empa = empagliflozin; Comp = comparator; Pt-yrs = patient-years

Source: Adapted from Table 1.2.1.1: 1, Table 1.2.2: 1, Table 1.2.2: 2, of the Summary of Clinical Safety and Table 4.4.1 of the Integrated Summary of Safety

Table 16: Summary of subjects and exposure to study drug for Study 1276.10

	Placebo	Empa 5 BID	Empa 10 QDay	Empa 12.5 BID	Empa 25 QDay
Subjects treated	107	219	220	219	218
Patient-years	34.9	69.3	69.2	70.3	69.4

Empa = empagliflozin; BID = twice daily; QDay = once daily
Source: Adapted from Table 10.1: 3 and Table 15.3.2.3: 5 of the study report for Study 1276.10

Data from one study site which participated in studies 1245.23_{met}, 1245.23_{met+SU}, and the extension study 1245.31 was excluded from the individual study reports and safety analyses due to findings of scientific misconduct. Additionally, subjects found to have been randomized at multiple sites in study 1275.1_{met} were also excluded from the analyses. This is reasonable. The numbers of excluded subjects were small and I do not believe they meaningfully impact any of the conclusions.

For SAF-C3, it was possible that some subjects were re-randomized. This was due to the inclusion of study 1245.24 (the extension of study 1245.10) which mandated a second randomization at enrollment. As such, some subjects were included in more than one treatment group for adverse events. For analysis of safety laboratory studies, the analysis was done by the first treatment (i.e. treatment arm in study 1245.10). Another notable consideration for this safety pool is the inclusion of study 1275.1. This study compared the combination empagliflozin and linagliptin on a background of metformin to the individual components on a background of metformin. No placebo group was included in this study; however the Applicant has included the subjects treated with linagliptin on a background of metformin into the placebo arm for this pool.

Baseline demographics for studies 1245.23_{met}, 1245.23_{met+SU}, 1245.28, 1275.1, and 1276.10 are discussed in section 6.1.2. In looking at the safety pools, the demographics were relatively balanced (Table 17).

Table 17: Baseline demographics for safety pools

	Placebo	Empa 10	Empa 25	All Comp
SAF-C1				
N	384	727	720	
Mean age (years [SD])	57.3 (9.9)	57.7 (10.3)	57.2 (10.0)	
Male gender (N [%])	203 (52.9)	392 (53.9)	401 (55.7)	
Mean BMI (kg/m^2 [SD])	30.13 (5.24)	30.90 (5.39)	31.15 (5.40)	
Diagnosis > 5 years (N [%])	211 (54.9)	415 (57.1)	398 (55.3)	
Race				
– White (N [%])	276 (71.9)	558 (76.8)	554 (76.9)	
– Asian (N [%])	93 (24.2)	116 (16.0)	125 (17.4)	

	Placebo	Empa 10	Empa 25	All Comp
SAF-C2				
N	1400	1670	1751	
Mean age (years [SD])	58.0 (9.8)	58.1 (9.7)	58.2 (9.7)	
Male gender (N [%])	738 (52.7)	919 (55.0)	960 (54.8)	
Mean BMI (kg/m^2 [SD])	30.80 (5.50)	31.19 (5.59)	31.35 (5.62)	
Diagnosis > 5 years (N [%])	987 (70.5)	1133 (67.8)	1194 (68.2)	
Race				
– White (N [%])	949 (67.8)	1223 (73.2)	1251 (71.4)	
– Asian (N [%])	385 (27.5)	354 (21.2)	410 (23.4)	
SAF-C3				
N	1532	1946	2794	2312
Mean age (years [SD])	57.8 (9.8)	57.8 (9.8)	57.4 (10.0)	51.7 (10.1)
Male gender (N [%])	805 (52.5)	1084 (55.7)	1531 (54.8)	1226 (53.0)
Mean BMI (kg/m^2 [SD])	30.78 (5.50)	31.13 (5.58)	30.95 (5.55)	30.61 (5.44)
Diagnosis > 5 years (N [%])	1062 (69.3)	1275 (65.5)	1698 (60.8)	1413 (61.1)
Race				
– White (N [%])	1046 (68.3)	1433 (73.6)	1949 (69.8)	1565 (67.7)
– Asian (N [%])	400 (26.1)	391 (20.1)	706 (25.3)	653 (28.2)
SAF-C4				
N	926	1271	1259	
Mean age (years [SD])	56.4 (9.9)	57.3 (9.9)	57.1 (9.8)	
Male gender (N [%])	458 (49.5)	682 (53.7)	678 (53.9)	
Mean BMI (kg/m^2 [SD])	30.46 (5.67)	30.91 (5.71)	31.14 (5.74)	
Diagnosis > 5 years (N [%])	646 (69.8)	840 (66.1)	826 (65.6)	
Race				
– White (N [%])	562 (60.7)	860 (67.7)	858 (68.1)	
– Asian (N [%])	315 (34.0)	334 (26.3)	333 (26.4)	

Empa = empagliflozin; Comp = comparator; N = number of subjects; SD = standard deviation; BMI = body mass index

Source: Adapted from Table 3.1.1.1, Table 3.1.2.1, Table 3.1.3.1, and Table 3.1.4.1 of the Integrated Summary of Safety

Demographics were similarly balanced between treatment arms for Study 1276.10 (Table 18).

Table 18: Baseline demographics for Study 1276.10

	Placebo	Empa 5 BID	Empa 10 QDay	Empa 12.5 BID	Empa 25 QDay
Study 1276.10					
N	107	215	214	215	214
Mean age (years [SD])	57.9 (11.2)	58.8 (9.8)	58.5 (10.8)	57.6 (9.9)	58.2 (10.2)
Male gender (N [%])	55 (51.4)	120 (55.8)	108 (50.5)	123 (57.2)	114 (53.3)
Mean BMI (kg/m^2 [SD])	32.03 (4.95)	31.46 (5.22)	31.85 (5.41)	31.57 (5.13)	32.06 (5.26)

	Placebo	Empa 5 BID	Empa 10 QDay	Empa 12.5 BID	Empa 25 QDay
Diagnosis > 5 years (N [%])	67 (62.6)	118 (54.9)	132 (61.7)	111 (51.6)	115 (53.7)
Race					
– White (N [%])	93 (86.9)	189 (87.9)	180 (54.1)	176 (81.9)	191 (89.3)
– Asian (N [%])	2 (1.9)	6 (2.8)	10 (4.7)	15 (7.0)	9 (4.2)

Empa = empagliflozin; BID = twice daily; QDay = once daily; SD = standard deviation; BMI = body mass index
Source: Adapted from Table 15.1.4.1: 1 of the study report for Study 1276.10

7.2.2 Explorations for Dose Response

Comparison of the incidence and event rate between the Empa 10 and Empa 25 treatment arms allows for some assessment of potential dose response for adverse events.

7.2.3 Special Animal and/or In Vitro Testing

No special animal or *in vitro* testing was performed to support this application.

7.2.4 Routine Clinical Testing

Vital signs were measured routinely during the clinical studies. Laboratory tests routinely measured in the phase 2 and phase 3 studies included hematologic laboratory tests, clinical chemistries, and urinalysis. In particular, measure of renal function and liver enzymes were monitored. Serum lipids were also routinely followed.

7.2.5 Metabolic, Clearance, and Interaction Workup

See the discussion of the clinical pharmacology in section 4.4.

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

The adverse events of special interest appear adequate to capture potential adverse events that would be associated with SGLT2 inhibitors. These include impacts on renal functions, hypoglycemia, volume depletion/hypotension, and genitourinary tract infections.

7.3 Major Safety Results

7.3.1 Deaths

Safety pools:

The overall incidence of death was low in all of the safety pools (Table 19). There was no marked difference between treatment arms.

Table 19: Incidence of death by safety pool

	Placebo	Empa 10	Empa 25	All Comp
SAF-C1	**384**	**727**	**720**	
– Deaths (N, %)	0 (0)	0 (0)	0 (0)	
SAF-C2	**1400**	**1670**	**1751**	
– Deaths (N, %)	2 (0.1)	2 (0.1)	4 (0.2)	
SAF-C3	**1532**	**2057**	**2904**	**2312**
– Deaths (N, %)	2 (0.1)	4 (0.2)	9 (0.3)	8 (0.3)
SAF-C4	**926**	**1271**	**1259**	
– Deaths (N, %)	1 (0.1)	1 (0.1)	2 (0.2)	

Empa = empagliflozin; Comp = comparator; N = number of subjects
Source: Adapted from Table 5.8.1.1., Table 5.8.2.1, Table 5.8.3.1, and Table 5.8.4.1 of the Integrated Summary of Safety

Review of the submitted information did not identify any clear single cause of death in any of the treatment arms (Table 20). At the Preferred Term (PT) level, only the PT "Sudden death" was reported as the cause of death in more than one subject in any of the safety pools.

Table 20: Causes of death

Subject Identification Number	Age (years)	Gender	Preferred term (s)
Placebo – on-treatment[1]			
1245.33.04571	79	F	Hemorrhagic stroke
1245.19.11081	55	F	Skin ulcer Myocardial ischemia Hemoglobin decreased
Placebo – post-study[2]			
1245.31.30096	76	M	Acute left ventricular failure
Empagliflozin 10 – on-treatment			
1275.1.90242	61	M	Lung neoplasm Non-small cell lung cancer metastatic
1245.23.33592	56	F	Acute myocardial infarction

Subject Identification Number	Age (years)	Gender	Preferred term (s)
1275.1.97041	53	M	Hypertensive heart disease
1245.49.14122	58	F	Sudden death
Empagliflozin 10 – post-treatment[3]			
1245.19.10844	56	M	Left ventricular failure
Empagliflozin 25 – on-treatment			
1245.28.80912	59	M	Adenocarcinoma pancreas
1245.28.82883	75	F	Lung adenocarcinoma stage IV Metastases to bone Metastases to liver
1245.49.78251	57	M	Lung cancer metastatic
1245.19.11480	60	F	Cerebrovascular accident
1245.19.10813	40	M	Cardio-respiratory arrest
1245.19.12054	74	m	Esophageal rupture
1245.28.84833	48	M	Hepatic cirrhosis Hepatic failure
1245.28.81806	59	F	Multi-organ failure
1245.28.82486	71	F	Sudden death
Empagliflozin 25 – post-treatment			
1245.23.34564	61	M	Sepsis
Empagliflozin 25 – post-study			
1245.28.86947	57	F	Pneumonia
Glimepiride – on-treatment			
1245.28.86537	49	M	Post procedural infection
1245.28.82414	57	M	Hepatic cancer
1245.28.87309	61	F	Malignant pleural effusion Pericardial effusion malignant Hypoxic-ischemic encephalopathy
1245.28.89031	50	F	Acute myocardial infarction
1245.28.84906	66	M	Cardiac tamponade
1245.28.81265	74	F	Respiratory failure

[1] from time of first dose of study drug to 7 days after last dose of study drug; [2] after completion of study; [3] after 7 days from last dose of study drug to completion of study
Source: Adapted from 2.1.3: 2 of the Summary of Clinical Safety

Based on my review of the data, I do not believe there to be an increased risk for death with the addition of empagliflozin to metformin.

All of the supplied narratives for deaths were reviewed. Most of the cases were previously discussed in the review for empagliflozin (NDA-204629). No concerns were raised during that review with regard to the accuracy of the assignment of PT. No concerns for the accuracy of assignment of PT or concerning trends were noted from review of the additional narratives included in this NDA.

Study 1276.10:

Study 1276.10 was designed to compare the safety and efficacy of once daily empagliflozin to an equivalent twice daily/divided dose of empagliflozin. No deaths occurred in this study. As a result no conclusions can be made about the effect of divided dosing on the risk for death. However, it seems unlikely that this change would increase the risk.

120-Day Safety Update:

The Applicant reports one death in the safety update. This was for a 68 year old female with a 15 year history of T2DM found dead at home. She was in the open-label empagliflozin treatment period of Study 1275.10. This additional death does not alter any of my conclusions based on the initially submitted safety database.

7.3.2 Serious Adverse Events

Safety pools:

The incidence of SAEs was not increased in either of the empagliflozin arms for any of the safety pools that included subjects with T2DM (Table 21).

