

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

204629Orig1s000

MEDICAL REVIEW(S)

NDA-204629 (Empagliflozin)
Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.
SD-34, eCTD-0036, General Correspondence
Date Received: March 18, 2013
Clinical Review
Reviewer: William H. Chong

Empagliflozin is a sodium-dependent glucose co-transporter 2 inhibitor that is being developed for use in the treatment of type 2 diabetes mellitus. The initial NDA was submitted on March 5th, 2013. A Complete Response letter was issued on March 4th, 2014. In preparation for resubmission of NDA-204629, the Sponsor has submitted the following proposal for the safety update.

"BI is proposing to provide the following information as a safety update:

- Updated listings of melanoma and lung cancer from all completed empagliflozin studies in patients with type 2 diabetes. New cases will be delineated from cases included in the original application. In addition, will include a description of how the updated SAF-5 dataset differs from the original SAF-5 dataset in terms of number of subjects exposed and duration of exposure.*
- Available detailed information on all cases of lung cancer and malignant melanoma from studies completed since submission of BI's response to FDA information request sent August 16, 2013 (SEQ 0016). The information in Seq 0016 pertained to patients listed in SCS Tables 2.1.5.8:3 (melanoma) and 2.1.5.8:4 (lung cancer).*
- Listings of reports of serious adverse events related to lung cancer and malignant melanoma for ongoing blinded studies (including the CV outcome study 1245.25). Those reports which are categorized as suspected unexpected serious adverse reactions (SUSARs) will be unblinded; the remaining events will be presented as blinded information.*

To address the additional safety information requested in the Complete Response letter, we call your attention to the attachment to this letter outlining the Phase 3 studies with empagliflozin completed since NDA 204629 was originally submitted. Please note that the safety profile of empagliflozin as presented in each of these clinical trial reports is consistent with the safety profile of empagliflozin as presented in the original NDA.

The attachment also provides an overview of US applications to which the reports for these studies have been, or are planned to be submitted, including:

- (b) (4) empagliflozin/linagliptin fixed dose combination tablets (submitted January 30, 2014)*

- (b) (4)*

NDA-204629 (Empagliflozin)
Sponsor: Boehringer Ingelheim Pharmaceuticals, Inc.
SD-34, eCTD-0036, General Correspondence
Date Received: March 18, 2013
Clinical Review
Reviewer: William H. Chong

- *IND 102145 for empagliflozin tablets*

(b) (4)

Question from Sponsor:

Does the Agency concur with BI's proposal for the safety update as outlined in this letter to support the resubmission of NDA 204629 in 2Q14?

FDA Response:

We do not concur with the proposed safety update.

(b) (4)

(b) (4)

To facilitate review, updated safety information as described in your proposal for melanoma and lung cancer should also be provided for deaths, serious adverse events, and all of the other adverse events of special interest. Analysis by age, gender, and baseline renal function should be performed as appropriate. New information should be clearly delineated from the information submitted with the initial NDA. As discussed in our Complete Response letter issued on March 4, 2014, you should:

- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.

Any significant changes to the safety profile or new safety findings that result from analysis of the updated safety information should be described in detail.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H CHONG
03/31/2014

Summary Basis for Regulatory Action

Date	March 4, 2014
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	204629
Applicant Name	Boehringer Ingelheim Pharmaceuticals Inc.
Proprietary / Established (USAN) Names	Jardiance Empagliflozin
Dosage Forms / Strength	10 and 25 mg tablets
Proposed Indication(s)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Action:	<i>Complete Response</i>

1. Introduction and Discussion

This will be a brief summary of the basis for the regulatory action regarding empagliflozin and the reader should review the action package for more detail. Empagliflozin is a new molecular entity developed to improve glycemic control (anti-diabetic therapy) by inhibiting the sodium glucose cotransporter-2 (SGLT2) receptor. Inhibition of this receptor prevents glucose reabsorption in the proximal tubules of the kidney resulting in glucosuria but also decreasing the serum hyperglycemia associated with diabetes. Control of hyperglycemia through glucose diuresis may have other effects that could be salutary, such as reducing blood pressure and weight loss.¹ There are currently two approved products in the same category as empagliflozin (SGLT2); Invokana (canagliflozin) and Farxiga (dapagliflozin).

The applicant has submitted data that demonstrate that empagliflozin is effective in reducing glycosylated hemoglobin (HbA1c) as monotherapy and as add-on to other antidiabetic regimens. The adverse event profile seems comparable to other approved SGLT2 products and the sponsor has fulfilled cardiac safety evaluation criteria that would allow for marketing. However, compliance has identified a number of manufacturing deficiencies that resulted in a 'withhold' recommendation. I therefore recommend a Complete Response until the manufacturing deficiencies are corrected.

¹ Regarding possible salutary blood pressure changes, it is unknown whether a glucose-induced 'diuretic' effect would provide the same beneficial cardiovascular outcome as traditional diuretic medications that exert their effects mainly through sodium balance.

Efficacy

In the pivotal phase 3 trials, the mean placebo-adjusted change in HbA1c, depending upon the trial, comparator and baseline therapy, ranged from -0.48% to -0.73%, and from -0.59 to -0.84% for empagliflozin 10- and 25-mg respectively. This is demonstrated in the table below from Dr. Chong's review (page 44-45).

Table 1 Change in Hemoglobin A1c – 24 weeks, Full Analysis Set, Last Observation Carried Forward, Analysis of Covariance Model

		Baseline		Change from Baseline				Difference from Placebo				
	N	Mean	SE	Mean	SE	Adj. Mean	SE	Adj. Mean	SE	95% CI		p-value
										LL	UL	
Study 1245.19												
Placebo	165	8.16	0.07	-0.13	0.08	-0.11	0.07					
Empa 10	165	8.07	0.07	-0.58	0.07	-0.59	0.07	-0.48	0.09	-0.67	-0.30	< 0.0001
Empa 25	168	8.06	0.06	-0.70	0.07	-0.71	0.07	-0.61	0.09	-0.79	-0.42	< 0.0001
Study 1245.20												
Placebo	228	7.91	0.05	0.06	0.05	0.07	0.05					
Empa 10	224	7.87	0.06	-0.66	0.06	-0.66	0.05	-0.73	0.07	-0.87	-0.59	< 0.0001
Empa 25	224	7.86	0.06	-0.77	0.06	-0.78	0.05	-0.84	0.07	-0.99	-0.70	< 0.0001
Study 1245.23_{met}												
Placebo	207	7.90	0.06	-0.13	0.05	-0.13	0.05					
Empa 10	217	7.94	0.05	-0.73	0.05	-0.71	0.05	-0.58	0.07	-0.71	-0.45	< 0.0001
Empa 25	213	7.86	0.06	-0.75	0.06	-0.77	0.05	-0.64	0.07	-0.77	-0.51	< 0.0001
Study 1245.23_{met+SU}												
Placebo	225	8.15	0.06	-0.19	0.05	-0.18	0.05					
Empa 10	225	8.07	0.05	-0.80	0.05	-0.82	0.05	-0.64	0.07	-0.77	-0.51	< 0.0001
Empa 25	216	8.10	0.06	-0.77	0.05	-0.77	0.05	-0.59	0.07	-0.73	-0.46	< 0.0001
EFF-1												
Placebo	600	7.98	0.04	-0.06	0.03	-0.05	0.03					
Empa 10	606	7.95	0.03	-0.66	0.03	-0.66	0.03	-0.61	0.04	-0.70	-0.52	< 0.0001
Empa 25	605	7.91	0.03	-0.74	0.03	-0.76	0.03	-0.71	0.04	-0.80	-0.62	< 0.0001
EFF-2												
Placebo	825	8.02	0.03	-0.10	0.03	-0.08	0.03					
Empa 10	831	7.98	0.03	-0.70	0.03	-0.70	0.03	-0.62	0.04	-0.69	-0.55	< 0.0001
Empa 25	821	7.96	0.03	-0.75	0.03	-0.76	0.03	-0.68	0.04	-0.75	-0.61	< 0.0001

SE = standard error; Adj. Mean = adjusted mean; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; EFF-1 = Efficacy Grouping 1; EFF-2 = Efficacy Grouping 2
Source: Table 3.2.1.1: 1 (Summary of Clinical Efficacy)

Also noted were mean decreases in body weight of 1.6-2.2 kg depending upon dose and trial. Blood pressure evaluations conducted during the efficacy trials revealed placebo-adjusted decreases of 2.1-4.9 mmHg and 0.5-2.5 mm Hg for systolic and diastolic blood pressure respectively. Study 1245.48, an ambulatory 24-hour blood pressure study in subjects with hypertension and diabetes mellitus demonstrated systolic and diastolic decreases of 3.44, 4.16 and 1.36, 1.72 for the empagliflozin 10- and 25-mg doses respectively. The clinical

significance of this change is uncertain (although the cardiovascular outcome trial may help to delineate).

As with other members of the SGLT2 class, empagliflozin had progressive reduction in efficacy as renal impairment increased.

In summary, efficacy was demonstrated for both empagliflozin 10- and 25-mg. There were numerically greater decreases of HbA1c for empagliflozin 25-mg compared to empagliflozin 10-mg. Empagliflozin was effective as add-on therapy with the other antidiabetic medications tested. As with other members of the SGLT2 class, there is progressive reduction in efficacy as renal impairment increases, and decreases of unknown clinical significance are noted in weight and blood pressure.

Safety

The overall safety profile is similar to other members of the SGLT2 class. As with other SGLT2 agents, there were increased genitourinary infections, increased urination and in older subjects some volume depletion events and renal impairment.

The primary reviewer noted a differential in the incidence of lung cancer (different cell types), bladder cancer and melanoma. For lung and bladder cancer, the incidence was 4 (2108 pt-yrs exposure) and 3 (2108 pt-yrs exposure) respectively for empagliflozin compared to 0 (1019 pt-yrs) for all comparators. Melanoma incidence was 3 (7872 pt-yrs exposure) compared to 0 (4184 pt-yrs exposure) for all comparators. The small number of events, differential in exposure and multiple different categories that are explored make evaluation of this imbalance for causality impossible. With such an evaluation, it is expected that there will be some categories whose results favor drug therapy and some that do not. This imbalance does not seem as extreme as that of others where we required more evaluation.

Attention was paid to any potential cases of drug-induced liver injury (DILI). There was some suggestion of a higher incidence of categorical transaminase shifts with drug therapy, but no definite cases fulfilling Hy's Law or DILI were identified. As such there is no indication that empagliflozin is likely to cause serious liver injury or dysfunction, although this will be further evaluated in the ongoing cardiovascular outcomes trial.

The cardiovascular evaluation was adequate and fulfilled the suggested recommendations outlined in the guidance to industry.² Specifically the sponsor demonstrated a reassuring point estimate and upper bound risk ratio less than 1.8 as demonstrated below in a table from Dr. Chong's review (page 167).³

² Guidance for Industry. Diabetes mellitus—Evaluating cardiovascular risk in new antidiabetic therapies to treat Type 2 diabetes. December 2008.

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf>

³ Based on 4-point MACE+ of CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina.

Table 2 Composite Major Adverse Cardiovascular Event Endpoints by Cox Regression – Treated Set

	All Empa	All Comp
# of patients	6206	3830
4-point MACE	(b) (4)	
# of patients w/ event		
Incidence (%)		
Incidence rate (per 1000 years at risk)		
Cox Regression		
- Hazard ratio (95% CI)		
- Hazard ratio (99.546% CI)		
3-point MACE		
# of patients w/ event		
Incidence (%)		
Incidence rate (per 1000 years at risk)		
Cox Regression		
- Hazard ratio (95% CI)		
- Hazard ratio (99.546% CI)		
5-point MACE		
# of patients w/ event		
Incidence (%)		
Incidence rate (per 1000 years at risk)		
Cox Regression		
- Hazard ratio (95% CI)		
7-point MACE		
# of patients w/ event		
Incidence (%)		
Incidence rate (per 1000 years at risk)		
Cox Regression		
- Hazard ratio (95% CI)		

All Empa = all randomized empagliflozin; All Comp = all randomized comparator; MACE = major adverse cardiovascular event; CI = confidence interval; 3-point MACE (CV death, nonfatal MI, nonfatal stroke), 5-point MACE (CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, and hospitalization for congestive heart failure), and 7-point MACE (CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, hospitalization for congestive heart failure, transient ischemic attack, and coronary revascularization procedures)

Source: Tables 7.5.1: 1, 7.5.2.1: 1 and 7.5.2.3: 1 (Interim cardiovascular safety meta-analysis)

The sponsor is currently completing a CVOT that should allow more precise characterization of cardiovascular risks (or perhaps benefits).

Advisory Committee Meeting

An AC meeting was not held as empagliflozin is not the first drug approved in its class, the safety profile is similar to that of other drugs in the SGLT2 class, the clinical study design is acceptable and evaluation of safety data did not raise significant safety or efficacy issues that were unexpected for a drug of this class in the intended population.

Conclusions and Recommendations

Empagliflozin has demonstrated efficacy for the 10- and 25-mg doses and the safety profile is similar to that of already approved SGLT2 products. If this application were to be based only on risk and benefit considerations, it could be approved. However, at present there is a withhold recommendation from compliance because of CMC issues at the manufacturing plant. As such, I recommend a complete response on this application. To resolve this action, the sponsor will need to successfully address issues identified by our compliance colleagues.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CURTIS J ROSEBRAUGH
03/04/2014

Cross-Discipline Team Leader Review

Date	January 27 th , 2014
From	Karen Murry Mahoney, MD, FACE
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA 204629
Supplement#	
Applicant	Boehringer Ingelheim
Date of Submission	March 5, 2013
PDUFA Goal Date	March 5, 2014
Proprietary Name / Established (USAN) names	Jardiance® (empagliflozin)
Dosage forms / Strength	Tablet (10 mg and 25 mg)
Proposed Indication(s)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommended:	Complete Response

1. Introduction

Jardiance® (empagliflozin), hereafter referred to as empa, is a sodium glucose co-transporter 2 inhibitor (SGLT2i), proposed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

This Cross-Discipline Team Leader (CDTL) memorandum will discuss the major findings of reviews by multiple FDA disciplines. Areas of focus in the memorandum include the following:

- Recommendation from the FDA's International Compliance Division for a "withhold" action, which has resulted in the CDTL's recommendation for a Complete Response action rather than an approval action
- Overall efficacy findings
- Hepatic safety
- Malignancy, and in particular lung cancer and melanoma
- Macrovascular adverse events
- Adverse events of special interest for the SGLT2i class, including genital mycotic infections, urinary tract infections, volume-depletion-related adverse effects, renal adverse effects, and fractures

2. Background

Type 2 diabetes mellitus (DM2) is one of the most prevalent diseases in the United States, having been diagnosed in over 7% of the U.S. adult population, and DM2 is rising in

incidence. The actual incidence far exceeds 7%, because screening studies have revealed that undiagnosed diabetes is even more common than diagnosed diabetes (Cowie et al 2009). The disease exerts a tremendous negative impact on the lives of patients. In the United States, diabetes is the leading cause of blindness among adults ages 20-74 years, of end-stage kidney disease, and of nontraumatic limb amputation. The cost of diabetes is enormous; in 2007, estimated direct medical costs were \$174 billion, with an additional \$58 billion in indirect costs such as disability, work loss and premature mortality (National Institute of Diabetes and Digestive and Kidney Diseases, National Diabetes Information Clearinghouse, accessed 20 Dec 2013). These costs continue to increase.

At present, most published guidelines recommend metformin as the first drug to be used in the treatment of type 2 diabetes. However, some patients cannot tolerate metformin, and many (perhaps most) patients with type 2 diabetes will require an additional agent in order to achieve adequate glycemic control, particularly if the patient begins with a higher hemoglobin A1c (HbA1c) (Inzucchi et al 2012). Therefore, there is a need for additional agents for the treatment of DM2. Each of the currently available classes of drugs for the treatment of DM2 has its own set of limitations. Two particularly desirable attributes of a drug for the treatment of DM2 are a low incidence of hypoglycemia, and body weight neutrality (or a favorable body weight effect). The SGLT2i class, which includes empagliflozin, appears to have both attributes.

Empagliflozin's inhibition of SGLT2 blocks the primary method by which the kidney reabsorbs glucose, and results in excretion of glucose in the urine.

There are currently two other SGLT2 inhibitors approved in the United States, canagliflozin and dapagliflozin. As of January 23rd, 2014, the website of the sponsor, Boehringer Ingelheim, did not report approval of empagliflozin in any country.

3. CMC/Device

3.1 Overall Recommendation of Chemistry, Manufacturing and Controls Reviewer

Please see Dr. Joseph Leginus' primary reviews (10 Sep 2013 and 6 Nov 2013), regarding Chemistry, Manufacturing and Controls. Dr. Leginus' recommendation was preliminarily for Approval; however, his recommendation was contingent upon an acceptable Good Manufacturing Practices (GMP) recommendation after an inspection by the Office of Compliance. Inspection results were pending at the time of Dr. Leginus' reviews. Since that time, the Office of Compliance has noted significant GMP concerns, and has recommended that approval be withheld.

3.2. Drug Substance

The drug substance, empagliflozin, is a new chemical entity, with a Chemical Abstracts name of D-glucitol, 1,5- anhydro-1-C-[4-chloro-3-[[4-[(3S)-tetrahydro-3-furanyl]oxy]phenyl]methyl]phenyl]-, (1S). Its molecular formula is C₂₃H₂₇ClO₇ and its

molecular weight is 450.91 g/mol. Information on drug substance specifications, batch analyses, reference standards and container closure system were considered acceptable.

3.3. Drug Product

Empagliflozin tablets are manufactured in two strengths; 10 and 25 mg. The two strengths contain the same excipients, (b) (4). No novel excipients were used; all have compendial references and are identified in FDA's Inactive Ingredients Database as inactive ingredients found in other oral tablet products at levels higher than those found in empa.

Proposed release specifications include description (visual), identification (high pressure liquid chromatography [HPLC] and ultraviolet), degradation products (HPLC), assay (HPLC), content uniformity, dissolution and microbiological quality. Batch analysis data from 29 clinical lots manufactured at commercial scale at the proposed site for commercial supply met the proposed specifications.

Dr. Leginus concurred with a shelf-life/ expiry of 36 months when empa is stored at room temperature.

Per Dr. Leginus, and Dr. Summan, the nonclinical reviewer, drug substance and drug product impurities were adequately qualified at or above the proposed limits in the specifications.

Both the drug substance and drug product are to be manufactured at the Boehringer Ingelheim facility in Ingelheim am Rhein, Germany.

3.4. Facilities Inspection Issue Resulting in Recommendation to Withhold Approval:

On May 6th, 2013, the FDA issued a Warning Letter to Boehringer Ingelheim (BI); this letter may be found at <http://www.fda.gov/iceci/enforcementactions/warningletters/2013/ucm352325.htm>. That Warning Letter refers to an inspection conducted November 5-12, 2012, which had identified "significant violations of current good manufacturing practice (cGMP) for the manufacture of active pharmaceutical ingredients (APIs) and the cGMP regulations for finished pharmaceuticals, Title 21, U.S. Code of Federal Regulations, Parts 210 and 211". The letter states that the violations cause the APIs and drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act, 21 USC 351(s)(2)(B).

The May 6th letter cites several violations, namely:

- "failure of your (BI's) Quality Unit to thoroughly investigate critical deviations in the manufacturing of your API"
- "failure to conduct thorough complaint investigations regarding the presence of foreign particles found in your APIs"
- failure "to reject drug products that did not meet established standard or specifications and any other relevant quality control criteria (21 CFR 211.165(f))", and

- failure “to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192)”.

Other details of the deficiencies may be found in the letter.

Boehringer Ingelheim informed Ms. Patricia Madara, the Project Manager in the Division of Metabolism and Endocrinology Products (DMEP), of this Warning Letter, and stated that BI was working to correct the deficiencies, and when correction was complete, a re-inspection date would be scheduled. On January 8th, 2014, BI informed Ms. Madara via telephone that the re-inspection had been scheduled for February 24th through March 7th, 2014. On January 14th, 2014, Dr. Steven Hertz stated via email that, per the Division Director of the FDA’s International Compliance Division, this will be an extensive inspection, including a full cGMP inspection, and multiple pre-approval inspections for multiple products. The physical inspection will not be completed until after the Prescription Drug User Fee Act (PDUFA) action date of March 5th, 2014. After the physical inspection is complete, the inspection team will have additional work to do with collation of exhibits and preparation of the Establishment Inspection Report. Therefore, per Dr. Hertz, the recommendation of the International Compliance Division is “withhold”, or withhold approval. As of January 24th, 2014, DMEP has not yet received the final written report of this recommendation from the International Compliance Division.

This failure of the manufacturing facility to meet current Good Manufacturing Practice standards is the primary reason for the Cross-Discipline Team Leader’s recommendation for a “Complete Response” action rather than an “Approval” action.

4. Nonclinical Pharmacology/Toxicology

4.1. Overall Recommendation of Nonclinical Pharmacology/Toxicology Review Team

Please see Dr. Mukesh Summan’s primary nonclinical review (DARRTS November 5th, 2013) and Dr. Todd Bourcier’s secondary review (DARRTS November 7th, 2013). Drs. Summan and Bourcier recommend approval.

4.2. General Pharmacology

Empagliflozin inhibits the sodium glucose cotransporter 2, a protein expressed by the renal tubular epithelium. This protein is involved in the primary mechanism by which the kidney reabsorbs filtered glucose. Inhibition of SGLT2 results in a loss of filtered glucose in the urine, with glucose loss in proportion to glomerular filtration rate and plasma glucose level.

Animal species chosen for the toxicological assessment exhibited the expected pharmacologic response to SGLT2 inhibition, with glucosuria and polyuria.

Per Dr. Bourcier, key issues in the nonclinical review included:

- renal findings

- tissue mineralization and bone health
- carcinogenicity
- pregnancy and lactation

4.3. Preclinical Renal Findings

In rats and mice, exposure at the lowest doses tested (2-5 times expected clinical exposure) resulted in mineralization of tubules and papillae; and dilatation of the renal pelvis, ureter and bladder. These histologic changes were not severe, and were considered a consequence of (or adaptive change to) chronic glucosuria/polyuria and calciuria. In dogs, exposure at the lowest tested dose (12-19 times expected clinical exposure, for 52 weeks), resulted in no adverse renal histologic changes. Serum blood urea nitrogen and creatinine were not significantly changed.

At 17-45x times the maximum recommended human dose (MRHD) rats developed tubule dilatation and vacuolation with lipid inclusions, and tubule basophilia and hyperplasia. Dogs and mice developed more severe findings. In dogs, chronic interstitial nephritis, and tubular nephropathy with fibrosis and degeneration occurred at approximately 220x MRHD. This renal pathology was not seen in other drugs of the SGLT2 class. In mice, chronic nephrotoxicity occurred at 45x MRHD, with single cell necrosis, karyomegaly, hypertrophy/atrophy, and atypical hyperplasia of the renal tubules. Renal tubule adenoma/carcinoma were noted in male mice at this exposure. Because of the high exposures at which these findings occurred, the nonclinical reviewers consider the toxicities to be of little risk to human subjects with normal renal function taking 25 mg empa per day.

4.4. Preclinical Findings Regarding Tissue Mineralization and Bone Health

Nonclinical studies show changes in calcium homeostasis across the class of SGLT2 inhibitors. In rats, this is manifest as trabecular bone accretion, calcification of soft tissues, hypercalciuria, and changes in bone biomarkers, e.g. decreases in serum (1,25)-dihydroxy vitamin D and parathyroid hormone. In non-rodents, changes in bone biomarkers were less marked, and bone histology did not change significantly in chronic toxicology studies. Empagliflozin was somewhat different from other SGLT2s, in that bone histology and biomarker changes were seen essentially only in the two-year rat study. Clinical monitoring occurred in human studies, and fractures were not increased in empa-treated humans. Overall, the nonclinical team considered empagliflozin to present a low risk to human subjects' bone health at the proposed clinical doses.

4.5. Nonclinical Carcinogenicity Findings

Four of the five Investigational New Drug SGLT2 inhibitors that have submitted rodent carcinogenicity study findings have reported neoplasms of the renal tubules, adrenal gland, or testicular Leydig cells. The fifth agent reported atypical renal tubular hyperplasia.

Empagliflozin was associated with an increased incidence of renal tubular carcinoma and adenoma in male mice at 45 times the clinical dose. The nonclinical team considered this to represent a minimal clinical risk.

Empagliflozin was also associated with an increased incidence of Leydig cell tumors in male rats. The nonclinical team considered the risk to humans to be low, based on:

- the safety margin relative to the No Observed Adverse Effect Level (NOAEL)
- greater sensitivity of rats versus humans to this tumor type
- the observation that levels of luteinizing hormone and testosterone have not been altered by SGLT2is in clinical trials.

Unlike other SGLT2is, empagliflozin was associated with an increase in hemangiomas at high doses, in the mesenteric lymph nodes of male rats. Lymphadenitis was also present at the high dose level. Clinical risk was considered low, based on:

- the small magnitude of the increased incidence, relative to the control group
- the high (42x) exposure multiple.

4.6. Pregnancy and Lactation Findings

In published juvenile rat toxicology studies (Suzuki 2009), SGLT2 inhibitors were associated with abnormalities in renal development and maturation. Empagliflozin is present in fetal tissues and maternal milk in rats. The (b) (4)

nonclinical team has informed the applicant that this information would need to be in the FPI, and that Pregnancy Category C would be appropriate. Alternative therapies should be considered during pregnancy, especially during the second and third trimesters. Regarding nursing, consideration should be given to discontinuing nursing or discontinuing empagliflozin, taking into account the importance of the drug to the mother. The language proposed by the nonclinical team is consistent with that for canagliflozin and dapagliflozin, the two currently approved SGLT2is.