Table 21: Incidence of serious adverse events by safety pool (includes fatal events)

	Placebo	Empa 10	Empa 25	All Comp
SAF-C1	384	727	720	
– SAE (N, %)	27 (7.0)	32 (4.4)	26 (3.6)	
SAF-C2	1400	1670	1751	
– SAE (N, %)	117 (8.4)	112 (6.7)	116 (6.6)	
SAF-C3	1532	2057	2904	2312
– SAE (N, %)	125 (8.2)	137 (6.7)	272 (9.4)	226 (9.8)
SAF-C4	926	1271	1259	
– SAE (N, %)	35 (3.8)	44 (3.5)	32 (2.5)	

Empa = empagliflozin; Comp = comparator; N = number of subjects; SAE = serious adverse event
Source: Adapted from Table 2.1.4: 1, Table 2.1.4: 2, and Table 2.1.4: 3 of the Summary of Clinical Safety and Table 5.7.4.1 of the Integrated Summary of Safety

Focusing on the pool of placebo-controlled studies (i.e., SAF-C2), there was no apparent increased risk for SAEs with empagliflozin. Small increases in event-rate were noted for some preferred terms, but it is unclear how meaningful these differences are (Table 22).

Table 22: Incidence and event rate of select serious adverse events in the pool of placebo-controlled studies (SAF-C2)

System organ class – Preferred term	Empa 25 N = 1751 Pt-yrs = 1427.51			Empa 10 N = 1670 Pt-yrs = 1372.33			Placebo N = 1400 Pt-yrs = 1223.23		
	N	%	per 100	N	%	per 100	N	%	per 100
Infections and infestations	17	1.0	1.14	18	1.1	1.26	15	1.1	1.17
– Cellulitis	2	0.1	0.13	3	0.2	0.21	1	0.1	0.08
– Gastroenteritis	3	0.2	0.20	0	0	0	0	0	0
Neoplasms benign, malignant and unspecified incl cysts and polyps	19	1.1	1.27	7	0.4	0.49	9	0.6	0.70
– Prostate cancer	2	0.1	0.13	1	0.1	0.07	1	0.1	0.08
– Prostatic adenoma	2	0.1	0.13	0	0	0	0	0	0
Metabolism and nutrition disorders	6	0.3	0.4	2	0.1	0.14	6	0.4	0.47
– Hypoglycemia	3	0.2	0.2	1	0.1	0.07	0	0	0
– Hyperglycemia	2	0.1	0.13	0	0	0	0	0	0
Nervous system disorders	17	1	1.14	12	0.7	0.84	15	1.1	1.17
– Cerebral infarction	3	0.2	0.2	1	0.1	0.07	1	0.1	0.08
– Cerebrovascular accident	3	0.2	0.2	1	0.1	0.07	2	0.1	0.16
– Syncope	2	0.1	0.13	2	0.1	0.14	0	0	0
Cardiac disorders	15	0.9	1	20	1.2	1.4	23	1.6	1.8
– Atrial fibrillation	2	0.1	0.13	2	0.1	0.14	0	0	0
– Atrial flutter	1	0.1	0.07	1	0.1	0.07	0	0	0
Eye disorders	5	0.3	0.33	5	0.3	0.35	2	0.1	0.16
Vascular disorders	7	0.4	0.47	5	0.3	0.35	7	0.5	0.54
– Deep vein thrombosis	2	0.1	0.13	0	0	0	0	0	0
– Peripheral arterial occlusive disease	2	0.1	0.13	2	0.1	0.14	0	0	0
Gastrointestinal disorders	16	0.9	1.07	13	0.8	0.91	9	0.6	0.7
– Hematochezia	1	0.1	0.07	2	0.1	0.14	0	0	0
– Pancreatitis acute	2	0.1	0.13	2	0.1	0.14	0	0	0
Renal and urinary disorders	6	0.3	0.4	7	0.4	0.49	8	0.6	0.62
– Renal failure acute	4	0.2	0.27	1	0.1	0.07	0	0	0

Empa = empagliflozin; Pt-yrs = patient-years; per 100 = per 100 patient-years
Source: Adapted from Table 5.7.2.1 of the submitted Integrated Summary of Safety

Study 1276.10:

For study 1276.10, the incidence and event-rate of SAEs was slightly higher with twice daily/divided dosing compared to once daily dosing (Table 23 and Table 61). Regardless of dosing regimen, there were more SAEs in the empagliflozin treated subjects than in the placebo treated subjects. The twice daily/divided dose arms had slightly higher event-rates for overall SAEs, review of the reported terms did not identify any concerning trends between the twice daily/divided dose groups and the once daily dose groups, or between the empagliflozin treated subjects and the placebo treated subjects.

Table 23: Incidence of serious adverse events in study 1276.10

	Placebo (N=107)		Empa 5 BID (N=219)		Empa 10 QDay (N=220)		Empa 12.5 BID (N=219)		Empa 25 QDay (N=218)	
	N	%	N	%	N	%	N	%	N	%
Subjects with SAE	1	0.9	7	3.2	5	2.3	5	2.3	2	0.9

Source: Adapted from Table 12.2.1: 1 of the study report for Study 1276.10

120-Day Safety Update:

In the safety update, an additional 21 subjects with SAEs in the open-label period of Study 1275.10 are reported. There are an additional eight subjects in the blinded period. No clear trend was identified from the reported terms for the SAEs (Table 62). No single preferred term was reported at a notable increase compared to the other preferred terms. The information included in the safety update does not change my conclusions for the risk of SAEs based on the initially submitted safety database.

7.3.3 Dropouts and/or Discontinuations

Safety pools:

Premature discontinuation occurred with a higher incidence in the placebo subjects compared to the empagliflozin treated subjects (Table 24). This increased incidence does not appear to be for reasons of safety (i.e. adverse events), but appears to be related to lack of efficacy and refusal by the subject to continue study drug.

Table 24: Incidence of premature discontinuation in the safety pool

	Placebo		Empa 10		Empa 25		All Comp	
	N	%	N	%	N	%	N	%
SAF-C1	**384**		**727**		**720**			
Premature discontinuation	52	13.5	67	9.2	62	8.6		
– Due to adverse event	11	2.9	38	3.9	22	3.1		
– Due to lack of efficacy	4	1.0	0	0.0	0	0.0		
– Refused to continue study drug	21	5.5	12	1.7	23	3.2		
SAF-C2	**1400**		**1670**		**1751**			
Premature discontinuation	208	14.9	190	11.4	193	11.0		
– Due to adverse event	57	4.1	72	4.3	80	4.6		
– Due to lack of efficacy	11	0.8	0	0.0	1	0.1		
– Refused to continue study drug	64	4.6	55	3.3	41	2.3		

	Placebo		Empa 10		Empa 25		All Comp	
	N	%	N	%	N	%	N	%
SAF-C3	**1532**		**1946**		**2794**		**2312**	
Premature discontinuation	229	14.9	228	11.7	352	12.6	371	16.0
– Due to adverse event	62	4.0	87	4.5	127	4.5	96	4.2
– Due to lack of efficacy	11	0.7	1	0.1	4	0.1	14	0.6
– Refused to continue study drug	68	4.4	60	3.1	85	3.0	99	4.3
SAF-C4	**926**		**1271**		**1259**			
Premature discontinuation	114	12.3	118	9.3	119	9.5		
– Due to adverse event	35	3.8	48	3.8	48	3.8		
– Due to lack of efficacy	7	0.8	0	0.0	0	0.0		
– Refused to continue study drug	26	2.8	25	2.0	21	1.7		

Source: Adapted from Table 1.2.1.2: 1, Table 1.2.1.2: 2, and Table 1.2.1.2: 3 of the Summary of Clinical Safety and Table 2.4.1 of the Integrated Summary of Safety

Study 1276.10:

In study 1276.10, no apparent increase in the incidence of premature discontinuation was seen in the twice daily/divided dose subjects compared to the once daily dose subjects (Table 25). Subjects treated with empagliflozin were more likely to discontinue prematurely than subjects treated with placebo. This appears to be primarily due to AEs. However, examination of the incidence due to an AE in the divided/twice daily dosed subjects compared to the once daily dosed subjects did not suggest that dividing the dose resulted in more discontinuations due to AEs.

Table 25: Incidence of premature discontinuation in Study 1276.10

	Placebo N=107		Empa 5 BID N=219		Empa 10 QDay N=220		Empa 12.5 BID N=218		Empa 25 QDay N=219	
	N	%	N	%	N	%	N	%	N	%
Premature discontinuation	4	3.7	17	7.8	19	8.6	14	6.4	13	6.0
– Due to adverse event	1	0.9	4	1.8	3	5.9	5	2.3	5	2.3
– Due to lack of efficacy	1	0.9	0	0.0	0	0.0	0	0.0	0	0.0
– Refused to continue study drug	1	0.9	4	1.8	1	0.5	6	2.8	3	1.4

Empa = empagliflozin; BID = twice daily; QDay = once daily
Source: Adapted from Table 10.1: 3 of the study report for Study 1276.10

120-Day Safety Update:

A total of 23 subjects discontinued prematurely due to an adverse event during the open-label period of Study 1275.10. An additional 16 subjects discontinued prematurely due to an adverse

event during the blinded period of Study 1275.10. The adverse events associated with premature discontinuation covered many SOCs and PTs (Table 63). The information included in the safety update does not change my conclusions for discontinuation due to an AE based on the initially submitted safety database.

7.3.4 Significant Adverse Events

Significant adverse events were defined based on the International Conference on Harmonisation Guideline for Structure and Content of Clinical Study Reports (ICH E3). As outlined in ICH E3, these include marked hematological abnormalities, marked laboratory abnormalities, and events leading to intervention. Events meeting the criteria to be considered SAEs are not included in these events.

Safety pools:

In evaluating significant adverse events, the Applicant has only considered two safety pools: SAF-C2 and SAF-C3. In both of these safety pools, the incidence of significant adverse events was slightly higher in the empagliflozin treated subjects compared to placebo (Table 26). Both of the safety pools showed more events relative to placebo for the "Infections and infestations", "Renal and urinary disorders", and "Reproductive system and breast disorders" system organ classes (SOCs). Review of the individual PTs showed that the events were primarily related to urogenital infections and to increased urination.

Table 26: Incidence of significant adverse event in the safety pool of all placebo-controlled studies (SAF-C2) and safety pool of all controlled studies (SAF-C3)

	Placebo		Empa 10		Empa 25		All Comp	
	N	%	N	%	N	%	N	%
SAF-C2	**1400**		**1670**		**1751**			
Significant adverse event	35	2.5	50	3.0	53	3.0		
System organ class								
– Infections and infestations	0	0.0	8	0.5	11	0.6		
– Renal and urinary disorders	1	0.1	11	0.7	3	0.2		
– Reproductive system and breast disorders	1	0.1	6	0.4	6	0.3		

	Placebo		Empa 10		Empa 25		All Comp	
	N	%	N	%	N	%	N	%
SAF-C3	**1532**		**2057**		**2904**		**2312**	
Significant adverse event	37	2.4	61	3.0	95	3.3	77	3.3
− Infections and infestations	0	0.0	11	0.5	24	0.8	2	0.1
− Renal and urinary disorders	1	0.1	12	0.6	4	0.1	1	< 0.1
− Reproductive system and breast disorders	1	0.1	7	0.3	11	0.4	1	< 0.1

Empa = empagliflozin; Comp = comparator
Source: Adapted from Table 5.11.2.1 and Table 5.11.3.1 of the Integrated Summary of Safety

Study 1276.10:

Significant adverse events were reported more commonly in the empagliflozin treated subjects compared to the placebo treated subjects (Table 27). In comparing the divided/twice daily dosing with the once daily dosing, there was no apparent increase in the incidence divided/twice daily dosing. The empagliflozin 10 mg once daily arm had the highest incidence. This appeared to be due events in the "Infections and infestations", "Gastrointestinal disorders", and "Renal and urinary disorders" SOCs. No single preferred term was reported in more than one subject.

Table 27: Incidence of significant adverse events in Study 1276.10 – includes listing of system organ classes with > 2 subjects

	Placebo N=107		Empa 5 BID N=219		Empa 10 QDay N=220		Empa 12.5 BID N=218		Empa 25 QDay N=219	
	N	%	N	%	N	%	N	%	N	%
Significant adverse event	1	0.9	2	0.9	11	5.0	4	1.8	3	1.4
System organ class										
− Infections and infestations	0	0.0	0	0.0	3	1.4	2	0.9	0	0.0
− Gastrointestinal disorders	0	0.0	1	0.0	3	1.4	0	0.0	1	0.5
− Renal and urinary disorders	0	0.0	2	0.9	4	1.8	0	0.0	0	0.0

Empa = empagliflozin BID = twice daily; QDay = once daily
Source: Adapted from Table 15.3.2.1: 8 of the study report for Study 1276.10

7.3.5 Submission Specific Primary Safety Concerns

Adverse events of special interest were defined by the Applicant and included decreased renal function, hepatic injury, urinary tract infection, genital infection, hypoglycemia, volume depletion, malignancy, and fracture. The discussion of these events will focus on the pool of placebo-controlled studies (i.e. SAF-C2). Findings from Study 1276.10 will also be discussed.