Empagliflozin was not teratogenic in rodents at 48x MRHD; at 154x MRHD, bent limb bone was seen. Effects on mating and fertility were not seen at doses up to 155x MRHD. Empa was not mutagenic or clastogenic in an *in vitro* Ames assay, *in vitro* mouse lymphoma assay, or *in vivo* assays.

5. Clinical Pharmacology/Biopharmaceutics

5.1. Overall Recommendation of Clinical Pharmacology Team

Please see Dr. Khurana's primary Clinical Pharmacology review (DARRTS November 8th, 2013). Dr. Khurana and Dr. Jain, the secondary clinical reviewer, recommend approval.

Other key Clinical Pharmacology recommendations include:

- a recommendation against use in patients with estimated glomerular filtration rate (eGFR) <45 mL/min/1.73m², due to lack of efficacy.
- close monitoring of renal function and volume status in the elderly and patients at high risk of volume depletion (e.g. those on loop diuretics or with renal impairment)

- no dose adjustment needed for hepatic impairment; or based on drug-drug interaction (DDI) studies with metformin, glimepiride, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, hydrochlorothiazide, torasemide, or oral contraceptives.
- although no pharmacokinetic DDIs were present for sulfonylurea, dose adjustment may be needed for coadministration with other insulin secretagogues, or insulin, to reduce the risk of hypoglycemia
- monitoring of hemoglobin A1c (HbA1c) levels when empa is coadministered with organic anion transporter 3 (OAT3) transporter inhibitors, such as probenecid; or with uridine 5'-diphospho-glucuronosyltransferase (UGT) inducers, such as rifampin.

Other general aspects of the Clinical Pharmacology review are discussed below.

5.2. Absorption

After single dose administration of 10 mg or 25 mg empagliflozin tablets under fasted conditions, absorption was rapid, with a median T_{max} of 1 hour. Thereafter, plasma levels declined in a biphasic fashion with a rapid distribution phase and a slower elimination phase. Exposure was dose-proportionate.

5.3. Distribution

Steady-state volume of distribution ranged from 180 to 230 liters. After administration of ¹⁴C-labeled empa to healthy subjects, total radioactivity exposure in blood was lower compared to plasma, consistent with moderate red blood cell partitioning. Protein binding of total radioactivity ranged from 80.3 to 86.2%.

5.4. Metabolism

No major metabolites were detected in human plasma. The most abundant metabolites were three glucuronide conjugates. Systemic exposure of each metabolite was <10% of total drug-related material. O-dealkylation gave rise to an active metabolite (EX 609); at the highest dose level, AUC and C_{max} of this metabolite were approximately 0.12% of parent drug. The primary route of metabolism of empa in humans appears to be glucuronidation.

5.5. Elimination

Terminal elimination half-life was 12.4 hours. A mean of 54.4% of the dose was excreted in urine and 41.2% in feces. Approximately 50% of drug excreted in urine was unchanged parent. Steady state concentrations of empa were reached by the fifth dose.

5.6. Intrinsic Factor Effects

No dose adjustment appears necessary for body weight, age, body mass index, race or gender. As noted above, however, the Clinical Pharmacology team recommends caution when using in the elderly. This is because the elderly may be more susceptible to adverse events related to mode of action of the drug, e.g. they may be more vulnerable to adverse events related to

volume depletion. Pediatric studies have not yet been conducted; for the two approved SGLT2is, pediatric pharmacokinetic/pharmacodynamic and clinical studies are Postmarketing Requirements.

5.7. Use in Renal Impairment

As eGFR declines, exposure to empa increases. However, the pharmacologic effect (glucosuria) is dependent on renal function, and the increase in exposure with eGFR does not overcome this dependence. Empagliflozin did not display a pharmacologic glucosuric effect in patients with an eGFR $<45 \text{ mL/min/1.73m}^2$.

5.8. Use in Hepatic Impairment

In patients with hepatic impairment, empa exposure increases with degree of hepatic impairment (AUC 0-inf increased 23, 47 and 75% respectively for Child-Pugh mild, moderate and severe, compared to normal). There was an increase in fraction of drug excreted in urine without an effect on the amount or rate of urinary glucose excretion. Therefore, no dose adjustment was recommended in patients with hepatic impairment.

5.9. Extrinsic Factors

Empagliflozin can be taken with or without food.

5.10. Drug-Drug Interactions:

Please see the key Clinical Pharmacology findings above.

A wide range of DDI studies was conducted. For most tested drugs, no dose adjustment is necessary.

As mentioned above, although no pharmacokinetic DDIs were present for sulfonylurea, dose adjustment may be needed for coadministration with insulin secretagogues, or insulin, to reduce the risk of hypoglycemia. Similar caution is recommended for the two approved SGLT2is.

When empagliflozin was coadministered with probenecid (an OAT3 inhibitor), the fractional excretion of empa was decreased. Monitoring of hemoglobin A1c (HbA1c) levels is recommended when empa is coadministered with OAT3 inhibitors.

Although single-dose coadministration with rifampin (a UGT inducer) was studied, multiple-dose coadministration was not. Therefore, the effect of UGT enzyme induction by rifampin on empa exposure could not be evaluated. Therefore, HbA1c monitoring is recommended if patients take rifampin or other inducers of UGT.

5.11. Effect on QT Interval

A thorough QT study was conducted, and no significant QT prolongation by empagliflozin (25 mg and 200 mg) was detected.

6. Clinical Microbiology

Per Dr. Leginus' review, microbiology review was not required, because empagliflozin is manufactured as a solid oral dosage form.

7. Clinical/Statistical- Efficacy

7.1. Overall Recommendation of Efficacy Statistics and Clinical Efficacy Review Team

Please see Dr. Liu's efficacy statistics review (DARRTS October 30th, 2013) and Dr. Chong's clinical review (November 5th, 2013). Both reviewers recommend approval.

7.2. Trials and Methods Used in the Efficacy Analyses

A total of six trials provided the main efficacy information for empa. One of these, an ongoing active control trial with glimepiride as a comparator, will not be discussed in the CDTL memo to protect the integrity of the ongoing trial. The other five trials are adequate to support the finding of efficacy for empagliflozin, without inclusion of discussion of the ongoing trial.

The following table lists the completed efficacy trials of empa:

Table 7.2: Completed Efficacy Trials of Empagliflozin					
Trial Number	Background Therapy	Number of Patients	Duration to Primary Endpoint (weeks)	Duration of Extension (weeks)	Treatment Arms
1245.20	None	986	24	52	Placebo Empa 10 mg Empa 25 mg Sitagliptin 100 mg
1245.23 (met)	Metformin	706	24	52	Placebo Empa 10 mg Empa 25 mg
1245.23 (met + SU)	Metformin + Sulfonylurea	767	24	52	Placebo Empa 10 mg Empa 25 mg
1245.10	Metformin + Pioglitazone	498	24	52	Placebo Empa 10 mg Empa 25 mg
1245.33	Basal Insulin + Metformin	494	18 (fixed dose insulin)	60 (insulin titration)	Placebo Empa 10 mg Empa 25 mg

In all these trials, the primary efficacy endpoint was the change from baseline in HbA1c. Several secondary endpoints were also examined, including changes in fasting plasma glucose, systolic blood pressure, diastolic blood pressure and body weight. The hierarchical testing order of these endpoints varied by study.

Across the pivotal efficacy trials, approximately 90% of patients completed the trial to the measurement of the primary endpoint. The percentage of discontinuations from the empa groups was lower than that for placebo groups. The most common reason for premature discontinuation was for adverse events, with a 4% overall discontinuation rate. Demographic characteristics were generally balanced between treatment groups. Overall 56% of patients were Asian, 41% were white, and 2% were black or African American. Efficacy for Asian and white patients was similar. The percentage of black patients studied is not reflective of the U.S. population; ideally more patients would have been studied. If empagliflozin is resubmitted, data from black patients enrolled in the ongoing CVOT will be considered. If these are inadequate, a Postmarketing Requirement for further study in African American patients could be considered; postmarketing study of under-represented minority patients has been conducted for other products (e.g. ezetimibe).

A last-observation-carried-forward (LOCF) approach was used for analysis of the primary and secondary endpoints. Several sensitivity analyses were performed, and resulted in similar findings. These are further described in Dr. Liu's review, and included:

- an observed case approach, in which all data were analyzed as observed, missing data were not imputed, and all values observed after rescue medication were excluded
- an original results analysis, in which values obtained after start of rescue therapy were used as measured, and
- a mixed model repeated measures approach.

7.3 Primary Efficacy Endpoint (Change from Baseline in Hemoglobin A1c)

The following table displays the primary endpoint results from the four trials with oral therapy.

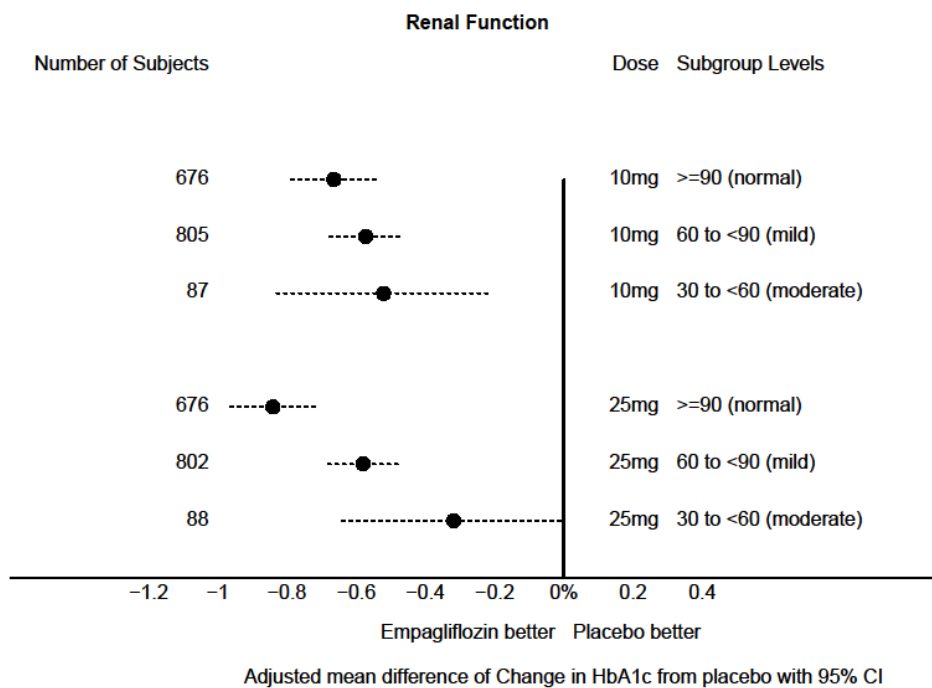
Table 7.3: Primary Endpoint Results from Pivotal Efficacy Trials with Oral Therapy

Trial	Treatment	Adjusted HbA1c Mean Difference from Placebo, Baseline to 24 Weeks % (95% CI)	p- value
1245.20 (monotherapy)	Empa 10 mg	-0.72 (-0.89, -0.56)	<0.0001
	Empa 25 mg	-0.83 (-0.99, -0.68)	<0.0001
	Sitagliptin	-0.70 (-0.86, -0.54)	<0.0001
1245.23 (metformin background)	Empa 10 mg	-0.57 (-0.72, -0.42)	<0.0001
	Empa 25 mg	-0.64 (-0.79, -0.48)	<0.0001
1245.23 (metformin + sulfonylurea background)	Empa 10 mg	-0.64 (-0.79, -0.49)	<0.0001
	Empa 25 mg	-0.60 (-0.76, -0.44)	<0.0001
1245.19 (metformin + pioglitazone background)	Empa 10 mg	-0.48 (-0.70, -0.26)	<0.0001
	Empa 25 mg	-0.63 (-0.85, -0.41)	<0.0001
Source: Dr. Liu statistical review, pg 15, Table 3			

Study 1245.33 (add-on to insulin) had similar results for change from baseline to 18 weeks in HbA1c, with placebo-adjusted changes of -0.62 for empa 10 mg and -0.74 for empa 25 mg, with p values of <0.0001.

Dr. Liu conducted subgroup analyses by age, gender, race, ethnicity, region, body mass index, baseline HbA1c, diabetes duration and renal function. In general, subgroup analyses were similar to the primary analysis. Some interaction was noted by age for the 25 mg empa dose (age <50 years mean change in HbA1c = -0.86%; age >75 years = -0.54%). Some interaction was also noted by gender for empagliflozin 25 mg (men -0.76%, women -0.58%). Differences in eGFR may have played a role in these subgroup differences. As discussed in the Clinical Pharmacology section, efficacy of empagliflozin declines with declining eGFR, as shown in the following subgroup analysis figure:

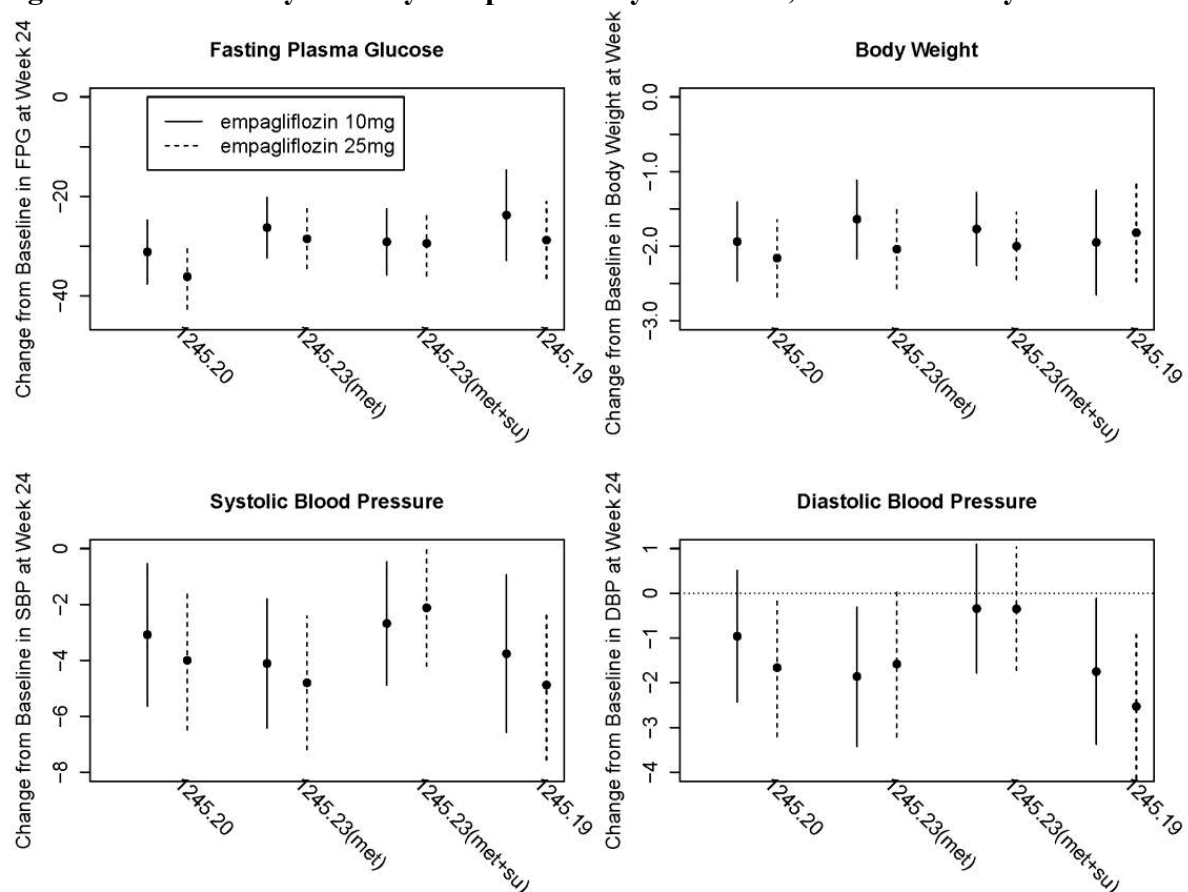
Figure 7.3: Subgroup Analysis of Change in Hemoglobin A1c by Baseline Renal Function



Source: Figure 14, Dr. Liu's efficacy statistics review, pg 29

7.4. Secondary Endpoint Analyses

The following figure summarizes the results of secondary efficacy endpoints analyses:

Figure 7.4: Secondary Efficacy Endpoint Analysis Results, Pivotal Efficacy Trials

Source: Table 4, Dr. Liu's efficacy statistics review, pg 17

In each trial, statistically significant changes in fasting plasma glucose and body weight were observed. Although statistically significant, the change in body weight was modest, with a placebo-adjusted difference between treatment groups of approximately 2 kg over 24 weeks.

In study 1245.20, changes in systolic and diastolic blood pressure were key secondary endpoints; in other trials, blood pressure was an exploratory endpoint. In 1245.20, the changes in systolic, but not diastolic, blood pressure were statistically significant. In general, the change in systolic blood pressure was -2 to -4 mmHg. Overall, Dr. Liu considered the reductions in FPG, body weight and systolic blood pressure to be consistent across trials.

7.5. Overall Efficacy Assessment

Empagliflozin appears to be effective in lowering hemoglobin A1c, and secondary efficacy data support desirable attributes of small reductions in body weight and systolic blood pressure.

8. Safety

8.1. Overall Recommendation of Safety Statistics and Clinical Safety Team

Please see the clinical review (DARRTS November 5th, 2013) by Dr. Chong and safety statistical review by Dr. Charles (DARRTS November 1st, 2013). Each reviewer recommends approval.

8.2. Exposure

A total of 8400 patients have been exposed to any dose of empagliflozin in studies in patients with type 2 diabetes. Total patient-years of exposure for empa 10 mg are 3258, and for 25 mg are 4448. A total of 6594 patients have been exposed to the 10 or 25 mg dose for at least six months; a total of 4261 patients have been exposed for at least one year.

The primary safety grouping used in the clinical safety review was that of all studies conducted in patients with type 2 diabetes. This was designated the SAF-5 population, and included data from 18 studies. It included a total of 3630 patients exposed to empa 10 mg, 4602 exposed to 25 mg, and 4676 exposed to comparator (of whom 3522 were exposed to placebo). Non-placebo comparators included metformin (N=80), glimepiride (N=780) and sitagliptin (N=294). The following table provides additional details of exposure for SAF-5.

Table 8.2: Exposure Data for Primary Safety Grouping (SAF-5; All Studies Conducted in Patients with Type 2 Diabetes)					
	Pbo N (%)	All Comp N (%)	Empa 10 mg N (%)	Empa 25 mg N (%)	Any Empa Dose N (%)
Total number of patients exposed to each treatment	3522 (100%)	4676 (100%)	3630 (100%)	4602 (100%)	8400 (100%)
Total number of patients exposed for ≥ 24 weeks	2464 (70%)	3514 (75%)	2856 (79%)	3738 (81%)	6603 (79%)
Total number of patients exposed for ≥ 52 weeks	1423 (40%)	2333 (50%)	1720 (47%)	2541 (55%)	4415 (53%)
Patient-years of exposure (total)	2758	4184	3258	4448	7828
Patient-years of exposure without or prior to rescue medication	2317	3635	3008	4185	7315
Patient-years of exposure from first intake of rescue medication	441	549	250	263	513
Source: Applicant's Table 4.5.1, page 1189, Summary of Clinical Safety, Section 5.3.5.3					

In the four-month safety update (4MSU), the applicant provided exposure information by numbers of patients, but not by patient-years. Almost all additional exposure in the 4MSU was blinded, primarily from the ongoing cardiovascular outcomes trial. Unblinded data were provided for 548 patients exposed to empagliflozin 10 mg, 700 patients exposed to

empagliflozin 25 mg, and 63 patients exposed to metformin. Almost all unblinded exposure came from a 52-week study in Japanese patients (Study 1245.52).

8.3. Deaths

Across SAF-5, a total of 41 deaths occurred among empa-treated patients (0.5%), and 33 deaths occurred among comparator-treated patients (0.7%). The incidence of death was equal between the 10 and 25 mg empa groups. The rates of death per 100 patient-years were 0.52 for empa and 0.78 for comparator. (Source Dr. Chong's review, pg 97, Table 54). Deaths due to neoplasms occurred at a somewhat higher numerical frequency among empa-treated patients (N=12, 0.14%) than among comparator-treated patients (N=1, 0.02%). However, the cell types for these neoplasms were varied, and 9/12 patients were diagnosed after <6 months of exposure; these features do not support a causal role of empagliflozin. Further data on malignancy will be gathered in the ongoing CVOT. Otherwise, the causes of death were similar between empa-treated and comparator-treated patients.

8.4. Serious Adverse Events

Nonfatal serious adverse events did not occur more frequently among empa-treated patients (9.6%) than among comparator-treated patients (10.8%). There were no individual Preferred Terms for serious adverse events which occurred with statistically significantly greater frequency among empa-treated patients than among comparator-treated patients. The following Preferred Terms for serious adverse events were reported for at least five empagliflozin-treated patients, and with a higher numerical frequency among empa-treated patients than among comparator-treated patients:

Table 8.4: Serious Adverse Events Occurring in at Least Five Empagliflozin-Treated Patients, and With a Higher Numerical Frequency Among Empagliflozin-Treated Patients than Among Comparator-Treated Patients, SAF-5 Population			
System Organ Class	Preferred Term	All Empa N=8400 n (%)	All Comp N=4676 n (%)
Any SOC	Any PT	805 (9.58)	503 (10.76)
Infections and Infestations	Any PT	128 (1.52)	80 (1.71)
	Gastroenteritis	11 (0.13)	3 (0.06)
Gastrointestinal Disorders	Any PT	91 (1.08)	41 (0.88)
	Vomiting	7 (0.08)	0
	Gastrointestinal hemorrhage	6 (0.07)	2 (0.04)
	Abdominal pain	5 (0.06)	1 (0.02)
	Gastritis	5 (0.06)	2 (0.04)
	Gastroesophageal reflux disease	5 (0.06)	1 (0.02)
Neoplasms	Any PT	76 (0.90)	35 (0.75)
	Breast cancer	5 (0.06)	2 (0.04)
Injury, poisoning and procedural complications	Any PT	63 (0.75)	38 (0.81)
	Fall	15 (0.18)	6 (0.13)

Table 8.4: Serious Adverse Events Occurring in at Least Five Empagliflozin-Treated Patients, and With a Higher Numerical Frequency Among Empagliflozin-Treated Patients than Among Comparator-Treated Patients, SAF-5 Population

System Organ Class	Preferred Term	All Empa N=8400 n (%)	All Comp N=4676 n (%)
Musculoskeletal and Connective Tissue Disorders	Any PT	53 (0.63)	35 (0.75)
	Osteoarthritis	15 (0.18)	7 (0.15)
General Disorders and Administration Site Conditions	Any PT	50 (0.60)	30 (0.64)
	Noncardiac chest pain	8 (0.10)	2 (0.04)
	Pyrexia	8 (0.10)	2 (0.04)
Metabolism and Nutrition Disorders	Any PT	26 (0.31)	29 (0.62)
	Hypoglycemia	11 (0.31)	3 (0.06)
	Dehydration	5 (0.06)	2 (0.04)
Hepatobiliary Disorders	Any PT	25 (0.30)	14 (0.30)
	Cholelithiasis	7 (0.08)	3 (0.06)
Reproductive System and Breast Disorders	Any PT	15 (0.18)	7 (0.15)
	Benign prostatic hypertrophy	8 (0.10)	3 (0.06)
Source: Dr. Chong's review, Table 60, beg pg 111			

In general, the incidence of any one type of serious adverse event was low. Serious adverse events of hypoglycemia and gastroenteritis occurred with somewhat higher numeric frequency among empa-treated patients than among comparator-treated patients, but the overall number of events is low, limiting conclusions. Malignancy events are discussed further below.

8.5. Discontinuations

Discontinuation from study occurred somewhat less frequently with empa (15.4%) than with comparator (19.7%). The most common reasons for discontinuation were adverse events (empa 3.9%; comparator 4.0%). Adverse events which more commonly led to discontinuation among empa-treated patients than among comparator-treated patients were urinary tract infections (empa 0.25%; comparator 0.06%), and “weight decreased” (empa 0.11% [n=9]; comparator 0).

8.6. Common Adverse Events

In general, the incidence of specific adverse events was balanced between treatment groups. Adverse events of special interest, including hepatic adverse events, malignancies, genital mycotic infections, urinary tract infections, volume depletion events, renal adverse events, fractures and hypoglycemia are discussed in Section 8.6 below. Cardiovascular safety is discussed in Section 14.

The following table displays adverse events which occurred in at least 1% of empagliflozin-treated patients, and which occurred more frequently among empagliflozin-treated patients than among placebo-treated patients.