7.3.5.1 Decreased renal function

Treatment with empagliflozin leads to an increase in urinary glucose and an increase in urinary volume. This diuretic effect could potentially detrimentally effect renal function. Additionally, metformin has renal function dependent labeling and decreases in renal function could increase the risk for the serious adverse event of lactic acidosis in metformin treated subjects. Thus it is important to consider the effect of treatment with this FCDP on renal function.

Decreased renal function was evaluated using the narrow standard MedDRA query (SMQ) for "acute renal failure" (SMQ20000003). Laboratory data were also used, and the frequency of subjects with a serum ≥ 2x baseline and above the upper limit of the reference range (ULRR) was compared between the treatment arms.

Safety pool:

In SAF-C2, the rate of events was low for all treatment arms, but it was higher in the empagliflozin treated subjects compared to placebo subjects (Table 28). This is consistent with the observations from the empagliflozin program. Notably, subjects with more advanced renal impairment at baseline had a higher incidence of events. This is also consistent with what was seen in the empagliflozin review. The incidence of subjects with a serum creatinine ≥ 2x baseline and above the ULRR was not increased in the empagliflozin treated subjects (0.3% for placebo, 0.1% for empagliflozin 10, and 0.1% for empagliflozin 25).

Table 28: Incidence of decreased renal function events in the pool of all placebo-controlled studies (SAF-C2)

	Placebo		Empa 10		Empa 25	
	N	%	N	%	N	%
All subjects	1400		1670		1751	
− with event	3	0.2	13	0.8	14	0.8
eGFR ≥ 60 ml/min/1.73m^2	1216		1554		1538	
− with event	1	0.1	5	0.3	7	0.5
eGFR < 60 ml/min/1.73 m^2	184		116		213	
− with event	2	1.1	8	6.9	7	3.3

Empa = empagliflozin; eGFR = estimated glomerular filtration rate
Source: Adapted from Table 2.1.6.1.1: 1 and Table 2.1.6.1.1: 2 of the Summary of Clinical Safety

Analysis of changes in eGFR showed that the empagliflozin treated subjects had a greater decrease in eGFR than the placebo subjects (Table 29). This appeared to be dose dependent. Similarly, the subjects with moderate renal impairment (i.e. eGFR < 60 ml/min/1.73 m^2) were

more likely to have a downward shift in renal function while on treatment (Table 30). This is consistent with what was seen in the empagliflozin review.

Table 29: Estimated glomerular filtration rate in the safety pool of all placebo-controlled studies (SAF-C2)

N	Placebo		Empa 10		Empa 25	
	1400		1670		1751	
Baseline, median	82.3		83.9		83.6	
– Q1, Q3	69.7	96.9	72.1	98.7	70.0	97.2
Last value on treatment, median	81.8		83.4		82.6	
– Q1, Q3	68.1	96.6	70.7	98.1	68.3	96.4
Change from baseline, median	-0.3		-1.1		-1.5	
– Q1, Q3	-7.0	5.7	-7.5	5.4	-8.3	5.3

Empa = empagliflozin; Q1 = first quartile; Q3 = third quartile
Source: Adapted from Table 2.1.6.1.2.2: 1 of the Summary of Clinical Safety

Table 30: Incidence of downward shifts in renal function based on estimated glomerular filtration rate in the safety pool of all placebo-controlled studies (SAF-C2) by lowest eGFR on treatment

		Lowest eGFR on treatment							
		≥ 90		60 to < 90		45 to < 60		< 45	
Baseline eGFR	**Total**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Placebo									
– ≥ 90	471	293	62.2	173	36.7	4	0.8	1	0.2
– 60 to < 90	701			548	78.2	107	15.3	8	1.1
– 45 to < 60	123					75	61.0	33	26.8
– < 45	54							45	83.3
Empa 10									
– ≥ 90	616	364	59.1	245	39.8	4	0.6	3	0.5
– 60 to < 90	891			681	76.4	156	17.5	10	1.1
– 45 to < 60	95					48	50.5	29	30.5
– < 45	13							13	100.0
Empa 25									
– ≥ 90	642	345	53.7	292	45.5	4	0.6	1	0.2
– 60 to < 90	838			636	75.9	156	18.6	9	1.1
– 45 to < 60	151					73	48.3	67	44.4
– < 45	53							50	94.3

eGFR = estimated glomerular filtration rate in ml//min/1.73 m^2 calculated by MDRD; Empa = empagliflozin
Source: Adapted from Table 6.5.2.2 of the Summary of Clinical Safety

Study 1276.10:

There were only three subjects in this study with AEs encompassed by the narrow SMQ or an increase in serum creatinine ≥ 2x baseline and above the ULRR. Of these three, two occurred in the empagliflozin 10 mg once daily arm and one occurred in the placebo arm. No evident increase risk for decreased renal function was seen between empagliflozin and placebo, or between divided/twice daily dosing and once daily dosing. Similar to the safety pool, subjects treated with empagliflozin had a greater decrease in eGFR than placebo (Table 31). Notably, the change in eGFR also appeared to greater with the once daily dose compared to the divided/twice daily dose.

Table 31: Estimated glomerular filtration rate in Study 1276.10

	Placebo N=107		Empa 5 BID N=219		Empa 10 QDay N=220		Empa 12.5 BID N=219		Empa 25 QDay N=218	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	89.54	18.46	89.87	22.33	89.20	20.61	88.57	20.02	88.87	19.47
Week 16	88.87	18.49	87.78	20.57	87.71	22.23	87.23	19.57	86.51	20.24
Change from baseline	-0.29	10.51	-1.67	10.79	-1.97	11.02	-1.16	13.82	-2.43	10.71

Empa = empagliflozin; BID = twice daily; QDay = once daily; SD = standard deviation
Source: Adapted from Table 12.3.3.2: 2 of the study report for Study 1276.10

120-Day Safety Update:

Renal failure events were assessed by reported adverse events using an SMQ and by laboratory criteria for decreased renal function (defined as serum creatinine > 2x baseline and above the ULRR). In Study 1275.10, seven subjects (1%) had an acute renal failure adverse event (four in open-label period, three in blinded-period). Blinded information is provided for the other two studies in the safety update. There was one subject (0.4%) in Study 1275.9 with an acute renal failure adverse event. There were two subjects (0.2%) in Study 1276.1 with an acute renal failure adverse event. No subjects in Study 1275.9 or Study 1275.10 met the laboratory criteria for decreased renal function. There was one subject in Study 1276.1 that had decreased renal function as defined by the laboratory criteria. The information included in the safety update does not change my conclusions for renal failure based on the initially submitted safety database.

7.3.5.2 Hepatic injury

There was an imbalance in the empagliflozin development program in elevations in liver enzymes, but this did not clearly correlate with any drug-induced liver injury events. This safety issue is being followed as an additional safety measure in the ongoing cardiovascular outcomes

trial for empagliflozin. Due to this previous concern, hepatic injury is reviewed as part of the FCDP review.

To evaluate for hepatic injury, the Applicant utilized selected sub-categories from SMQ 20000006 "Drug related hepatic disorders". These include SMQ 20000008 "Signs and symptoms of liver related investigations", SMQ 20000009 "Cholestasis and jaundice of hepatic origin", SMQ 20000010 "Hepatitis, non-infectious", and SMQ 20000013 "Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions". The terms included appear to be adequate to capture potential drug related liver events (see Table 1.12.1 of the Integrated Summary of Safety).

Safety pool:

Though there was some concern for drug-induced hepatic injury during the review for empagliflozin, it was ultimately felt that there was not a compelling signal which would preclude approval. This is being further monitored in the ongoing cardiovascular outcomes trial. Examining the population of subjects treated with empagliflozin and metformin does not alter the conclusion from the empagliflozin NDA. The incidence of hepatic injury events was low in all arms from the pool of all placebo-controlled studies (Table 32). Importantly, the incidence was not higher in the empagliflozin treated subjects compared to placebo. The most commonly reported events were the preferred terms "Hepatic steatosis", "Alanine aminotransferase increased", and "Aspartate aminotransferase". There was no clear imbalance in any individual term. There does not appear to be any evidence of increased risk for hepatic injury from the available data.

Table 32: Incidence of hepatic injury events in the safety pool of all placebo-controlled studies (SAF-C2)

	Placebo		Empa 10		Empa 25	
Number of subjects	**1400**		**1670**		**1751**	
	N	**%**	**N**	**%**	**N**	**%**
Any hepatic event (from SMQs)	32	2.3	18	1.1	32	1.8
Preferred terms						
– Hepatic steatosis	8	0.6	4	0.2	13	0.7
– Alanine aminotransferase increased	8	0.6	8	0.5	3	0.2
– Aspartate aminotransferase increased	4	0.3	4	0.2	2	0.1
– Hepatic enzyme increased	3	0.2	0	0.0	5	0.3

Empa = empagliflozin; SMQ = standardized MedDRA Query
Source: Adapted from Table 2.1.6.2.1: 1 of the Summary of Clinical Safety

Treatment with empagliflozin did not appear to increase the likelihood of hepatic enzyme increases (Table 33). Additionally, there were no subjects with a biochemical profile consistent with Hy's Law[1], which has been used to predict which drug has a high-risk for fatal drug-induced liver injury.

Table 33: Incidence of increased liver enzymes in the safety pool of all placebo-controlled studies (SAF-C2)

	Placebo		Empa 10		Empa 25	
Number of subjects	**1400**		**1670**		**1751**	
	N	**%**	**N**	**%**	**N**	**%**
ALT/AST ≥ 3x ULRR	16	1.1	8	0.5	15	0.9
ALT/AST ≥ 5x ULRR	0	0.0	1	0.1	5	0.3
ALT/AST ≥ 10x ULRR	0	0.0	0	0.0	0	0.0
ALT/AST ≥ 3x ULRR and T. Bili. ≥ 2x ULRR	0	0.0	0	0.0	0	0.0
– Alk Phos < 2x ULRR	0	0.0	0	0.0	0	0.0
– Alk Phos ≥ 2x ULRR	0	0.0	0	0.0	0	0.0

Empa = empagliflozin; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULRR = upper limit of reference range; T. Bili. = total bilirubin; Alk Phos = alkaline phosphatase
Source: Adapted from Table 6.4.2.2 of the Integrated Summary of Safety

Study 1276.10:

Review of the submitted datasets showed no evident difference between treatment arms for adverse events that may be considered to be hepatic injury events (Table 34). One subject had study drug discontinued due to an event. Examination of the incidence of increase liver enzymes similarly did not raise concerns for an increased risk for hepatic injury with empagliflozin regardless of dosage or manner of dose administration (Table 35).

Table 34: Incidence of hepatic injury adverse events in Study 1276.10

	Placebo		Empa 5 BID		Empa 10 QDay		Empa 12.5 BID		Empa 25 QDay	
Number of subjects	**107**		**219**		**220**		**219**		**218**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Alanine aminotransferase increased	1	0.9	0	0	2	0.9	0	0	0	0
Aspartate aminotransferase increased	0	0	1	0.5	1	0.5	0	0	0	0

[1] Biochemical criteria for Hy's Law: (1) ALT/AST ≥ 3x ULRR, (2) T. Bili. ≥ 2x ULRR. , and (3) Alk Phos < 2x ULRR. To fulfill Hy's Law, there also needs to be no other explanation.

	Placebo		Empa 5 BID		Empa 10 QDay		Empa 12.5 BID		Empa 25 QDay	
Number of subjects	**107**		**219**		**220**		**219**		**218**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Hepatic enzyme increased	0	0	0	0	0	0	0	0	1	0.5
Hepatic steatosis	1	0.9	0	0	0	0	0	0	0	0

Empa = empagliflozin; BID = twice daily; QDay = once daily
Source: Reviewer generated based on the submitted AE.xpt and DM.xpt files for Study 1276.10

Table 35: Incidence of increased liver enzymes in Study 1276.10

	Placebo		Empa 5 BID		Empa 10 QDay		Empa 12.5 BID		Empa 25 QDay	
Number of subjects	**107**		**219**		**220**		**219**		**218**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
ALT/AST ≥ 3x ULRR	0	0	2	0.9	3	1.4	0	0	2	0.9
ALT/AST ≥ 5x ULRR	0	0	0	0	1	0.5	0	0	0	0
ALT/AST ≥ 10x ULRR	0	0	0	0	0	0	0	0	0	0
ALT/AST ≥ 3x ULRR and T. Bili. ≥ 2x ULRR	0	0	0	0	0	0	0	0	0	0
– Alk Phos < 2x ULRR	0	0	0	0	0	0	0	0	0	0
– Alk Phos ≥ 2x ULRR	0	0	0	0	0	0	0	0	0	0

Empa = empagliflozin; BID = twice daily; QDay = once daily; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULRR = upper limit of reference range; T. Bili. = total bilirubin; Alk Phos = alkaline phosphatase
Source: Adapted from Table 15.3.3.2: 1 of the clinical study report for Study 1276.10

120-Day Safety Update:

Potential liver injury events were identified in two ways in the safety update. The first was potential Hy's Law cases, and the second was identification of AST/ALT > 5x ULRR. No potential Hy's Law cases were identified in any of the studies included in the safety update. There were two subjects with an AST/ALT > 5x ULRR (one from study 275.9 and one from the blinded period of Study 1275.10). In an open-label arm of empagliflozin BID + metformin from Study 1276.1, there was one subject with an AST/ALT > 5x ULRR. The information included in the safety update does not change my conclusions for hepatic injury based on the initially submitted safety database.