Table 8.6: Treatment-Emergent Adverse Events Which Occurred in $\geq 1\%$ of Empagliflozin-Treated Patients, and Which Occurred More Frequently Among Empagliflozin-Treated Patients than Among Placebo-Treated Patients, SAF-5 Population

System Organ Class	Preferred Term	Empa 10 mg N=3630 n (%)	Empa 25 mg N=4602 n (%)	All Empa N=8400 n (%)	Pbo N=3522 n (%)
Infections and Infestations	Any PT	1653 (45.5)	2265 (49.2)	3918 (46.6)	1455 (41.3)
	Nasopharyngitis	289 (8.0)	360 (7.8)	679 (8.1)	238 (6.8)
	Urinary tract infection	259 (7.1)	328 (7.1)	594 (7.1)	228 (6.5)
	Sinusitis	45 (1.2)	56 (1.2)	103 (1.2)	35 (1.0)
	Pharyngitis	36 (1.0)	54 (1.2)	93 (1.1)	28 (0.8)
Gastrointestinal Disorders	Any PT	734 (20.2)	982 (21.3)	1716 (20.4)	702 (19.9)
	Vomiting	49 (1.4)	58 (1.3)	108 (1.3)	37 (1.1)
	Gastritis	35 (1.0)	62 (1.4)	100 (1.2)	30 (0.9)
	Abdominal pain upper	41 (1.1)	43 (0.9)	88 (1.1)	33 (0.9)
Musculoskeletal and Connective Tissue Disorders	Any PT	665 (18.3)	931 (20.2)	1596 (19.0)	654 (18.6)
	Osteoarthritis	44 (1.2)	50 (1.1)	95 (1.1)	38 (1.1)
General Disorders and Administration Site Conditions	Any PT	355 (9.8)	478 (10.4)	833 (9.9)	412 (11.7)
	Thirst	35 (1.0)	62 (1.4)	105 (1.3)	2 (0.1)
Renal and Urinary Disorders	Any PT	351 (9.7)	447 (9.7)	798 (9.5)	266 (7.6)
	Pollakiuria	83 (2.3)	101 (2.2)	203 (2.4)	31 (0.9)
	Polyuria	40 (1.1)	48 (1.0)	93 (1.1)	9 (0.3)
Skin and Subcutaneous Tissue Disorders	Any PT	250 (6.9)	425 (9.2)	675 (8.0)	259 (7.4)
	Pruritus	33 (0.9)	58 (1.3)	96 (1.1)	27 (0.8)
Reproductive System and Breast Disorders	Any PT	197 (5.4)	248 (5.4)	445 (5.3)	81 (2.3)
	Vulvovaginal pruritus	35 (1.0)	49 (1.1)	85 (1.0)	3 (0.1)
Source: Dr. Chong's review, Table 126, beg pg 234 All groups are as randomized; placebo-treated patients may have received rescue therapy if glycemic control was inadequate.					

Individual event terms which occurred at a frequency at least 1% higher among empagliflozin-treated patients than among placebo-treated patients included nasopharyngitis, thirst and pollakiuria.

8.7. Adverse Events of Special Interest

8.7.1. Hepatic Adverse Events

During the 2011 first cycle review of dapagliflozin, concern arose regarding a potential case of drug-induced liver injury. This concern with dapagliflozin led to a request for systematic evaluation of liver safety for empagliflozin. (It should be noted that in the 2013/2014 resubmission review cycle for dapagliflozin, the FDA's hepatic safety consultant and the Endocrine and Metabolic Drugs Advisory Committee members felt that the dapagliflozin case was more consistent with autoimmune hepatitis than with drug-induced liver injury, although a contribution of dapagliflozin could not be ruled out entirely.)

The applicant analyzed hepatic adverse events using several standardized queries from the Medical Dictionary for Regulatory Activities (MedDRA SMQs). These included SMQs 20000008 ("Signs and symptoms of liver related investigations"), 20000009 ("Cholestasis and jaundice of hepatic origin"), 20000010 ("Hepatitis, non-infectious"), and 20000013 ("Hepatic failure, fibrosis and other liver damage-related conditions"). The incidence and rate of events from the combination of the above into SMQ 20000006 "Drug related hepatic disorders" was lower for patients treated with empagliflozin (1.3%; 1.42 events per 100 patient-years) than for comparator (1.9%; 2.09 events per 100 PY) (Source NDA 204629 ISS, Table 2.1.5.2.1:1, beg pg 123). All contributing Preferred Terms within this SMQ occurred at equal or lower frequency for empagliflozin versus comparator, except for the Preferred Term hyperbilirubinemia, which was reported for 8 (0.1%) of empa patients and zero comparator patients.

The incidence of categorical increases in transaminases was analyzed, and is presented below for the SAF-5 population. Increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) to 5, 10 or 20x the upper limit of the reference range (ULRR) occurred somewhat more frequently numerically among empa-treated patients than among comparator-treated patients, and somewhat more frequently among patients treated with 25 mg empa than among those treated with 10 mg empa.

Table 8.7.1.1: Incidence of Categorical Increases in Transaminases, SAF-5 Population						
Transaminase	Categorical Increase	Empa 10 mg N=3630 n (%)	Empa 25 mg N=4602 n (%)	All Empa N=8400 n (%)	All Comp N=4676 n (%)	Pbo N=3522 n (%)
Alanine aminotransferase (ALT)	≥3x ULRR	17 (0.47)	24 (0.52)	43 (0.51)	37 (0.79)	23 (0.65)
	≥5x ULRR	6 (0.17)	10 (0.22)	16 (0.19)	3 (0.06)	2 (0.06)
	≥10x ULRR	2 (0.06)	5 (0.11)	7 (0.08)	0	0
	≥20x ULRR	0	1 (0.02)	1 (0.01)	0	0
Aspartate aminotransferase (AST)	≥3x ULRR	9 (0.25)	17 (0.37)	27 (0.32)	20 (0.43)	17 (0.48)
	≥5x ULRR	4 (0.11)	7 (0.15)	12 (0.14)	5 (0.11)	4 (0.11)
	≥10x ULRR	0	3 (0.07)	4 (0.05)	1 (0.02)	1 (0.03)
	≥20x ULRR	0	1 (0.02)	1 (0.01)	0	0
Source: Dr. Chong's review, Table 96, pg 189						

In addition, there were a total of nine cases in which a peak transaminase was ≥3x ULRR and total bilirubin was ≥2x ULRR. These cases are considered to be of special concern, and

required further evaluation for possible drug-induced liver injury. Eight patients received empagliflozin and one received glimepiride. Dr. John Senior, an FDA expert in drug-induced liver injury, was consulted. Please see his consultations (DARRTS October 20th and 30th, 2013). Using the eDISH tool, he identified seven of the cases, and evaluated an eighth case that the applicant submitted later. Dr. Chong identified an additional case (Patient 84833).

The following table lists these patients, their peak laboratory values, and the FDA reviewer's conclusion regarding the likely cause of their liver laboratory abnormalities. For all patients except Patient 84833, the cause listed was that assessed by Dr. Senior. As mentioned above, Patient 84833 was an additional patient identified by Dr. Chong.

Table 8.7.1.2: Patients with Transaminase $\geq 3x$ ULRR and Total Bilirubin $\geq 2x$ ULRR								
Pt ID	Gender	Age	Tx	Peak Laboratory Value, Multiples of ULRR				Likely Cause per FDA Reviewer
				ALT	AST	TBL	ALP	
004394	M	74	Empa 25	5.0	3.5	6.0	1.0	Pancreatic cancer
008963	F	56	Empa 10	4.0	5.0	2.0	7.0	Cholangiocarcinoma
021141	M	55	Empa 25	4.1	3.1	3.6	1.2	Biliary duct cancer
023063	M	49	Empa 25	8.5	3.3	9.5	1.1	Acute viral hepatitis, A or E
056393	M	62	Empa 10	13.9	8.0	3.9	1.0	Acute cholecystitis
056546	M	64	Empa 25	15.2	9.0	2.0	1.4	Ciprofloxacin-induced acute reversible liver injury
082414	M	57	Glim	3.9	9.5	7.8	3.7	Hepatocellular carcinoma
084833	M	48	Empa 25	25.8	110.8	16.1	1.1	Prior cirrhosis and acute alcoholic hepatitis
227016	M	55	Empa 25	8.7	14.7	3.4	1.4	Acute alcoholic hepatitis
Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; empa = empagliflozin; glim = glimepiride; ID = identification; M = male; pt = patient; TBL = total bilirubin; Tx = treatment assignment; ULRR = upper limit of reference range For all patients other than Patient 084833, FDA reviewer was Dr. John Senior. For Patient 084833, FDA reviewer was Dr. William Chong								

For all patients who had an ALT $\geq 3x$ ULRR and a total bilirubin $\geq 2x$ ULRR, another etiology was present which appeared more likely than study drug to have been the cause of the patient's laboratory abnormalities.

At this time, there is not a clear liver safety signal with empagliflozin. However, the numerical imbalance in cases of ALT $\geq 3x$ ULRR with bilirubin $\geq 2x$ ULRR (although all cases seem to have another etiology), along with a small numerical imbalance in categorical shifts in transaminase values, will warrant continued evaluation of the hepatic safety of empagliflozin. In the ongoing cardiovascular outcomes trial, which includes a large study population, hepatic events are being prospectively evaluated; this additional information will likely be of use in further assessment of empagliflozin's hepatic safety.

8.7.2. Malignancies

Overall, malignancies occurred at a similar frequency among empa-treated and comparator-treated patients.

Table 8.7.2.1: Incidence of Malignancies, SAF-5 Population

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	N	%	N	%	N	%	N	%	N	%
Number of patients	3630	100	4602	100	8400	100	3522	100	4676	100
All malignancies	37	1.02	51	1.11	89	1.06	32	0.91	42	0.90
Malignancies with onset \geq 6 months after initiation of study drug	22	0.61	25	0.54	49	0.58	16	0.45	25	0.53

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators

Source: Tables 5.17.5.1 and 5.17.5.2 (Integrated Summary of Safety)

There were two types of malignancies for which there was a numeric imbalance, not favoring empa. These were lung neoplasms and malignant melanoma.

Regarding lung neoplasms, Dr. Chong identified a total of seven cases which occurred six months or longer after randomization. All patients were treated with empagliflozin. The following table displays these cases:

Table 8.7.2.2: Lung Neoplasm Cases Reported \geq 6 Months After Randomization, SAF-5 Population

Patient ID	Treatment Arm	Days since Randomization	Preferred Term	Diagnosis on Pathology Report
1245-0020-020704	Empa 25	472	Bronchial carcinoma	Invasive squamous cell carcinoma
1245-0023-034564 ¹	Empa 25	371	Lung squamous cell carcinoma stage unspecified	Small cell lung cancer
1245-0025-(b) (4)	Empa 10	241	Lung neoplasm malignant	Poorly differentiated squamous cell carcinoma
1245-0025-(b) (4)	Empa 25	427	Lung neoplasm malignant	Keratinizing squamous epithelium carcinoma
1245-0033-004331 ²	Empa 10	193	Lung neoplasm malignant	Undifferentiated bronchial adenocarcinoma
1245-0033-006859	Empa 10	461	Lung neoplasm malignant	Carcinoma, pavement cell in situ
1245-0038-809006 ³	Empa 10	194	Lung cancer metastatic	NA

Empa 25 = empagliflozin 25 mg; Empa 10 = empagliflozin 10 mg; NA = not applicable

¹Not included in Applicant's Table 2.1.5.8: 4 or in Table 119 above as this was coded to the "Non-small cell neoplasms malignant of the respiratory tract cell type specified" High Level Term; ²Not included in Applicant's Table 2.1.5.8: 4 as lung cancer event occurred $>$ 7 days after last dose of study medication and the patient was only exposed to study drug for 167 days;

³Was not a case of lung cancer, but was a case of colon cancer that was metastatic to the lung

Source: Table 2.1.5.8: 4 (Summary of Clinical Safety), and submitted AE xpt and DM.xpt files, Additional information submitted in the Sponsor's August 16, 2013 Response to Information Request (NDA-204629, SD-18, eCTD-0016)

Source: Dr. Chong's review, Table 120, pg 227

Dr. Chong notes that Patient 809006 actually had colon cancer metastatic to lung, rather than a primary lung neoplasm. Patient 34564 appears to have had a recurrence of a prior lung cancer, which had occurred before randomization to empagliflozin. All the remaining patients were current or prior smokers.

Dr. Chong noted six cases of melanoma occurring 6 months or more after randomization. All patients were randomized to empa. The following table displays these patients:

Table 8.7.2.3: Patients with Melanoma Diagnosis >6 Months After Randomization, SAF-5 Population

Patient ID	Treatment Arm	Days since randomization	Preferred Term
1245-0010-003402	Empa 25	238	Malignant melanoma
1245-0025-(b) (4)	Empa 10	236	Malignant melanoma
1245-0025-(b) (4)	Empa 25	216	Malignant melanoma
1245-0025-(b) (4)	Empa 10	345	Malignant melanoma
1245-0028-080040	Empa 25	351	Malignant melanoma in situ
1245-0036-001815	Empa 25	233	Malignant melanoma

Empa 25 = empagliflozin 25 mg; Empa 10 = empagliflozin 10 mg

Source: Table 2.1.5.8: 4 (Summary of Clinical Safety), and submitted AE xpt and DM xpt files

Source: Dr. Chong's review, Table 122, pg 229

Of these six patients, two had a prior melanoma, one had multiple prior skin carcinomas, and one had "sun damaged skin".

Dr. Chang of the Division of Oncology Products was consulted regarding this imbalance in lung neoplasms and melanoma. She noted that these cases appeared to occur in high risk patients, and that it was unclear if this was a true signal or a chance finding. She recommended continued collection of clinical trial data in a long-term clinical trial. This will occur in Study 1245.25. She also recommended consultation with the Office of Surveillance and Epidemiology regarding possible postmarketing pharmacovigilance approaches. In discussions with OSE Pharmacovigilance and Epidemiology, it was noted that the lung neoplasms were of differing cell types, which would be very unusual for a drug-associated malignancy. They also stated that "enhanced" postmarketing pharmacovigilance methods would be unlikely to be of use for evaluation of these types of malignancies. In discussions with the nonclinical team, the nonclinical carcinogenicity evaluation appears to be adequate, and no new mechanistic studies were recommended.

The most appropriate approach to this question of an imbalance in lung neoplasms and melanoma appears to be continued evaluation in the ongoing CVOT, and should empagliflozin be approved, routine pharmacovigilance.

8.7.3. Genital Infections

Genital infections, particularly mycotic infections, occurred more commonly among empa-treated patients than among comparator-treated patients. To evaluate genital infections, the

applicant used a custom MedDRA query (CMQ) of 89 Preferred Terms; these are listed on pages 200-201 of Dr. Chong's review. Events from this CMQ occurred among 4.6% of empa-treated patients, and among 1.1% of comparator-treated patients. The most commonly occurring terms from the CMQ among empa-treated patients were vulvovaginal mycotic infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vaginal infection and balanitis candida.

Serious genital infection events were uncommon (one empa 10 mg; two empa 25 mg; one placebo).

Discontinuations from study due to genital infection occurred for 14 patients treated with empa 10 mg, 15 patients treated with empa 25 mg, and one patient treated with placebo.

Most patients had a single episode of genital infection, but some patients had two or more. There was no dose-response relationship for risk of recurrence.

Table 8.7.3: Number of Genital Infections per Patient, SAF-5 Population		
Number of Genital Infections	All Empa N=8400 n (%)	All Comp N=4676 n (%)
1	306 (3.6)	47 (1.0)
2	56 (0.7)	4 (0.1)
3 or 4	20 (0.2)	1 (<0.1)
≥5	4	0
Categories are exclusive, i.e. patients listed in the row for "1" had only one genital infection during study. Source: Integrated Summary of Safety, Table 5.13.5.10, pg 9645		

Genital infections responded to standard therapy.

These findings are similar to those seen with canagliflozin and dapagliflozin.

8.7.4. Urinary Tract Infection

The applicant used a CMQ of 70 Preferred Terms, which may be found on pages 201-202 of Dr. Chong's review. Overall, the incidence of terms from this CMQ was similar among patients treated with empa (8.8%) and comparator-treated patients (8.1%). The Preferred Term (PT) "urinary tract infection" occurred among 7.5% of empa-treated patients and among 7.0% of comparator-treated patients. The PT "cystitis" occurred among 0.6% of empa-treated patients vs 0.5% of comparator-treated patients.

Serious events occurred in 0.3% of patients in both the empa and comparator groups. Acute pyelonephritis or urosepsis occurred among 6 (0.1%) of empa-treated and 5 (0.1%) of comparator-treated patients. For both empa and comparator, the majority of patients had only

one event, and the percentages of patients who had two or more events was equal between empa and comparator.

8.7.5. Volume Depletion

The applicant used a CMQ of eight terms for volume depletion. Events from this CMQ are displayed in the following table:

Table 8.7.5: Volume Depletion Events, SAF-5 Population

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
Treated	3630		4602		8400		3522		4676	
	N	%	N	%	N	%	N	%	N	%
Volume depletion CMQ	52	1.43	67	1.46	119	1.42	49	1.39	57	1.22
Rate per 100 patient-years	1.60		1.51		1.52		1.78		1.36	
Preferred Term										
Hypotension	22	0.61	25	0.54	47	0.56	28	0.80	32	0.68
Syncope	16	0.44	22	0.48	38	0.45	11	0.31	14	0.30
Orthostatic hypotension	8	0.22	11	0.24	19	0.23	6	0.17	6	0.13
Dehydration	9	0.25	8	0.17	17	0.20	4	0.11	6	0.13
Hypovolemia	0	0.00	1	0.02	1	0.01	2	0.06	2	0.04
Blood pressure decreased	0	0.00	2	0.04	2	0.02	1	0.03	1	0.02

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; CMQ = customized MedDRA query

Source: Table 2.1.5.7: 1 (Summary of Clinical Safety)

Source: Dr. Chong's review, Table 100, pg 198

Overall, PTs from this CMQ did not occur with markedly increased frequency among empa-treated patients versus comparator-treated patients. The PTs syncope, orthostatic hypotension and dehydration occurred somewhat more commonly among empa-treated patients than among comparator-treated patients.

8.7.6. Renal Function Events

Events from the MedDRA SMQ for acute renal failure occurred among 1.2% of empa-treated patients and 0.9% of comparator-treated patients.

Using a laboratory-based definition of a serum creatinine ≥ 2 x baseline and above ULRR, events meeting this definition occurred among 0.3% of empa-treated and 0.2% of comparator-treated patients.

Dr. Chong identified some subgroups of patients who appeared to be at higher risk for events of decreased renal function. These included:

- Women (event from renal failure SMQ: empa 1.4%, comp 0.4%)
- Hispanic patients (empa 1.3%, comp 0.8%)
- Patients with eGFR 30-<60 mL/min/1.73m² (empa 4.3%, comp 2.7%)

Elderly patients (over age 75 years) did not have a difference in the overall SMQ event incidence, but did have a modest difference for the individual PT “renal failure acute” (empa 0.8%, comp 0.4%).

Small changes in mean eGFR occurred during study (empa -2% vs comparator -1%). These changes were reversible on follow-up in Study 1245.33.

8.7.7. Fractures

Fractures occurred with similar frequency among empa-treated patients (1.3%) and comparator-treated patients (1.5%). No fractures of specific bones occurred with greater frequency among empa-treated patients, nor did groupings of fractures (small vs large bones; upper vs lower extremities).

8.7.8. Hypoglycemia

Overall, adverse events of hypoglycemia occurred among 19.9% of empagliflozin-treated patients and 21.9% of placebo-treated patients. Severe hypoglycemic events (i.e. an event requiring the assistance of another person) occurred among 0.3% of empa-treated patients and 0.4% of placebo-treated patients.

However, when empagliflozin was added to background sulfonylurea in Study 1245.23 and Study 1245.31; and to background insulin in Study 1245.33, hypoglycemia occurred more frequently among empa-treated patients than among placebo-treated patients.

This finding is similar to that for the approved SGLT2is. The Full Prescribing Information for those products recommends consideration of dose reduction of sulfonylurea or insulin when empagliflozin is added, to reduce the risk of hypoglycemia.

8.8. Laboratory Findings

The following laboratory findings occurred:

- An increase in mean hematocrit of 2.8% for empa-treated patients, with no change in hematocrit for comparator-treated patients. There was no increase in thromboembolic events. These hematocrit changes are similar to those seen with the approved SGLT2is.
- A somewhat higher percentage of patients who developed a serum phosphorus >1.7 mmol/L (2.1% empa vs 1.0% comparator). This was also seen with the two approved SGLT2is.
- A placebo-adjusted mean increase in total and low density lipoprotein (LDL) cholesterol of 3-4%. This was also seen with the two approved SGLT2is.

8.9. Vital Signs

Please see the efficacy section for blood pressure and body weight findings. There was no change in heart rate associated with empa.

9. Advisory Committee Meeting

No Advisory Committee meeting was held for empagliflozin.

10. Pediatrics

Empagliflozin has not been studied in patients under age 18 years. If empa is approved, a pharmacokinetic/pharmacodynamic study, and a clinical efficacy and safety study, would be required in patients with type 2 diabetes mellitus who are between the ages of 10 and 18 years. These are Postmarketing Requirements for the two approved SGLT2is.

11. Other Relevant Regulatory Issues

11.1. Financial Disclosure

Dr. Chong examined the financial disclosure information for investigators. Please see Dr. Chong's Table 2 on page 26 of his review for a listing of investigators who had significant financial information to report (n=7). The total number of patients contributed by these investigators was small, and would not have affected the outcomes of the studies.

11.2. Clinical Site Inspection

The Division of Scientific Investigations conducted clinical site audits, and found no significant violations that would preclude an approval recommendation. However, as noted earlier, during a separate inspection of the manufacturing facility, significant negative findings were noted regarding Good Manufacturing Practices, resulting in a recommendation against approval.

12. Labeling

The proprietary name of Jardiance® has been reviewed and found acceptable (DARRTS July 25th, 2013).

Because approval is not recommended, significant labeling negotiations are not expected to occur.

13. Recommendations/Risk Benefit Assessment

13.1. Recommended Regulatory Action

The Cross-Discipline Team Leader recommends a "Complete Response" action.

13.2. Risk:Benefit Assessment:

Because significant Good Manufacturing Process violations have been noted, the safety of the drug product cannot be assured at this time. Therefore, the risk associated with this product exceeds the benefit associated with the introduction of a third SGLT2 inhibitor into the U.S. market.

If the significant GMP violations had not been present, the Cross-Discipline Team Leader recommendation would likely have been for approval. Empagliflozin is effective in lowering hemoglobin A1c, and has desirable attributes of a low risk of hypoglycemia, and of small decreases in systolic blood pressure and body weight. Empagliflozin's risks appear to be similar to the currently approved SGLT2 inhibitors, canagliflozin and dapagliflozin. Particular safety concerns which merit further evaluation include hepatic adverse events and malignancy events (lung cancer and melanoma), but after careful review, these events would not appear to preclude approval in and of themselves. These events can be examined further with data from the ongoing cardiovascular outcomes trial.

Should the applicant be able to resolve their manufacturing problems, and resubmit their application, safety data will need to be reassessed at the time of that submission. A safety update with any new clinical trial data would be appropriate.

14. Appendix: Cardiovascular Safety

Dr. Charles conducted the safety statistical review (DARRTS November 1st, 2013) of cardiovascular safety. At this time, all drugs intended for the treatment of type 2 diabetes mellitus are expected to meet the standards outlined in the FDA Guidance entitled "Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes". That Guidance states that, before submission of an NDA, "Sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8."

For empagliflozin, the preplanned method for evaluation of cardiovascular safety was a meta-analysis of data from eight Phase II and Phase III trials, one of which is an ongoing dedicated cardiovascular outcomes trial (Study 1245.25). Interim data from Study 1245.25 were used in the CV meta-analysis. It is very important to protect the integrity of that ongoing trial, and interim data from it should not be disclosed. Therefore, the cardiovascular meta-analysis results are being presented in this separate appendix, to separate these data from those which can be disclosed in the event of a future approval action. Should empagliflozin be approved prior to completion of Study 1245.25, this section should not be publicly disclosed, in order to protect the integrity of the ongoing cardiovascular outcomes trial (CVOT).

The primary endpoint for the premarketing meta-analysis for cardiovascular safety was "MACE+", which is a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina. A key secondary endpoint was MACE,

which stands for major adverse cardiovascular events, and which includes cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

The following table displays the results from the meta-analysis:

Table 14.1: Summary of Cardiovascular Meta-Analysis Results

Outcome	Number of Patients with Events		
	Empagliflozin ¹	Comparator ²	HR
	(N=6206)	(N=3830)	(95% CI)
MACE+ MACE	(b) (4)		

¹Pooled 10 mg and 25 mg empagliflozin doses

²Pooled active and placebo comparators

Source: Created by the reviewer using dataset "adttecv.xpt"

Source: Dr. Charles' review, Table 1, pg 7

Per the prespecified analysis, the upper bound of the 95% confidence interval for the risk ratio for MACE+ is <1.8. Therefore, empagliflozin meets the standard for evaluation of cardiovascular risk in the premarketing setting. Study 1245.25 is to be completed, and will be used to meet the postmarketing standard, which must exclude an upper bound of 1.3; for that, the MACE endpoint will be used.

There are a few additional points of interest from the CV meta-analysis.