7.3.5.3 Urinary tract infections

Due to the mechanism of action for empagliflozin, there is concern for an increased risk of infections particularly genitourinary infections. Urinary tract infections are a labeled adverse event for empagliflozin. A customized MedDRA query (CMQ) was utilized by the Applicant to analyze urinary tract infection events (see

Table 66 for included terms).

Safety pool:

In the safety pool of placebo-controlled studies, the incidence of urinary tract infections was similar between empagliflozin and placebo. Though more fungal urinary tract infections were reported in the empagliflozin subjects, the incidence was < 1%. There was also no evidence of an imbalance for urinary tract infections that qualified as a serious adverse event (Table 37).

Table 36: Incidence and event-rate of urinary tract infections in the safety pool of all placebo-controlled studies (SAF-C2)

	Placebo	Empa 10	Empa 25
Number of subjects	**1400**	**1670**	**1751**
Exposure (patient-years)	**1150.83**	**1299.48**	**1379.63**
Urinary tract infection events	168	94	185
– Incidence (%)	12.0	11.6	10.6
– Event-rate (per 100 patient-years)	14.60	14.93	13.41

Empa = empagliflozin
Source: Adapted from Table 2.1.6.3: 1 of the Summary of Clinical Safety and Table 5.14.2.2 of the Integrated Summary of Safety

Table 37: Incidence and event rate of serious urinary tract infections in the safety pool of all placebo-controlled studies (SAF-C2)

	Placebo		Empa 10		Empa 25	
Preferred Term	**%**	**Per 100**	**%**	**Per 100**	**%**	**Per 100**
Urinary tract infection	0.2	0.23	0.1	0.07	0.1	0.13
Pyelonephritis	0	0	0	0	0.1	0.07
Pyelonephritis acute	0.1	0.08	0	0	0	0
Urosepsis	0.1	0.08	0.1	0.14	0	0

Empa = empagliflozin
Source: Adapted from Table 5.7.2.1 of the Integrated Summary of Safety

Study 1276.10:

The incidence of urinary tract infections was slightly higher for the empagliflozin treated subjects compared to placebo (Table 38). The incidence of urinary tract infections was slightly higher in the Empa 10 QDay arm compared to the other treatment arms. There were no urinary tract infections that met criteria for an SAE. Treatment with a twice daily/divided dose did not appear to increase the risk for urinary tract infections compared to once daily dosing.

Table 38: Incidence of urinary tract infection for Study 1276.10

	Placebo N=107		Empa 5 BID N=219		Empa 10 QDay N=220		Empa 12.5 BID N=219		Empa 25 QDay N=218	
	N	%	N	%	N	%	N	%	N	%
Investigator-defined	4	3.7	12	5.5	17	7.7	12	5.5	10	4.6
By CMQ	4	3.7	17	7.8	21	9.5	13	5.9	12	5.5

Empa = empagliflozin; BID = twice daily; QDay = once daily; CMQ = customized MedDRA query
Source: Adapted from Table 12.3.3.3: 1 of the clinical study report for Study 1276.10

120-Day Safety Update:

Only serious urinary tract infections were reported in the safety update. These were either events of sepsis due to a urinary tract infection or acute pyelonephritis. There were no cases of sepsis due to a urinary tract infection in any of the studies included in the safety update. There were no cases of acute pyelonephritis in Study 1275.9 or Study 1275.10. There were three subjects (0.2%) with acute pyelonephritis in Study 1276.1. The information included in the safety update does not change my conclusions for urinary tract infections based on the initially submitted safety database.

7.3.5.4 Genital infections

Due to the mechanism of action for empagliflozin, there is concern for an increased risk of infections particularly genitourinary infections. Genital infections are a labeled adverse event for empagliflozin. Identification of genital infection events was based on a Sponsor defined CMQ (see Table 67 for included terms).

Safety pool:

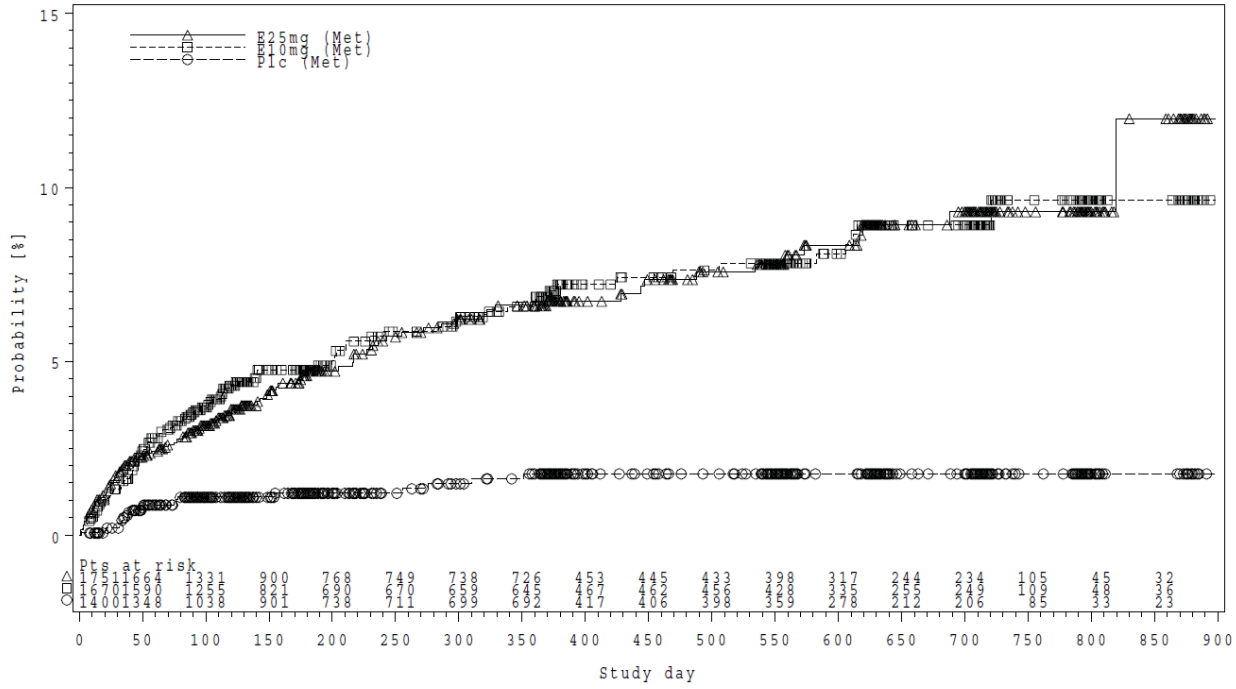
There were more genital infections in the empagliflozin treated subjects than in the placebo subjects (Table 39). This imbalance occurred early in the treatment period and was maintained over the course of follow-up (Figure 4).

Table 39: Incidence and event-rate for genital infections in the pool of all placebo-controlled studies (SAF-C2)

	Placebo	Empa 10	Empa 25
Number of subjects	**1400**	**1670**	**1751**
Exposure (patient-years)	**1273.13**	**1374.40**	**1434.99**
Genital infection events	20	97	97
– Incidence (%)	1.4	5.8	5.5
– Event-rate (per 100 patient-years)	1.57	7.06	6.76

Empa = empagliflozin
Source: Adapted from Table 2.1.6.4: 1 of the Summary of Clinical Safety and Table 5.15.2.2 of the Integrated Summary of Safety

Figure 4: Time to onset of first genital infection for the pool of all placebo-controlled studies (SAF-C2)



Source: Excerpted from Figure 5.15.2.1 of the Integrated Summary of Safety

Study 1276.10:

Genital infections were reported more commonly in the empaliflozin treated subjects compared to the placebo treated subjects (Table 40). Comparison of twice daily/divided dosing with once daily dosing did not reveal any apparent differences by dosing regimen.

Table 40: Incidence of genital infections in Study 1276.10

	Placebo		Empa 5 BID		Empa 10 QDay		Empa 12.5 BID		Empa 25 QDay	
Number of subjects	**107**		**219**		**220**		**219**		**218**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Investigator-defined	4	3.7	12	5.5	9	4.1	13	5.9	12	5.5
By CMQ	3	2.8	8	3.7	7	3.2	9	4.1	9	4.1

Empa = empagliflozin; BID = twice daily; QDay = once daily; CMQ = customized MedDRA query
Source: Adapted from Table 12.3.3.6: 1 of the clinical study report for Study 1276.10

120-Day Safety Update:

Genital infections are not addressed in the safety update.

7.3.5.5 Hypoglycemia

Hypoglycemia is a concern with all antidiabetic agents. Nevertheless, examination of hypoglycemic events is necessary in the evaluation of the FCDP. Hypoglycemia was assessed based on information reported in specific case report forms. For potential hypoglycemia events, blood glucose value category (i.e. ≤ 70 mg/dL or < 54 mg/dL), presence/absence of symptoms, and need for external assistance were to be recorded. The Applicant has defined the following categories for hypoglycemic events:

Category	Criteria
Confirmed hypoglycemia	Plasma glucose ≤ 70 mg/dL or requiring assistance
– Confirmed symptomatic	Plasma glucose ≤ 70 mg/dL or requiring assistance, plus symptoms
– Confirmed asymptomatic	Plasma glucose between 54 mg/dL and 70 mg/dL, no symptoms
– Major hypoglycemia	Requiring assistance

Safety pool:

Hypoglycemia occurred with similar frequency between treatment arms for the pool of placebo controlled studies (Table 41). Further, examination of the number of events per subject did not show an increase in the number of events per subject with empagliflozin.

Table 41: Incidence of hypoglycemia for the pool of all placebo-controlled studies (SAF-C2)

	Placebo		Empa 10		Empa 25	
Number of subjects	**1400**		**1670**		**1751**	
	N	**%**	**N**	**%**	**N**	**%**
Confirmed hypoglycemia	216	15.4	216	12.9	246	14.0
– Confirmed symptomatic	186	13.3	181	10.5	221	12.6
– Confirmed asymptomatic	76	5.4	72	4.3	79	4.5
– Major hypoglycemia	6	0.4	3	0.2	7	0.4
Number of events per subject						
– 1 or 2	106	7.6	105	6.3	106	6.1
– 3 or 4	28	2.0	37	2.2	35	2.0
– 5 to 9	36	2.6	33	2.0	39	2.2
– ≥ 10	46	3.3	41	2.5	66	3.8

Empa = empagliflozin
Source: Adapted from Table 5.16.2.4 of the Integrated Summary of Safety

Study 1276.10:

There were few hypoglycemic events in Study 1276.10 (Table 42). There were too few events to make a meaningful comparison between arms. Based on the limited data available, there does not appear to be an increased risk for hypoglycemia for the twice daily/divided dosing regimen compared to the once daily dosing regimen.

Table 42: Incidence of hypoglycemia in Study 1276.10

	Placebo		Empa 5 BID		Empa 10 QDay		Empa 12.5 BID		Empa 25 QDay	
Number of subjects	**107**		**219**		**220**		**219**		**218**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Confirmed hypoglycemia	1	0.9	1	0.5	1	0.5	1	0.5	0	0.0
– Confirmed symptomatic	1	0.9	1	0.5	1	0.5	1	0.5	0	0.0
– Confirmed asymptomatic	0	0	0	0	0	0	0	0	0	0
– Major hypoglycemia	0	0	0	0	0	0	0	0	0	0

Empa = empagliflozin; BID = twice daily; QDay = once daily; CMQ = customized MedDRA query
Source: Adapted from Table 12.3.3.1: 1 of the clinical study report for Study 1276.10

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120-Day Safety Update:

There was no additional information on hypoglycemia in the safety update.

7.3.5.6 Volume depletion

Similar to the concerns for changes in renal function, the mechanism of action for empagliflozin raises concern that subjects treated with empagliflozin could have hypotension and volume depletion. This is a labeled concern for empagliflozin, thus it is being considered as part of review of the FCDP. To assess volume depletion events, the Applicant utilized a CMQ which contained the following preferred terms:

Blood pressure ambulatory decreased	Blood pressure decreased	Blood pressure systolic decreased
Dehydration	Hypotension	Hypovolemia
Orthostatic hypotension	Syncope	

Safety pool:

There was a small increase in the incidence and event rate of volume depletion events for the empagliflozin treated subjects (Table 44). Use in combination with a diuretic appears to further increase this risk, particular when used in combination with a loop diuretic (Table 45).

Table 44: Incidence and event-rate of volume depletion events for the pool of all placebo-controlled studies

	Placebo	Empa 10	Empa 25
Number of subjects	**1400**	**1670**	**1751**
Exposure (patient-years)	**1285.23**	**1432.01**	**1486.05**
Volume depletion events	7	16	17
– Incidence (%)	0.5	1.0	1.0
– Event-rate (per 100 patient-years)	0.54	1.12	1.14

Empa = empagliflozin
Source: Adapted from Table 2.1.6.7: 1 of the Summary of Clinical Safety and Table 5.19.2.1 of the Integrated Summary of Safety

Table 45: Incidence of volume depletion by baseline diuretic use for the pool of all placebo-controlled studies (SAF-C2)

	Placebo		Empa 10		Empa 25	
Number of subjects	**1400**		**1670**		**1751**	
	N	**%**	**N**	**%**	**N**	**%**
Volume depletion events	7	0.5	16	1.0	7	1.0
– with diuretics	2	0.5	7	1.7	11	2.3
– without diuretics	5	0.5	9	0.7	6	0.5
– with loop diuretics	1	1.8	4	7.0	1	2.0
– without loop diuretics	6	0.4	12	0.7	16	0.9

Empa = empagliflozin
Source: Adapted from 2.1.6.7: 2 of the Summary of Clinical Safety

Study 1276.10:

There were three reported volume depletion adverse events in Study 1276.10. Two events came from the Empa 10 QDay arm, and the third came from the Empa 12.5 BID arm. There were no placebo events. There were too few events to draw any meaningful conclusions, but there was no apparent increase in the risk for these events with twice daily/divided dosing compared to once daily dosing.

120-Day Safety Update:

Volume depletion events were identified using an SMQ. In Study 1275.10, there were six subjects (0.9%) with volume depletion events (four in open-label period, two in blinded period). No volume depletion events were reported in Study 1275.9, and eight subjects (0.6%) had volume depletion events in Study 1276.1. The information included in the safety update does not change my conclusions for volume depletion based on the initially submitted safety database.

7.3.5.7 Malignancy

During the review of empagliflozin and the other SGLT2 inhibitors, there were numerical imbalances noted for a variety of malignancies. None of the findings for these various malignancies raise sufficient concern to warrant labeling, but they are being further evaluated in the ongoing cardiovascular outcomes trials. Malignancy events were analyzed using the standardized MedDRA query (SMQ) for "malignant or unspecified tumors" and the SMQ for "malignancy related conditions". The PT "acanthosis nigricans" was excluded.

Safety pool:

The incidence of malignancies was relatively balanced between the empagliflozin treated subjects and placebo (Table 46). In the pool of all placebo-controlled studies (SAF-C2), there were no apparent concerning imbalances for any specific type of malignancy.

Table 46: Incidence and event-rate for malignancy events in the pool of all placebo-controlled studies (SAF-C2)

	Placebo	Empa 10	Empa 25
Number of subjects	**1400**	**1670**	**1751**
Exposure (patient-years)	**1283.80**	**1436.11**	**1493.55**
Malignancy event	11	10	18
– Incidence (%)	0.8	0.6	1.0
– Event-rate (per 100 patient-years)	0.86	0.70	1.21

Empa = empagliflozin
Source: Adapted from Table 5.20.2.1 of the Integrated Summary of Safety

Study 1276.10:

There were three reported malignancies during this study. One subject came from the Empa 5 BID arm, one from the Empa 10 QDay arm, and one from the Empa 12.5 BID arm. All three cases were different and unrelated type of malignancy (recurrent squamous cell carcinoma, prostate cancer, and transitional cell bladder cancer). There were no placebo events. No

meaningful conclusions can be drawn from the small number of events, but there does not appear to be any increased risk with twice daily/divided dosing compared to once daily dosing.

120-Day Safety Update:

There were three subjects (0.4%) with malignancies identified in Study 1275.10 (two in the open-label period, one in the blinded period). Both cases in the open-label period were pancreatic cancer. The case in the blinded period was a prostate adenoma. In Study 1275.9, three subjects (1.2%) were found to have malignancies. Three different types of malignancies were reported (basal cell carcinoma, bladder neoplasm, and breast cancer). In Study 1276.1, there were two subjects (0.2%) with malignancies. Only one (a case of chronic lymphocytic leukemia) was considered to be a serious adverse event. The other cancer type is not reported. The information included in the safety update does not change my conclusions for malignancy based on the initially submitted safety database.

7.3.5.8 Fracture

An imbalance in upper extremity fractures was noted in the development program for another SGLT2 inhibitor, and the mechanism of action for the class could plausibly result in shifts in mineral metabolism that could increase the risk for fractures. Additionally, the divided dosing of the FCDP could result in an increase in nocturia. An increase in nocturia could subsequently translate into an increased risk for nighttime falls, which in turn could lead to fractures. Fractures were analyzed using an Applicant defined CMQ (Table 68).

Safety pool:

Fracture events occurred slightly less frequently in the empagliflozin treated subjects compared to placebo (Table 47). There were no individual preferred terms which showed an increase in the empagliflozin treated subjects.

Table 47: Incidence and event-rate of fracture events in the pool of placebo-controlled studies (SAF-C2)

	Placebo	Empa 10	Empa 25
Number of subjects	**1400**	**1670**	**1751**
Exposure (patient-years)	**1271.44**	**1424.27**	**1487.87**
Fracture event	30	24	18
– Incidence (%)	2.1	1.4	1.0
– Event-rate (per 100 patient-years)	2.36	1.69	1.21

Empa = empagliflozin
Source: Adapted from Table 2.1.6.6: 1 of the Summary of Clinical Safety and Table 5.18.2.1 of the Integrated Summary of Safety

Study 1276.10:

There were few fracture events, thus no meaningful conclusions can be drawn (Table 48). There was no apparent increase in fracture events with empagliflozin treatment compared to placebo. There was no apparent increase in fracture events with twice daily/divided dosing compared to once daily dosing.

Table 48: Incidence of fracture events in Study 1276.10

	Placebo		Empa 5 BID		Empa 10 QDay		Empa 12.5 BID		Empa 25 QDay	
Number of subjects	**107**		**219**		**220**		**219**		**218**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Fracture event	1	0.9	1	0.5	3	1.4	1	0.5	0	0

Source: Adapted from Table 15.3.2.10: 1 of the clinical study report for Study 1276.10

120-Day Safety Update:

Only one fracture was reported in the safety update. This was a skull base fracture that occurred during open-label period of Study 1275.10. From review of the narrative, this event occurred following a fall down a flight of stairs. Events of intracerebral hemorrhage and cerebral hematoma were concurrently reported. The information included in the safety update does not change my conclusions for fracture based on the initially submitted safety database.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Safety Pool:

In SAF-C2, the overall incidence and event-rate of adverse events was similar between treatment groups (Table 49). Findings for common adverse events were consistent with the previous findings from the empagliflozin NDA.

Table 49: Incidence of adverse events that occurred in > 2% of subjects and more commonly in empagliflozin treated subjects (by incidence or event rate) in the pool of placebo-controlled studies (SAF-C2)

	Placebo			Empa 10			Empa 25		
Number of subjects	**1400**			**1670**			**1751**		
Mean exposure (days)	**329.2**			**308.0**			**306.1**		
System organ class – Preferred Term	**N**	**%**	**Per 100**	**N**	**%**	**Per 100**	**N**	**%**	**Per 100**
Any adverse event	1019	72.8	226.3	1109	66.4	213.9	1161	66.3	202.4
Infections and infestations	536	38.3	61.94	588	35.2	59.28	615	35.1	59.0
– Urinary tract infection	139	9.9	11.8	157	9.4	11.9	159	9.1	11.4
Metabolism and nutrition disorders	470	33.6	51.9	396	23.7	36.6	433	24.7	38.1
– Dyslipidemia	41	2.9	3.3	51	3.1	3.7	38	2.2	2.6
Musculoskeletal and connective tissue disorders	242	17.3	22.1	255	15.3	20.8	301	17.2	23.5
– Back pain	59	4.2	4.8	73	4.4	5.3	78	4.5	5.4
Nervous system disorders	182	13.0	15.8	190	11.4	14.7	236	13.5	18.0
– Dizziness	48	3.4	3.9	56	3.4	4.0	71	4.1	4.9
– Headache	58	4.1	4.7	55	3.3	4.0	69	3.9	4.8
Renal and urinary disorders	96	6.9	7.9	147	8.8	11.1	136	7.8	9.7
– Pollakiuria	15	1.1	1.2	43	2.6	3.1	43	2.5	2.9

Empa = empagliflozin; per 100 = events per 100 patient-years
Source: Adapted from Table 2.1.2.1: 2 of the Summary of Clinical Safety and Table 5.2.2.2 of the Integrated Summary of Safety

7.4.2 Laboratory Findings

This section will focus on changes on the observed changes in laboratory tests not previously discussed. Discussion of renal function, liver function tests, and blood glucose can be found in sections 7.3.5.1, 7.3.5.2, and 7.3.5.5, respectively.

7.4.2.1 Hematology

Consistent with the observed changes for hematological laboratory tests described in the empagliflozin review, subjects treated with empagliflozin has a small increase in hematocrit compared to placebo (Table 50). This appeared to be dose-dependent but was reversible following discontinuation of empagliflozin. The clinical significance of this change is uncertain, but it did not appear to translate into a clinically meaningful event (i.e. no observed difference in embolic/thrombotic events based on SMQ 20000084).

Table 50: Changes in hematocrit in the pool of placebo-controlled studies (SAF-C2)

	Placebo	Empa 10	Empa 25
N	**1344**	**1610**	**1682**
Baseline (Median, [Q1, Q3])	41.7 (38.8, 44.5)	42.5 (38.8, 45.7)	41.7(38.8,45.2)
LVOT (Median, [Q1, Q3])	41.7 (38.8, 44.5)	45.9 (42.5, 49.1)	45.9 (42.1, 48.8)
Change from baseline (Median, [Q1, Q3])	0.0 (-2.4, 1.4)	3.4 (1.3, 5.7)	3.9 (1.4, 5.7)
% with increase from RR to > ULRR	0.6	1.7	1.9
Incidence of embolic/thrombotic events (%)	0.1	0.1	0.3
Event-rate of embolic/thrombotic events (per 100)	0.16	0.07	0.33

Empa = empagliflozin; Q1 = first quartile; Q3 = third quartile; LVOT = last value on treatment; RR = reference range; ULRR = upper limit of reference range
Source: Adapted from Table 3.1: 1,3.1:2, and Table 6.1.2.1 of the Summary of Clinical Safety

7.4.2.2 Serum Electrolytes

Electrolytes considered include serum sodium, potassium, calcium magnesium, chloride, phosphate, and bicarbonate. As was seen in the empagliflozin review, there were no notable changes in median values for electrolytes. Differences in changes in electrolytes from the normal range were seen with more empagliflozin subjects having increases in serum potassium above the reference range and decreases in serum bicarbonate below the reference range (Table 51). Overall the event-rate for potentially associated adverse events was low, and there does not appear to be a clinically meaningful effect of the observed changes in serum electrolytes (Table 52).

Table 51: Changes in serum electrolytes

	Placebo	Empa 10	Empa 25
Serum Potassium			
– - % within RR at baseline to > ULRR at LVOT	0.9	1.8	1.3
Serum Bicarbonate			
– % within RR at baseline to < LLRR at LVOT	7.5	11.9	12.1

Empa = empagliflozin; RR = reference range; ULRR = upper limit of reference range; LVOT = last value on treatment; LLRR = lower limit of reference range
Source: Adapted from Table 3.2: 2 of the Summary of Clinical Safety

Table 52: Incidence and event-rate for high serum potassium or low serum bicarbonate adverse events in the pool of all placebo-controlled studies (SAF-C2)

	Placebo		Empa 10		Empa 25	
Preferred Term	**%**	**Per 100**	**%**	**Per 100**	**%**	**Per 100**
Hyperkalemia	0.2	0.23	0.3	0.35	0.5	0.53
Blood potassium increased	0.2	0.23	0.3	0.35	0.2	0.27
Diabetic ketoacidosis	0.1	0.16	0.0	0.0	0.1	0.07
Lactic acidosis	0.0.	0.0	0.0	0.0	0.1	0.07

Empa = empagliflozin; per 100 = per 100 patient-years
Source: Adapted from Table 5.2.2.1 of the Integrated Summary of Safety

7.4.2.3 Lipids

Analysis of changes in cholesterol was limited to studies of at least 52 weeks duration in SAF-C2 (i.e., Study 1245.19$_{pio+met}$ [plus extension], Study 1245.23$_{met}$ [plus extension].Study 1245.23$_{met+SU}$ [plus extension], and Study 1245.36). The findings were consistent with what was seen during the empagliflozin review. Subjects treated with empagliflozin had small increases in cholesterol compared to placebo (Table 53). This appears to be dose dependent. Whether these changes are clinically meaningful is unclear.