The individual components of MACE+ were evaluated, and there was no statistically significant difference between empagliflozin and comparator:

Table 14.2: Analyses of Components of MACE+			
Endpoint	Empa N=6206 n (%)	Comp N=3830 n (%)	HR (95% CI)
Cardiovascular death	(b) (4)		
Nonfatal myocardial infarction			
Nonfatal stroke			
Hospitalization for unstable angina			
Source: Dr. Charles’ review, Table 14, pg 36			

References:

Cowie C et al 2009. Full accounting of diabetes and prediabetes in the U.S. population in 1988-94 and 2005-6. *Diabetes Care* 32:2; 287-94

Inzucchi S et al 2013. Management of hyperglycemia in type 2 diabetes: a patient-centered approach. Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetologia* 55(6):1577-96

National Institute of Diabetes and Digestive and Kidney Diseases, National Diabetes Information Clearinghouse, Complications of Diabetes in the United States
<http://diabetes.niddk.nih.gov/dm/pubs/statistics/#Complications> , accessed 20 Dec 2013.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KAREN M MAHONEY
02/27/2014

CLINICAL REVIEW

Application Type	NME NDA
Application Number(s)	NDA-204629, IND-102145
Priority or Standard	Standard
Submit Date(s)	March 5, 2013
Received Date(s)	March 5, 2013
PDUFA Goal Date	March 5, 2014
Division / Office	OND/ODE-II/DMEP
Reviewer Name(s)	William H. Chong
Review Completion Date	November 5, 2013
Established Name	Empagliflozin
(Proposed) Trade Name	Jardiance
Therapeutic Class	Sodium-dependent glucose co-transporter-2 inhibitor
Applicant	Boehringer Ingelheim Pharmaceuticals Inc.
Formulation(s)	Tablet
Dosing Regimen	25 mg tablet once daily
Indication(s)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Intended Population(s)	Adults with type 2 diabetes mellitus
Team Leader	Karen Mahoney
Division Director	Jean-Marc Guettier
Clinical Pharmacology Reviewer	Manoj Khurana
Pharmacology Toxicology Reviewer	Mukesh Summan
Statistical Reviewer – Efficacy	Dongmei Li
Statistical Reviewer – Cardiovascular Safety	Janelle Charles
Product Quality Reviewer	Joseph Leginus
Project Manager	Patricia Madara

Table of Contents

TABLE OF TABLES.....	6
TABLE OF FIGURES.....	14
ABBREVIATIONS.....	16
1. RECOMMENDATIONS/RISK BENEFIT ASSESSMENT.....	19
1.1 Recommendation on Regulatory Action	19
1.2 Risk Benefit Assessment	19
1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies.....	22
1.4 Recommendations for Postmarket Requirements and Commitments	22
2. INTRODUCTION AND REGULATORY BACKGROUND.....	22
2.1 Product Information.....	22
2.2 Currently Available Treatments for Proposed Indications	22
2.3 Availability of Proposed Active Ingredient in the United States	23
2.4 Important Safety Issues with Consideration to Related Drugs.....	23
2.5 Summary of Presubmission Regulatory Activity Related to Submission	24
2.6 Other Relevant Background Information	24
3. ETHICS AND GOOD CLINICAL PRACTICES	24
3.1 Submission Quality and Integrity	24
3.2 Compliance with Good Clinical Practices.....	25
3.3 Financial Disclosures.....	25
4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....	26
4.1 Chemistry Manufacturing and Controls	26
4.2 Clinical Microbiology.....	27
4.3 Preclinical Pharmacology/Toxicology	27
4.4 Clinical Pharmacology	28
4.4.1 Mechanism of Action	28
4.4.2 Pharmacodynamics.....	28
4.4.3 Pharmacokinetics.....	29
5. SOURCES OF CLINICAL DATA.....	31
5.1 Tables of Studies/Clinical Studies.....	31
5.2 Review Strategy.....	35

5.3	Discussion of Individual Studies/Clinical Studies.....	35
6.	REVIEW OF EFFICACY	37
6.1	Indication	37
6.1.1	Methods	37
6.1.2	Demographics.....	39
6.1.3	Subject Disposition.....	41
6.1.4	Analysis of Primary Endpoint(s).....	43
6.1.5	Analysis of Secondary Endpoints(s)	49
6.1.5.1	Change from Baseline in Fasting Plasma Glucose	49
6.1.5.2	Change from Baseline in Body Weight	50
6.1.5.3	Change from Baseline in Blood Pressure (Systolic and Diastolic)	52
6.1.6	Other Endpoints.....	58
6.1.6.1	Percentage of Patients Achieving Hemoglobin A1c < 7.0%	58
6.1.6.2	Percentage of Patients Achieving Blood Pressure < 130/80 mmHg	59
6.1.6.3	Percentage of Patients With > 5% Reduction in Body Weight	60
6.1.6.4	Percentage of Patients Requiring Rescue Medication	61
6.1.7	Subpopulations	62
6.1.7.1	By Baseline Renal Function	62
6.1.7.2	By Age.....	65
6.1.7.3	By Baseline Hemoglobin A1c	68
6.1.8	Analysis of Clinical Information Relevant to Dosing Recommendations	69
6.1.9	Discussion of Persistence of Efficacy and/or Tolerance Effects.....	78
6.1.10	Additional Efficacy Issues/Analyses	82
7.	REVIEW OF SAFETY	88
7.1	Methods	89
7.1.1	Studies/Clinical Studies Used to Evaluate Safety	90
7.1.2	Categorization of Adverse Events.....	91
7.1.3	Pooling of Data across Studies/Clinical Studies to Estimate and Compare Incidence	92
7.2	Adequacy of Safety Assessments.....	93
7.2.1	Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	93
7.2.2	Explorations for Dose Response	96
7.2.3	Special Animal and/or In Vitro Testing	96
7.2.4	Routine Clinical Testing.....	96
7.2.5	Metabolic, Clearance, and Interaction Workup.....	96

7.2.6	Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	96
7.3	Major Safety Results	97
7.3.1	Deaths	97
7.3.1.1	Deaths – Four Month Safety Update	109
7.3.2	Nonfatal Serious Adverse Events	110
7.3.2.1	Nonfatal Serious Adverse Events – Four Month Safety Update	122
7.3.3	Dropouts and/or Discontinuations	122
7.3.4	Significant Adverse Events	126
7.3.5	Submission Specific Safety Concerns	131
7.3.5.1	Cardiovascular Safety	131
7.3.5.2	Liver Adverse Events/Hepatic Injury	181
7.3.5.3	Fractures	191
7.3.5.4	Volume Depletion	198
7.3.5.5	Genital Infections/Urinary Tract Infections	200
7.3.5.6	Decreased Renal Function	209
7.3.5.7	Hypoglycemic Events	220
7.3.5.8	Malignancy Events	224
7.4	Supportive Safety Results	231
7.4.1	Common Adverse Events	231
7.4.2	Laboratory Findings	248
7.4.2.1	Increases in Hematocrit	248
7.4.2.2	Electrolytes	251
7.4.2.3	Enzymes	257
7.4.2.4	Serum Uric Acid	263
7.4.2.5	Lipids	265
7.4.3	Vital Signs	267
7.4.4	Electrocardiograms (ECGs)	268
7.4.5	Special Safety Studies/Clinical Studies	269
7.4.6	Immunogenicity	269
7.5	Other Safety Explorations	269
7.5.1	Dose Dependency for Adverse Events	269
7.5.2	Time Dependency for Adverse Events	270
7.5.3	Drug-Demographic Interactions	272
7.5.3.1	Age	272
7.5.3.2	Gender	274
7.5.3.3	Race/Ethnicity	275
7.5.3.4	Renal function	279
7.5.4	Drug-Disease Interactions	283

7.5.5	Drug-Drug Interactions	284
7.6	Additional Safety Evaluations	284
7.6.1	Human Carcinogenicity	284
7.6.2	Human Reproduction and Pregnancy Data	284
7.6.3	Pediatrics and Assessment of Effects on Growth.....	285
7.6.4	Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	285
7.7	Additional Submissions / Safety Issues.....	286
8.	POSTMARKET EXPERIENCE.....	286
9.	APPENDICES.....	286
9.1	Literature Review/References	286
9.2	Labeling Recommendations	286
9.3	Advisory Committee Meeting	287

Table of Tables

Table 1 Summary of Presubmission Regulatory Activity	24
Table 2 Investigators with Financial Disclosures	26
Table 3 Dose-Dependent Changes in Renal Glucose Handling	29
Table 4 Listing of Clinical Studies	31
Table 5 Grouping of Studies for Evaluation of Efficacy	38
Table 6 Subjects in Pivotal Studies – Full Analysis Set	39
Table 7 Baseline Demographics for Pivotal Studies and Efficacy Groupings – Full Analysis Set	40
Table 8 Subject Disposition	42
Table 9 Reasons for Not Continuing in Extension Study 1245.31	43
Table 10 Change in Hemoglobin A1c – 24 weeks, Full Analysis Set, Last Observation Carried Forward, Analysis of Covariance Model	44
Table 11 Change in Hemoglobin A1c – 24 Weeks, Per-Protocol Set, Last Observation Carried Forward, Analysis of Covariance Model	45
Table 12 Change in Hemoglobin A1c – 24 Weeks, Full Analysis Set (Observed Cases), Mixed-Effects Model Repeated Measures.....	46
Table 13 Change in Hemoglobin A1c – 24 Weeks, Full Analysis Set, Observed Cases Including Values After Rescue Medication, Mixed-Effects Model Repeated Measures	47
Table 14 Change in Hemoglobin A1c – Study 1245.25, Dipeptidyl Peptidase-4 Inhibitor +/- Metformin, Full Analysis Set, Last Observation Carried Forward.....	48
Table 15 Change in Fasting Plasma Glucose (mg/dL) – 24 Weeks, Full Analysis Set, Last Observation Carried Forward	49
Table 16 Change in Body Weight (kg) – 24 Weeks, Full Analysis Set, Last Observation Carried Forward	51
Table 17 Change in Systolic Blood Pressure (mmHg) – 24 Weeks, Full Analysis Set, Last Observation Carried Forward	53
Table 18 Change in Diastolic Blood Pressure (mmHg) – 24 Weeks, Full Analysis Set, Last Observation Carried Forward	54
Table 19 Change in 24-hour Blood Pressure – Study 1245.48, Week 12, Full Analysis Set, Last Observation Carried Forward Following Change in Antihypertensive Therapy.....	55
Table 20 Percentage of Patients Achieving Hemoglobin A1c < 7.0% - 24 Weeks, Full Analysis Set, Noncompleters Considered Failure	58
Table 21 Percentage of Patients Achieving Blood Pressure < 130/80 mmHg – 24 Weeks, Full Analysis Set, Noncompleters Considered Failure	59

Table 22 Percentage of Patients Achieving > 5% Body Weight Reduction – 24 Weeks, Full Analysis Set, Noncompleters Considered Failure	60
Table 23 Percentage of Patients Requiring Rescue Medication – 24 Weeks, Full Analysis Set..	62
Table 24 Change in Hemoglobin A1c by Baseline Renal Function – Efficacy Grouping 2, 24 Weeks, Full Analysis Set, Last Observation Carried Forward	63
Table 25 Change in Hemoglobin A1c by Baseline Renal Function – Study 1245.36, 24 Weeks, Full Analysis Set, Last Observation Carried Forward	65
Table 26 Change in Hemoglobin A1c by Age – Efficacy Grouping 2, 24 Weeks, Full Analysis Set, Last Observation Carried Forward	66
Table 27 Change in Hemoglobin A1c by Age – Study 1245.25, Full Analysis Set, Last Observation Carried Forward	66
Table 28 Change in Hemoglobin A1c for Patients \geq 75 Years Old by Estimated Glomerular Filtration Rate – Study 1245.25, Full Analysis Set, Last Observation Carried Forward	67
Table 29 Change in Hemoglobin A1c by Baseline Hemoglobin A1c – 24 Weeks, Efficacy Grouping 2, Full Analysis Set, Last Observation Carried Forward.....	68
Table 30 Comparison of Dose on Change in Hemoglobin A1c – 24 Weeks, Full Analysis Set, Last Observation Carried Forward.....	70
Table 31 Comparison of Dose on Change in Hemoglobin A1c – 52 Weeks, Full Analysis Set, Last Observation Carried Forward.....	70
Table 32 Comparison of Dose on Change in Hemoglobin A1c from Baseline – Study 1245.25, Full Analysis Set, Last Observation Carried Forward	71
Table 33 Comparison of Dose on Ability to Achieve Hemoglobin A1c < 7.0% –Full Analysis Set, Noncompleters Considered Failure, Logistic Regression.....	71
Table 34 Comparison of Dose on Ability to Achieve Hemoglobin A1c < 7.0% - Study 1245.25, Full Analysis Set, Noncompleters Considered Failure, Logistic Regression	72
Table 35 Comparison of Dose on Changes in Fasting Plasma Glucose (mg/dL) –Full Analysis Set, Last Observation Carried Forward	73
Table 36 Comparison of Dose on Changes in Fasting Plasma Glucose (mg/dL) – Study 1245.25, Full Analysis Set, Last Observation Carried Forward	74
Table 37 Comparison of Dose on Change in Body Weight (kg) –Full Analysis Set, Last Observation Carried Forward	74
Table 38 Comparison of Dose on Change in Body Weight (kg) – Study 1245.25, Full Analysis Set, Last Observation Carried Forward	75
Table 39 Comparison of Dose on Change in Systolic Blood Pressure (mmHg) – Full Analysis Set, Last Observation Carried Forward	75
Table 40 Comparison of Dose on Change in Systolic Blood Pressure (mmHg) – Study 1245.25, Full Analysis Set, Last Observation Carried Forward	76