Table 53: Changes in serum lipids from selected studies from the pool of all placebo-controlled studies

	Placebo	Empa 10	Empa 25
N	**726**	**647**	**741**
Total cholesterol (mg/dL)			
Baseline (mean, SE)	173.42 (1.51)	171.54 (1.51)	175.35 (1.49)
Change from baseline (mean, SE)	3.35 (1.10)	5.96 (1.18)	7.74 (1.09)
Difference from placebo (mean, 95% CI)	--	2.62(-0.56,5.79)	4.39((1.36, 7.42)
% with increase from RR to > ULRR	14.3	18.6	18.8

	Placebo	Empa 10	Empa 25
N	**726**	**647**	**741**
HDL (mg/dL)			
Baseline (mean, SE)	48.53 (0.45)	48.95 (0.49)	49.71 (0.49)
Change from baseline (mean, SE)	-0.59 (0.27	1.88 (0.29	1.09 (0.27)
Difference from placebo (mean, 95% CI)	--	2.47 (1.69, 3.25)	1.68 (0.93, 2.42)
% with increase from RR to > ULRR	1.0	2.4	1.9
LDL (mg/dL)			
Baseline (mean, SE)	93.56 (1.28)	90.96 (1.33)	93.78 (1.23
Change from baseline (mean, SE)	2.72 (0.89)	4.58 (0.96)	5.37 (0.88)
Difference from placebo (mean, 95% CI)	--	1.85 (-0.72, 4.43)	2.65 (0.20, 5.10)
% with increase from RR to > ULRR	8.9	11.2	10.8
Triglycerides (mg/dL)			
Baseline (mean, SE)	160.93 (4.01)	166.53 (5.00)	163.84 (4.42)
Change from baseline (mean, SE)	8.67 (4.08)	-3.42 (4.37)	5.46 (4.03)
Difference from placebo (mean, 95% CI)	--	-12.09 (-23.88, -0.30)	-3.21 (-14.44, 8.03)
% with increase from RR to > ULRR	8.8	6.9	8.6

Empa = empagliflozin; SE = standard error; RR = reference range; ULRR = upper limit of reference range; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol
Source: Adapted from Table 3.5: 1 and Table 3.5: 2 of the Summary of Clinical Safety

7.4.2.4 Serum Lipase

Compared to placebo, subjects treated with empagliflozin had a small increase in serum lipase (Table 54). It is unclear if this is clinically meaningful. It was not associated with an increase in clinical pancreatitis adverse events (Table 55).

Table 54: Change in serum lipase for the pool of placebo-controlled studies (SAF-C2)

	Placebo	Empa 10	Empa 25
N	**1344**	**1614**	**1683**
Baseline (Median, [Q1, Q3])	96 (72, 133)	93 (72, 128)	96 (72, 131)
LVOT (Median, [Q1, Q3])	96 (72, 136)	99 (72, 133)	99 (75, 136)
Change from baseline (Median, [Q1, Q3])	0 (-13, 16)	3 (-13, 19)	3 (-13, 19)
% with increase from RR to > ULRR	8.2	9.6	9.9

Empa = empagliflozin; Q1 = first quartile; Q3 = third quartile; LVOT = last value on treatment; RR = reference range; ULRR = upper limit of reference range
Source: Adapted from Table 3.3: 1 and Table 3.3: 2 of the Summary of Clinical Safety

Table 55: Incidence and event-rate for pancreatitis adverse events for the pool of placebo-controlled studies (SAF-C2)

	Placebo		Empa 10		Empa 25	
Preferred Term	**%**	**Per 100**	**%**	**Per 100**	**%**	**Per 100**
Pancreatitis	0.1	0.08	0	0	0	0
Pancreatitis acute	0.1	0.08	0.1	0.13	0.1	0.14
Pancreatitis chronic	0.1	0.08	0	0	0	0
Total	0.2	0.23	0.1	0.13	0.1	0.14

Empa = empagliflozin; per 100 = per 100 patient-years
Source: Adapted from Table 5.2.2.1 of the Integrated Summary of Safety

7.4.3 Vital Signs

Vital signs that were measured during the clinical studies included blood pressure (systolic and diastolic) and heart rate. In the pool of placebo-controlled studies, there was a greater median decrease in both systolic and diastolic blood pressure with empagliflozin compared to placebo (Table 56). No notable changes in heart rate were reported.

Table 56: Change in vital signs for pool of placebo-controlled studies (SAF-C2)

	Placebo	Empa 10	Empa 25
N	**1400**	**1670**	**1751**
Systolic blood pressure (mmHg)			
Baseline (median, [Q1, Q3])	132.0 (122.0, 142.3)	131.7 (122.0, 142.3)	131.7 (122.0, 142.3)
LVOT (median, [Q1, Q3])	132.0 (122.3, 142.3)	128.3 (119.3, 138.3)	127.7 (118.7, 137.7)
Difference from baseline (median, [Q1, Q3])	0 (-8.0, 8.0)	-3.3 (-11.7, 4.0)	-4.3 (-12.0, 3.7)
Diastolic blood pressure (mmHg)			
Baseline (median, [Q1, Q3])	80.0 (73.0, 85.0)	80.0 (73.0, 85.0)	79.7 (73.3, 85.0)
LVOT (median, [Q1, Q3])	79.3 (72.7, 79.3)	78.0 (71.7, 82.7)	77.3 (70.7, 82.3)
Difference from baseline (median, [Q1, Q3])	-0.3 (-5.3, 4.7)	-1.7 (-7.0, 2.7)	-0.3 (-7.3, 2.7)
Heart rate (bpm)			
Baseline (median, [Q1, Q3])	74.0 (68.0, 80.0)	73.0 (67.0, 80.0)	73.0 (67.0, 80.0)
LVOT (median, [Q1, Q3])	73.0 (67.0, 80.0)	73.0 (66.0, 80.0)	72.0 (66.0, 79.0)
Difference from baseline (median, [Q1, Q3])	0 (-6, 5)	-1 (-6, 4)	0 (-6, 4)

Empa = empagliflozin; Q1 = first quartile; Q3 = third quartile; LVOT = last value on treatment
Source: adapted from Table 4.1: 1 and Table 4.1: 2 of the Summary of Clinical Safety, and Table 7.1.2.3 of the Integrated Summary of Safety

7.4.4 Electrocardiograms (ECGs)

A thorough QT study was not performed to support the FCDP product. A study was performed for the empagliflozin NDA. No evidence of an increase in QT interval was seen.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

In the safety population SAF-C2, there was not a strong suggestion of dose-dependency for AEs. However, in the sub-group of subjects ≥ 65 years old there was suggestion of dose-dependency for volume depletion events. This is consistent with observations from the empagliflozin NDA and language regarding cautious use in older subjects is included in the label.

7.5.2 Time Dependency for Adverse Events

In the presented safety data, a difference in time to first event was noted for genital infections (Figure 4).

7.5.3 Drug-Demographic Interactions

7.5.3.1 By Age

Safety Pool:

The majority of subjects (56%) from SAF-C2 were between ages 50 and 65 years old. Subjects between the ages of 65 and 75 years old were another 21% of the subject pool. Subjects < 50 years old composed 19%, and subjects ≥ 75 years old made up the remaining 4%. The small proportion of subjects ≥ 75 years old limits the ability to assess the effect of age on safety for this subgroup. Thus, while the Applicant has presented the data in these four separate age sub-groups, I have opted to compare incidence for subjects < 65 years old with subjects ≥ 65 years old.

Comparing subjects based on the age cut-off of 65 years old, there appears to be a small dose dependent increase in adverse events with the older age group (Table 57). This observation is also seen in the incidence of serious adverse events, though the incidence is higher in placebo-

treated subjects. There is a suggestion of an increased incidence of decreased renal function and volume depletion in older subjects.

Table 57: Comparison of incidence of selected adverse events by age sub-group for the pool of placebo-controlled studies (SAF-C2)

	Age < 65 years		Age ≥ 65 years	
	N	%	N	%
Placebo	**1052**	**100**	**348**	**100**
Empa 10	**1242**	**100**	**428**	**100**
Empa 25	**1300**	**100**	**451**	**100**
All Empa	**2542**	**100**	**879**	**100**
Any AE				
– Placebo	769	73.1	250	71.8
– Empa 10	824	66.3	285	66.6
– Empa 25	842	64.8	319	70.7
– All Empa	1666	65.5	604	68.7
Any SAE				
– Placebo	75	7.1	42	12.1
– Empa 10	75	6.0	37	8.6
– Empa 25	73	5.6	43	9.5
– All Empa	148	5.8	80	9.1
Decreased renal function				
– Placebo	1	0.1	2	0.6
– Empa 10	8	0.6	5	1.2
– Empa 25	8	0.6	6	1.3
– All Empa	16	0.6	11	1.3
Volume depletion				
– Placebo	5	0.5	2	0.6
– Empa 10	11	0.9	5	1.2
– Empa 25	9	0.7	8	1.8
– All Empa	20	0.8	13	1.5

Empa = empagliflozin; AE = adverse event; SAE = serious adverse event
Source: Adapted from Table 5.1.1: 1 of the Summary of Clinical Safety

These observations are consistent with what was seen in the empagliflozin monotherapy program.

7.5.3.2 By baseline renal function

There is limited information on subjects with moderate or severe renal impairment. This is to be expected given the current labeling for metformin which contraindicates use in renal impairment for safety reasons and the current labeling for empagliflozin which contraindicates use in subjects with an eGFR < 45 ml/min/1.73 m^2 due to lack of efficacy and for safety concerns.

Nevertheless, examination of adverse events by baseline renal function showed some suggestion of a greater risk for certain events (e.g. decreased renal function) in subjects with more advanced renal impairment (Table 58).

Table 58: Comparison of incidence of selected adverse events by renal function sub-group for the pool of placebo-controlled studies (SAF-C2)

	eGFR ≥ 90		eGFR 60 to < 90		eGFR < 60	
Placebo	**490**		**726**		**184**	
Empa 10	**639**		**915**		**116**	
Empa 25	**669**		**869**		**213**	
All Empa	**1308**		**1784**		**329**	
	N	**%**	**N**	**%**	**N**	**%**
Any AE						
– Placebo	345	70.4	529	72.9	145	78.8
– Empa 10	406	63.5	618	67.5	85	73.3
– Empa 25	431	64.4	558	64.2	172	80.8
– All Empa	837	64.0	1176	65.9	257	78.1
Any SAE						
– Placebo	35	7.1	66	9.1	16	8.7
– Empa 10	35	5.5	67	7.3	10	8.6
– Empa 25	39	5.8	57	6.6	20	9.4
– All Empa	74	5.7	124	7.0	30	9.1
Decreased renal function						
– Placebo	0	0.0	1	0.1	2	1.1
– Empa 10	1	0.2	4	0.4	8	6.9
– Empa 25	3	0.4	4	0.5	7	3.3
– All Empa	4	0.3	8	0.4	15	4.6
Volume depletion						
– Placebo	1	0.2	3	0.4	3	1.6
– Empa 10	5	0.8	9	1.0	2	1.7
– Empa 25	5	0.7	7	0.8	5	2.3
– All Empa	10	0.8	16	0.9	7	2.1

eGFR = estimated glomerular filtration rate in ml/min/1.37 m^2 (using MDRD equation); Empa = empagliflozin; AE = adverse event; SAE = serious adverse event
Source: Adapted from Table 5.1.2.8 and Table 5.12.2.8 of the Integrated Summary of Safety, and from Table 3 of the Response to Information Request received on January 16, 2015 (NDA-206111, SD-9)

Further analysis of the subjects with a baseline eGFR < 60 ml/min/1.73 m^2 suggests that this is due primarily to the subjects with an eGFR < 45 ml/min/1.73 m^2 (Table 59).

Table 59: Comparison of incidence of selected adverse events by moderate renal impairment sub-groups for the pool of placebo-controlled studies (SAF-C2)

	eGFR 45 to < 60		eGFR 30 to < 45	
Placebo	**128**		**50**	
Empa 10	**102**		**13**	
Empa 25	**157**		**52**	
All Empa	**259**		**65**	
	N	**%**	**N**	**%**
Any AE				
– Placebo	101	78.9	41	82.0
– Empa 10	73	71.6	11	84.6
– Empa 25	124	79.0	44	84.6
– All Empa	197	76.1	55	84.6
Any SAE				
– Placebo	9	7.0	7	14.0
– Empa 10	7	6.9	2	15.4
– Empa 25	11	7.0	8	15.4
– All Empa	18	6.9	10	15.4
Decreased renal function				
– Placebo	1	0.8	1	2.0
– Empa 10	5	4.9	2	15.4
– Empa 25	3	1.9	3	5.8
– All Empa	8	3.1	5	7.7
Volume depletion				
– Placebo	2	1.6	1	2.0
– Empa 10	0	0.0	1	7.7
– Empa 25	3	1.9	2	3.8
– All Empa	3	1.2	3	4.6

eGFR = estimated glomerular filtration rate in ml/min/1.37 m^2 (using MDRD equation); Empa = empagliflozin; AE = adverse event; SAE = serious adverse event
Source: Adapted from Table 2 of the Response to Information Request received on January 16, 2015 (NDA-206111, SD-9)

These findings are consistent with the safety profile of empagliflozin. The proposed label recommends discontinuation of therapy in subjects with a persistent eGFR < 60 ml/min/1.73 m^2 which is more restrictive than the current approved empagliflozin label, presumably based on the safety concerns with metformin. This is acceptable

7.5.4 Drug-Drug Interactions

See section 4.4, and section 7.2.5 for discussion of drug-drug interactions.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See the discussion of malignancies in section 7.3.5.7.

7.6.2 Human Reproduction and Pregnancy Data

There is no controlled data on the effect of using empagliflozin and/or metformin use in pregnancy. Pregnant women and nursing women were excluded from the clinical trials. Subjects that became pregnant had study medication stopped, but were followed to delivery or termination of the pregnancy.

From the clinical studies submitted to support the NDA, there were eight subjects that became pregnant while receiving study drug. Of these eight, three were treated with empagliflozin + metformin. The remaining five subjects were treated with glimepiride + metformin. In the 120-Day Safety Update, one additional subject from Study 1276.1 was reported to have become pregnant while being treated with study drug. Study for this subject remains blinded. Outcomes of the pregnancies are provided in Table 60.

Table 60: List of pregnancies and pregnancy outcomes

Subject ID	Rx	Exp Before	Exp During	Outcome
1245.0023.034570	E25 + Met	60	217	Healthy girl
1245.0023.034134	E10 + Met	384	39	Premature boy (32 weeks)
1245.0028.086509	Gl + Met	320	46	Miscarriage
1245.0028.082578	Gl + Met	113	36	Healthy girl
1245.0028.081645	Gl + Met	580	66	Healthy girl
1245.0028.084047	Gl + Met	710	57	Unknown
1245.0028.088965	Gl + Met	570	61	Low birth weight boy
1245.0049.078341	E25 + Met	56	3	Miscarriage
1276.0001.013966	Blinded	52	30	Healthy twin delivery (1 male, 1 female)

ID = identification number; Rx = treatment; Exp Before = exposure before pregnancy (based on day of last menstrual period – day of first dose of study drug + 1); Exp During = exposure during pregnancy (based on day of last dose of study drug – day of last menstrual period + 1); E25 + Met = empagliflozin 25 mg + metformin; E10 + Met = empagliflozin 10 mg + metformin; Gl + Met = glimepiride + metformin
Source: Adapted from Table 5.4: 1 of the Summary of Clinical Safety and Section 6.1 of the 120-Day Safety Update

From this limited information, no meaningful conclusions regarding the risk of empagliflozin + metformin exposure in pregnancy can be made.

7.6.3 Pediatrics and Assessment of Effects on Growth

Not applicable. No pediatric data is included in this submission.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable.

8 Postmarket Experience

There is no postmarketing experience with this FCDP product. There is limited postmarketing experience with empagliflozin added to a background of metformin.

Acidosis has been reported in the post-marketing setting with the SGLT2 inhibitor class. No clear imbalance in acid-base disorders was seen in the data submitted to support this NDA, but it remains an issue of concern and is a tracked safety issue.

9 Appendices

9.1 Labeling Recommendations

With regard to labeling, I would favor focusing on data from those studies that specifically inform the use of this fixed combination product. (b) (4) Labeling negotiations are ongoing at the time of finalization of this review, and additional labeling recommendations may be communicated to the Applicant.

9.2 Advisory Committee Meeting

Not applicable. No Advisory Committee was held to discuss this application.

9.3 Financial Disclosures

Clinical Investigator Financial Disclosure
Review Template

Application Number: 206111
Submission Date(s): August 4, 2014
Applicant: Boehringer Ingelheim
Product: Empagliflozin and metformin fixed combination drug product

Reviewer: William H. Chong, MD
Date of Review: August 20, 2014
Covered Clinical Study (Name and/or Number): Studies 1275.1, 1276.10, 1245.10, 1245.19, 1245.23, 1245.24, 1245.28, 1245.31, 1245.33, 1245.36, 1245.48, and 1245.49

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 5215		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 1		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 6		
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: 2 Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: 2		
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) 658[1]		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from applicant)

[1] These investigators did not have a completed financial disclosure questionnaire. Though the Applicant did not submit a separate form FDA 3454 identifying these investigators as "investigators with certification of due diligence" I interpret the separate presentation of these investigators as the Applicant's intent to do so. The majority of these investigators either did not participate or were at a site that did not enroll any subjects. There were some with incomplete financial disclosure questionnaires, but I do not feel that this will substantially impact the integrity or approvability of the application.

I believe that the Applicant has adequately disclosed the financial interests/arrangements of the clinical investigators. Given the large number of investigators, and the large number of subjects studied to support this application, the small number of investigators with disclosable financial interests is unlikely to substantially affect the integrity of the data. Additionally, each of the investigator's with disclosable financial interests contributed only small percentage of subjects to the studies in which they participated. This further reassures me that their participation is unlikely to affect the integrity of the data or impact the approvability of the application.

9.4 Additional Tables and Figures

Table 61: Event rate of serious adverse events in study 1276.10

- includes only system organ classes with ≥ 2 events in any arm

System organ class - High level term - Preferred term	Placebo (N=107)		Empa 5 BID (N=219)		Empa 10 QDay (N=220)		Empa 12.5 BID (N=219)		Empa 25 QDay (N=218)	
Patient-years	**32.8**		**65.1**		**65.0**		**66.1**		**65.2**	
	N	**Per 100**	**N**	**Per 100**	**N**	**Per 100**	**N**	**Per 100**	**N**	**Per 100**
Number of SAEs	**1**	**3.0**	**9**	**13.8**	**8**	**12.3**	**7**	**10.6**	**2**	**3.1**
Gastrointestinal disorders	0	0.0	1	0.5	2	0.9	3	1.4	0	0.0
- Acute and chronic pancreatitis	0	0.0	1	0.5	1	0.5	0	0.0	0	0.0
- Pancreatitis acute	0	0.0	1	0.5	1	0.5	0	0.0	0	0.0
- Inguinal hernias	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0
- Inguinal hernia	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0
- Intestinal hemorrhages	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0
- Rectal hemorrhage	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0
- Salivary gland disorders NEC	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0
- Salivary gland pain	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0
- Salivary gland enlargements	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0
- Parotid gland enlargement	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0
Hepatobiliary disorders	0	0.0	2	0.9	2	0.9	0	0.0	0	0.0
- Bile duct infections and inflammations	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0
- Cholangitis	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0
- Cholecystitis and cholelithiasis	0	0.0	1	0.5	1	0.5	0	0.0	0	0.0
- Cholecystitis acute	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0
- Cholelithiasis	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0
- Obstructive bile duct disorders (excl neoplasms)	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0
- Bile duct stone	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0

System organ class – **High level term** – **Preferred term**	**Placebo (N=107)**		**Empa 5 BID (N=219)**		**Empa 10 QDay (N=220)**		**Empa 12.5 BID (N=219)**		**Empa 25 QDay (N=218)**	
Patient-years	**32.8**		**65.1**		**65.0**		**66.1**		**65.2**	
	N	**Per 100**	**N**	**Per 100**	**N**	**Per 100**	**N**	**Per 100**	**N**	**Per 100**
Musculoskeletal and connective tissue disorders	0	0.0	2	0.9	1	0.5	0	0.0	0	0.0
– Bone disorders NEC	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0
– Exostosis of jaw	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0
– Osteoarthropathies	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0
– Spinal osteoarthritis	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0
– Synovial disorders	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0
– Synovial cyst	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0.0	1	0.5	2	0.9	1	0.5	0	0.0
– Bladder neoplasms malignant	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0
– Bladder transitional cell carcinoma	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0
– Hepatobiliary neoplasms benign	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0
– Biliary adenoma	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0
– Neoplasms malignant site unspecified NEC	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0
– Squamous cell carcinoma	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0
– Prostatic neoplasms malignant	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0
– Prostate cancer	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0
Nervous system disorders	1	0.9	0	0.0	0	0.0	2	0.9	0	0.0
– Central nervous system hemorrhages and cerebrovascular accidents	1	0.9	0	0.0	0	0.0	1	0.5	0	0.0
– Cerebrovascular accident	1	0.9	0	0.0	0	0.0	0	0.0	0	0.0
– Ischemic stroke	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0
– Transient cerebrovascular events	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0
– Transient ischemic attack	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0

Empa = empagliflozin; BID = twice daily; QDay = once daily; N = number of events; Per 100 = events per 100 patient-years
Source: Adapted from Table 12.1: 1 of the study report and review of the AE.xpt and DM.xpt data files for Study 1276.10

Table 62: Serious adverse events reported from Study 1275.10 in the 120-Day Safety Update

System organ class – **Preferred term**	**Empa + Met N=705**	
	N	%
Total	28	4.0
Not yet coded	1	0.1
Cardiac disorders	5	0.7
– Angina unstable	1	0.1
– Atrial fibrillation	1	0.1
– Coronary artery disease	1	0.1
– Myocardial infarction	1	0.1
– Myocardial ischemia	1	0.1
Gastrointestinal disorders	5	0.7
– Pancreatitis acute	2	0.3
– Diverticulum intestinal	1	0.1
– Gastritis	1	0.1
– Gastrointestinal hemorrhage	1	0.1
Infections and infestations	6	0.9
– Abscess limb	1	0.1
– Gangrene	1	0.1
– Upper respiratory tract infection	1	0.1
– Osteomyelitis	2	0.3
– Urinary tract infection	1	0.1
Hepatobiliary disorders	3	0.4
– Cholecystitis acute	2	0.3
– Liver injury	1	0.1
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	3	0.4
– Pancreatic carcinoma metastatic	1	0.1
– Pancreatic neoplasm	1	0.1
– Prostatic adenoma	1	0.1
Nervous system disorders	3	0.4
– Cerebral hematoma	1	0.1
– Cerebral hemorrhage	1	0.1
– Ischemic stroke	1	0.1
– Cerebrovascular accident	1	0.1
General disorders and administration site conditions	2	0.3
– Calcinosis	1	0.1
– Death	1	0.1
Injury, poisoning and procedural complications	2	0.3
– Skull fractured base	1	0.1
– Fall	1	0.1
Reproductive system and breast disorders	2	0.3
– Metrorrhagia	1	0.1

System organ class – Preferred term	Empa + Met N=705	
	N	%
– Balanoposthitis	1	0.1
Respiratory, thoracic and mediastinal disorders	2	0.3
– Nasal turbinate hypertrophy	1	0.1
– Pharyngeal lesion	1	0.1
Vascular disorders	1	0.1
– Extremity necrosis	1	0.1
Musculoskeletal and connective tissue disorders	3	0.4
– Hemarthrosis	1	0.1
– Rhabdomyolysis	1	0.1
– Rotator cuff syndrome	1	0.1

Empa = empagliflozin; Met = metformin
Source: Adapted from Listing 2.5 and Listing 2.7 of the 120-Day Safety Update

Table 63: Premature discontinuation due to adverse event from Study 1275.10 in the 120-Day Safety Update

System organ class – Preferred term	Empa + Met N=705	
	N	%
Total	39	5.5
Total (open-label)	23	3.3
Total (blinded)	16	2.3
Infections and infestations	11	1.6
– Fungal infection	1	0.1
– Gangrene	1	0.1
– Genitourinary tract infection	1	0.1
– Urinary tract infection	4	0.6
– Vaginal infection	1	0.1
– Vulvovaginitis	1	0.1
– Bronchitis	1	0.1
– Osteomyelitis	1	0.1
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1	0.1
– Pancreatic carcinoma metastatic	1	0.1
Metabolism and nutrition disorders	2	0.3
– Polydipsia	1	0.1
– Hyperglycemia	1	0.1
Eye disorders	1	0.1
– Dry eye	1	0.1
Gastrointestinal disorders	8	1.1
– Abdominal pain upper	1	0.1
– Constipation	1	0.1
– Dry mouth	1	0.1

System organ class – Preferred term	Empa + Met N=705	
	N	%
– Pancreatitis chronic	1	0.1
– Rectal discharge	1	0.1
– Swollen tongue	1	0.1
– Dysphagia	1	0.1
Skin and subcutaneous tissue disorders	1	0.1
– Rash erythematous	1	0.1
Musculoskeletal and connective tissue disorders	1	0.1
– Flank pain	1	0.1
Renal and urinary disorders	7	1.0
– Micturition urgency	2	0.3
– Pollakiuria	2	0.3
– Polyuria	2	0.3
– Renal failure	1	0.1
General disorders and administration site conditions	1	0.1
– Fatigue	1	0.1
Investigations	6	0.9
– Amylase increased	3	0.4
– Glomerular filtration rate increased	2	0.3
– Lipase increased	4	0.6
Respiratory, thoracic and mediastinal disorders	2	0.3
– Cough	1	0.1
– Pharyngeal lesion	1	0.1
Reproductive system and breast disorders	1	0.1
– Vulvovaginal pruritus	1	0.1

Empa = empagliflozin; Met = metformin
Source: Adapted from Listing 2.6 and Listing 2.8 of the 120-Day Safety Update

Table 64: List of preferred terms used in analysis of decreased renal function

Acute phosphate nephropathy	Crystal nephropathy	Proteinuria
Acute prerenal failure	Dialysis	Renal failure
Albuminuria	Glomerular filtration rate abnormal	Renal failure acute
Anuria	Glomerular filtration rate decreased	Renal failure neonatal
Azotemia	Hemodialysis	Renal function test abnormal
Blood creatinine abnormal	Hemofiltration	Renal impairment
Blood creatinine increased	Hypercreatininemia	Renal impairment neonatal
Blood urea abnormal	Neonatal anuria	Renal transplant
Blood urea increased	Nephritis	Renal tubular disorder
Blood urea nitrogen/creatinine ratio increased	Nephropathy toxic	Renal tubular necrosis
Continuous hemodiafiltration	Edema due to renal disease	Tubulointerstitial nephritis

Creatinine renal clearance decreased	Oliguria	Urea renal clearance decreased
Creatinine renal clearance abnormal	Peritoneal dialysis	Urine output decreased
Creatinine urine abnormal	Prerenal failure	
Creatinine urine decreased	Protein urine present	

Source: Adapted from Table 1.12.1 of the Integrated Summary of Safety

Table 65: List of preferred terms used in analysis of hepatic injury

5'nucleotidase increased	Hemorrhage	Liver function test abnormal
Acute graft versus host disease in liver	Hemorrhagic ascites	Liver induration
Acute hepatic failure	Hepaplastin abnormal	Liver injury
Acute yellow liver atrophy	Hepaplastin decreased	Liver operation
Alanine aminotransferase abnormal	Hepatectomy	Liver palpable subcostal
Alanine aminotransferase increased	Hepatic artery flow decreased	Liver sarcoidosis
Allergic hepatitis	Hepatic atrophy	Liver scan abnormal
Ammonia abnormal	Hepatic calcification	Liver tenderness
Ammonia increased	Hepatic cirrhosis	Liver transplant
Anorectal varices	Hepatic congestion	Lupoid hepatic cirrhosis
Ascites	Hepatic encephalopathy	Lupus hepatitis
Aspartate aminotransferase increased	Hepatic encephalopathy prophylaxis	Mitochondrial aspartate aminotransferase increased
Aspartate aminotransferase abnormal	Hepatic enzyme abnormal	Mixed liver injury
Asterixis	Hepatic enzyme decreased	Molar ratio of total branched−chain amino acid to tyrosine
Autoimmune hepatitis	Hepatic enzyme increased	Nodular regenerative hyperplasia
Bacterascites	Hepatic failure	Non−alcoholic
Bile output abnormal	Hepatic fibrosis	Non−alcoholic steatohepatitis
Bile output decreased	Hepatic fibrosis marker abnormal	Ocular icterus
Biliary ascites	Hepatic function abnormal	Edema due to hepatic disease
Biliary cirrhosis	Hepatic hydrothorax	Esophageal varices hemorrhage
Biliary cirrhosis primary	Hepatic infiltration eosinophilic	Parenteral nutrition associated liver disease
Biliary fibrosis	Hepatic lesion	Perihepatic discomfort
Bilirubin conjugated abnormal	Hepatic mass	Peripancreatic varices
Bilirubin conjugated increased	Hepatic necrosis	Periportal edema
Bilirubin excretion disorder	Hepatic pain	Peritoneal fluid protein abnormal
Biopsy liver abnormal	Hepatic sequestration	Peritoneal fluid protein decreased
Blood alkaline phosphatase abnormal	Hepatic steatosis	Peritoneal fluid protein increased
Blood alkaline phosphatase increased	Hepatic vascular resistance increased	Peritoneovenous shunt
Blood bilirubin abnormal	Hepatitis	phosphatase abnormal
Blood bilirubin increased	Hepatitis acute	Pneumobilia

Blood bilirubin unconjugated increased	Hepatitis cholestatic	Portal hypertension
Blood cholinesterase abnormal	Hepatitis chronic active	Portal hypertensive
Blood cholinesterase decreased	Hepatitis chronic persistent	Portal shunt
Bromosulphthalein test abnormal	Hepatitis fulminant	Portal triaditis
Child−Pugh−Turcotte score increased	Hepatitis toxic	Portal vein cavernous transformation
Cholemia	Hepatobiliary disease	Portal vein dilatation
Cholestasis	Hepatobiliary scan abnormal	Portal vein flow decreased
Cholestatic liver injury	Hepatocellular foamy cell syndrome	Portal vein pressure increased
Cholestatic pruritus	Hepatocellular injury	Portopulmonary
Chronic graft versus host disease in liver	Hepatomegaly	Radiation hepatitis
Chronic hepatic failure	Hepatopulmonary syndrome	Renal and liver transplant
Chronic hepatitis	Hepatorenal failure	Retinol binding protein decreased
Coma hepatic	Hepatorenal syndrome	Retrograde portal vein flow
Cryptogenic cirrhosis	Hepatosplenomegaly	Reye's syndrome
Deficiency of bile secretion	Hepatotoxicity	Reynold's syndrome
Diabetic hepatopathy	Hyperammonemia	Small−for−size liver syndrome
Drug−induced liver injury	Hyperbilirubinemia	Spider nevus
Duodenal varices	Hypercholia	Splenic varices
Enteropathy	Hypertension	Steatohepatitis
Fetor hepaticus	Hypertransaminasemia	Subacute hepatic failure
Galactose elimination capacity test abnormal	Hypoalbuminemia	Total bile acids increased
Galactose elimination capacity test decreased	Icterus index increased	Transaminases abnormal
Gallbladder varices	Intestinal varices	Transaminases increased
Gamma−glutamyltransferase abnormal	Intrahepatic portal hepatic venous fistula	Ultrasound liver abnormal
Gamma−glutamyltransferase increased	Ischemic hepatitis	Urine bilirubin increased
Gastric varices	Jaundice	Urobilinogen urine decreased
Gastric varices hemorrhage	Jaundice cholestatic	Urobilinogen urine increased
Gastropathy	Jaundice hepatocellular	Varices esophageal
Glutamate dehydrogenase increased	Kaiser−Fleischer ring	Varicose veins of abdominal wall
Graft versus host disease in liver	Leucine aminopeptidase increased	X−ray hepatobiliary abnormal
Granulomatous liver disease	Liver and small intestine transplant	Yellow skin
Guanase increased	Liver disorder	

Source: Adapted from Table 1.12.1 of the Integrated Summary of Safety

Table 66: List of preferred terms used in analysis of urinary tract infections

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

Source: Adapted from Table 1.12.1 of the Integrated Summary of Safety

Table 67: List of preferred terms used in analysis of genital infections

Bacterial	Hydrocele male infected	Salpingo−oophoritis
Bacterial prostatitis	Infection	Scrotal abscess
Balanitis	Intrauterine infection	Scrotal gangrene
Balanitis candida	Myometritis	Scrotal infection
Balanoposthitis	Oophoritis	Seminal vesicular infection
Balanoposthitis infective	Orchitis	Seminal vesiculitis
Bartholin's abscess	Ovarian abscess	Spermatic cord funiculitis
Bartholinitis	Ovarian bacterial infection	Testicular abscess
Candida cervicitis	Ovarian infection	Toxic shock syndrome staphylococcal

Cellulitis of male external genital organ	Parametric abscess	Toxic shock syndrome streptococcal
Cervicitis	Parametritis	Tubo−ovarian abscess
Cervicitis cystic	Pelvic abscess	Urogenital infection bacterial
Cervicitis streptococcal	Pelvic infection	Urogenital infection fungal
Clitoris abscess	Pelvic inflammatory disease	Uterine abscess
Cytolytic vaginosis	Pelvic inflammatory disease mycoplasmal	Uterine infection
Endometritis	Pelvic sepsis	Vaginal abscess
Epididymal infection	Penile abscess	Vaginal cellulitis
Epididymitis	Penile infection	Vaginal infection
Erosive balanitis	Perineal abscess	Vaginitis bacterial
Escherichia vaginitis	Perineal infection	Vaginitis gardnerella
Fallopian tube abscess	Posthitis	Vaginitis viral
Gangrenous balanitis	Prostate infection	Vulval abscess
Genital abscess	Prostatic abscess	Vulval cellulitis
Genital candidiasis	Prostatitis	Vulvitis
Genital infection	Prostatitis Escherichia coli	Vulvovaginal candidiasis
Genital infection female	Prostatovesiculitis	Vulvovaginal human papilloma virus infection
Genital infection fungal	Pyometra	Vulvovaginal mycotic infection
Genital infection male	Pyospermia	Vulvovaginitis
Genital infection viral	Rectovaginal septum abscess	Vulvovaginitis streptococcal
Genitourinary tract	Salpingitis	

Source: Adapted from Table 1.12.1 of the Integrated Summary of Safety

Table 68: List of preferred terms used in analysis of fractures

Acetabulum fracture	Ilium fracture	Cervical certebral fracture
Ankle fracture	Jaw fracture	Lumbar vertebral fracture
Clavicle fracture	Multiple fractures	Thoracic vertebral fracture
Complicated fracture	Open fracture	Comminuted fracture
Compression fracture	Osteoporotic fracture	Epiphyseal fracture
Elevation skull fracture	Patella fracture	Pelvic fracture
Facial bones fracture	Pathological fracture	Skull fracture
Femoral neck fracture	Radius fracture	Upper limb fracture
Femur fracture	Rib fracture	Lower limb fracture
Fibula fracture	Scapula fracture	Tooth fracture
Foot fracture	Skull fractured base	Torus fracture
Forearm fracture	Spinal compression fracture	Avulsion fracture
Fracture	Spinal fracture	Impacted fracture
Fractured ischium	Sternal fracture	Periprosthetic fracture

Fractured sacrum	Stress fracture	Pubis fracture
Fractured skull depressed	Tibia fracture	Atypical femur fracture
Greenstick fracture	Ulna fracture	Fracture pain
Hand fracture	Wrist fracture	Atypical fracture
Hip fracture	Fractured coccyx	Chance fracture
Humerus fracture	Traumatic fracture	Osteochondral fracture

Source: Adapted from Table 1.12.1 of the Integrated Summary of Safety

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/s/

WILLIAM H CHONG
05/18/2015

JEAN-MARC P GUETTIER
06/04/2015

Dr. Chong's review summarizes the data in this application and the review findings across each discipline involved in the review. I agree that the applicant has established the safety and effectiveness of the product. I recommend a complete response to the application due to the fact that agreement on the content of the full prescribing information was not reached. Refer to my memorandum for details.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA Number: 206111 **Applicant: Boehringer Ingelheim** **Stamp Date: August 4, 2014**

Drug Name: Fixed dose combination of empagliflozin and metformin **NDA Type: New combination**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: Study Title: Sample Size: Arms: Location in submission:			X	
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application?	X			
15.	Do all pivotal efficacy studies appear to be adequate and	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?				
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?			X	
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			MedDRA v16.1
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			X	
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

William H. Chong, MD

Reviewing Medical Officer/Clinical Team Leader Date

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/s/

WILLIAM H CHONG
09/25/2014