Table 41 Comparison of Dose on Change in Diastolic Blood Pressure (mmHg) – 24 Weeks, Full Analysis Set, Last Observation Carried Forward	77
Table 42 Comparison of Dose on Change in Diastolic Blood Pressure (mmHg) – Study 1245.25, Full Analysis Set, Last Observation Carried Forward	78
Table 43 Change in Hemoglobin A1c – 52 Weeks, Full Analysis Set, Last Observation Carried Forward	79
Table 44 Summary of Efficacy Results from Study 1245.19 – 24 Weeks, Full Analysis Set, Last Observation Carried Forward	83
Table 45 Summary of Efficacy Results from Study 1245.20 – 24 Weeks, Full Analysis Set, Last Observation Carried Forward	84
Table 46 Summary of Efficacy Results from Study 1245.23 _{met} – 24 Weeks, Full Analysis Set, Last Observation Carried Forward.....	85
Table 47 Summary of Efficacy Results from Study 1245.23 _{met+SU} – 24 Weeks, Full Analysis Set, Last Observation Carried Forward.....	86
Table 49 Summary of Efficacy Results from Study 1245.33 – 18 and 78 Weeks, Full Analysis Set, Last Observation Carried Forward	87
Table 50 Safety Population Groupings	90
Table 51 Number of Patients in Safety Grouping 5 and Safety Grouping 3 by Treatment Grouping	94
Table 52 Overall Exposure to Randomized Empagliflozin – Safety Grouping 5.....	95
Table 53 Overall Exposure to Randomized Empagliflozin – Safety Grouping 3.....	95
Table 54 Estimated Exposures for Subgroups of Safety Grouping 5	96
Table 55 Incidence of Death (On-Treatment) – Safety Grouping 5	97
Table 56 Incidence of Death (On-Treatment, Post-Treatment, and Post-Study).....	98
Table 57 Incidence of Fatal Events by System Organ Class and Preferred Term – Safety Grouping 5	99
Table 58 Incidence of Fatal Events by System Organ Class and Preferred Term – Safety Grouping 5 Excluding Study 1245.25	102
Table 59 Incidence of Fatal Events by System Organ Class and Preferred Term – Safety Grouping 5, Completed Studies Only.....	103
Table 60 Patients Treated with Empagliflozin and with Fatal Events – Safety Grouping 5	105
Table 61 Incidence of Nonfatal Serious Adverse Events (by System Organ Class and Preferred Term), Occurring in > 2 Patients of the All Empagliflozin Group – Safety Grouping 5	111
Table 62 Incidence of Nonfatal Serious Adverse Events (by System Organ Class and Preferred Term), Occurring in > 2 Patients of the All Empagliflozin Group – Safety Grouping 5 Excluding Study 1245.25	115

Table 63 Incidence of Nonfatal Serious Adverse Events (by System Organ Class and Preferred Term), Occurring in > 2 Patients of the All Empagliflozin Group – Safety Grouping 5, Completed Studies Only	118
Table 64 Incidence of Premature Discontinuations by Treatment Group – Safety Grouping 5	123
Table 65 Incidence of Adverse Events Leading to Discontinuation – Safety Grouping 5, Treated Set	124
Table 66 Incidence of Premature Discontinuation by Treatment Group – Safety Grouping 3 ..	125
Table 67 Incidence of Adverse Events Leading to Discontinuation – Safety Grouping 3, Treated Set	125
Table 68 Other Significant Adverse Events (by System Organ Class and Preferred Term), Occurring in $\geq 0.2\%$ of Patients in Any Group - Safety Grouping 5.....	128
Table 69 Other Significant Adverse Events (by System Organ Class and Preferred Term), Occurring in $\geq 0.2\%$ of Patients in Any Group – Safety Grouping 3	129
Table 70 Incidence of Death – Safety Grouping 5, Excluding Study 1245.25 and for Completed Studies.....	132
Table 71 Summary of Deaths in Empagliflozin Treated Patients from Study 1245.25	133
Table 72 Incidence of Fatal Cardiovascular Events – Safety Grouping 5	146
Table 73 Incidence of Fatal Cardiovascular Events – Safety Grouping 5, Excluding Study 1245.25.....	147
Table 74 Incidence of Fatal Cardiovascular Events – Safety Grouping 5, Completed Studies Only	148
Table 75 Incidence of Nonfatal Cardiovascular Serious Adverse Events – Safety Grouping 5	150
Table 76 Incidence of Nonfatal Cardiovascular Serious Adverse Events – Safety Grouping 5, Excluding Study 1245.25	151
Table 77 Incidence of Nonfatal Cardiovascular Nonfatal Adverse Events = Safety Grouping 5, Completed Studies Only	152
Table 78 Incidence of Events in the “Ischemic Cerebrovascular Conditions” Standardized Medical Dictionary for Regulatory Activities Query – Safety Grouping 5.....	153
Table 79 Incidence of Events in the “Ischemic Cerebrovascular Conditions” Standardized Medical Dictionary for Regulatory Activities Query – Safety Grouping 5, Excluding Study 1245.25.....	154
Table 80 Incidence of Events in the “Ischemic Cerebrovascular Conditions” Standardized Medical Dictionary for Regulatory Activities Query – Safety Grouping 5, Completed Studies Only.....	156
Table 81 Incidence of Discontinuation Due to Adverse Events in the “Cardiac Disorders” and “Nervous System Disorders” System Organ Class – Safety Grouping 5	161
Table 82 Studies Included in the Cardiovascular Meta-Analysis	162

Table 83 Baseline Use of Aspirin, Lipid-Lowering Drugs, and Antihypertensive Drugs - Treated Set	164
Table 84 Frequency of Relevant Medical Diagnoses at Baseline – Treated Set	165
Table 85 Composite Major Adverse Cardiovascular Event Endpoints by Cox Regression – Treated Set	167
Table 86 Incidence of Individual Cardiovascular Endpoints – Treated Set	168
Table 87 Incidence and Estimated Hazard Ratio for All-Cause Mortality – Cardiovascular Meta-Analysis Pool	169
Table 88 Comparison of Incidence of Adjudicated Cardiovascular Events – Treated Set.....	170
Table 89 Incidence of Four-Point Major Adverse Cardiovascular Events and Fatal/Nonfatal Stroke Over Time – Cardiovascular Meta-Analysis Pool.....	173
Table 90 Comparison of Hazard Ratios for Selected Endpoints by Dose – Cox-Regression, Treated Set	175
Table 91 Incidence of Four-Point Major Adverse Cardiovascular Events by Baseline Renal Function - Treated Set.....	176
Table 92 Hazard Ratios for Selected Cardiovascular Events by Age – Treated Set	178
Table 93 Incidence of Four-Point Major Adverse Cardiovascular Events by Gender - Treated Set	179
Table 94 Incidence of Four-Point Major Adverse Cardiovascular Events by Race - Treated Set	179
Table 95 Hepatic Injury Adverse Events (by Preferred Term) Occurring in ≥ 2 Patients - Safety Grouping 5, Treated Set.....	182
Table 96 Subjects with Liver Enzyme Elevation – Safety Grouping 5	184
Table 97 Incidence of Categorical Increases in Liver Laboratory Tests	189
Table 98 Incidence of Fractures by Preferred Term - Safety Grouping 5	193
Table 99 Change in Laboratory Markers of Bone Health – Safety Grouping 5	196
Table 100 Categorical Shifts for Intact Parathyroid Hormone and 25-Hydroxy Cholecalciferol – Safety Grouping 5	197
Table 101 Volume Depletion Events - Safety Grouping 5	198
Table 102 Incidence of Volume Depletion Events With and Without Baseline Diuretic Use – Safety Grouping 5, Treated Set.....	199
Table 103 Incidence of Urinary Tract Infections and Genital Infections - Safety Grouping 5 ..	203
Table 104 Incidence of Pyelonephritis and Sepsis Due to Urinary Tract Infection – SAF-5.....	206
Table 105 Incidence of Fungal Urinary Tract and Genital Infections – Safety Grouping 5	207
Table 106 Incidence of Phimosis – Safety Grouping 5	208
Table 107 Incidence of Decreased Renal Function Adverse Events – Safety Grouping 5.....	211
Table 108 Subjects with Preferred Term “Epidermal Growth Factor Receptor Decreased”	212

Table 109 Incidence for “Acute Renal Failure” Standardized Medical Dictionary for Regulatory Activities Query With and Without Patients from Table 108.....	212
Table 110 Incidence of Decreased Renal Function Based on Serum Creatinine \geq 2x Baseline and Above Upper Limit of Reference Range – Safety Grouping 5.....	212
Table 111 Incidence of Decreased Renal Function Adverse Events – Safety Grouping 5, by Subgroups	213
Table 112 Change in Estimated Glomerular Filtration Rate by Modification of Diet in Renal Disease Formula – Safety Grouping 5, Treated Set.....	215
Table 113 Changes in Estimated Glomerular Filtration Rate from Baseline and After Cessation of Empagliflozin Therapy – 4 Week Follow-Up, Study 1245.33.....	216
Table 114 Changes in Estimated Glomerular Filtration Rate from Baseline and After Cessation of Empagliflozin Therapy, by Degree of Baseline Renal Impairment – 3 Week Follow-Up, Study 1245.36.....	217
Table 115 Change in Estimated Glomerular Filtration Rate from Baseline and After Cessation of Empagliflozin Therapy – 2 Week Follow-Up, Study 1245.48	218
Table 116 Incidence of Hypoglycemic Events - Safety Grouping 5, Treated Set.....	221
Table 117 Incidence of Hypoglycemic Events – Safety Grouping 3, Treated Set	222
Table 118 Incidence of Hypoglycemia in Phase 3 Studies by Background Therapy	223
Table 119 Incidence of Malignancy Events – Safety Grouping 5	225
Table 120 Incidence of Selected Malignancy Events (by High Level Term and Preferred Term) Occurring After \geq 6 Months of Treatment – Safety Grouping 5	226
Table 121 Subjects with Lung Neoplasm Diagnosis > 6 Months after Randomization – Safety Grouping 5	227
Table 122 Lung Cancer Risk Factors.....	228
Table 123 Subjects with Melanoma Diagnosis > 6 Months after Randomization – Safety Grouping 5	229
Table 124 Melanoma Risk Factors	229
Table 125 Adverse Events (by Preferred Term), Occurring in > 5% of Any Group – Safety Grouping 5, Treated Set.....	233
Table 126 Adverse Events (by Preferred Term), Occurring in > 5% of Any Group – Safety Grouping 3, Treated Set.....	233
Table 127 Treatment-Emergent Adverse Events (by System Organ Class and Preferred Term), Occurring in \geq 1% of Patients of the All Empagliflozin Group and Occurring More Frequently Among Empagliflozin-Treated Patients than Among Placebo-Treated Patients - Safety Grouping 5, Treated Set	234
Table 128 Treatment-Emergent Adverse Events (by System Organ Class and Preferred Term), Occurring in \geq 1% of Patients of the All Empagliflozin Group and Occurring More Frequently	

Among Empagliflozin-Treated Patients than Among Placebo-Treated Patients - Safety Grouping 3, Treated Set	236
Table 129 Treatment-Emergent Adverse Events (by System Organ Class and Preferred Term), Occurring in $\geq 1\%$ of Patients of the All Empagliflozin Group and Occurring More Frequently Among Empagliflozin-Treated Patients than Among Placebo-Treated Patients - Safety Grouping 5 Excluding Study 1245.25	241
Table 130 Treatment-Emergent Adverse Events (by System Organ Class and Preferred Term), Occurring in $\geq 1\%$ of Patients of the All Empagliflozin Group and Occurring More frequently Among Empagliflozin-Treated Patients than Among Placebo-Treated Patients – Safety Grouping 5, Completed Studies Only	243
Table 131 Treatment-Emergent Adverse Events (by System Organ Class and Preferred Term) in $\geq 1\%$ of Either Empagliflozin Dose and Occurring More Frequently Among Empagliflozin-Treated Patients than Among Placebo-Treated Patients – Pool of Pivotal Studies (at 24 Weeks) and Add-On to Basal Insulin Study (at 18 Weeks).....	246
Table 132 Median Change from Baseline – Hematocrit, Treated Set	248
Table 133 Incidence of Selected Categorical Shifts – Hematocrit, SAF-5, Treated Set	249
Table 134 Incidence of Thromboembolic Events - Safety Grouping 5	250
Table 135 Median Change from Baseline – Electrolytes, Treated Set	252
Table 136 Incidence of Selected Categorical Shifts – Electrolytes, Treated Set.....	254
Table 137 Percent of Patients with Possibly Clinically Significant Abnormalities – Selected Electrolytes, SAF-5	255
Table 138 Incidence of Treatment-Emergent Acid-Base Adverse Events – Safety Grouping 5	256
Table 139 Median Change from Baseline – Enzymes, Safety Grouping 5	258
Table 140 Incidence of Selected Categorical Shifts - Enzymes, Treated Set	261
Table 141 Percentage of Patients with Possibly Clinically Significant Abnormalities – Enzymes, Safety Grouping 5	262
Table 142 Incidence of Pancreatitis Events – SAF-5	263
Table 143 Median Change from Baseline – Serum Uric Acid, Safety Grouping 5.....	264
Table 144 Incidence of Categorical Shifts – Serum Uric Acid, Safety Grouping 5	264
Table 145 Mean Change from Baseline – Lipids, Treated Set (Observed Cases Including Values After Rescue Medication)	265
Table 146 Incidence in shifts from Values Within the Reference Range to Values Above the Upper Limit of the Reference Range - Lipids	267
Table 147 Median Change from Baseline – Blood Pressure, Safety Grouping 5.....	267
Table 148 Median Change from Baseline – Heart Rate, Safety Grouping 5.....	268
Table 149 Incidence of Adverse Events of Special Interest Over Time – Safety Grouping 5, Treated Set	271
Table 150 Incidence of Adverse Events by Age – Safety Grouping 5	273

Table 151 Incidence of Adverse Events by Gender – Safety Grouping 5	274
Table 152 Incidence of Adverse Events by Race – Safety Grouping 5.....	276
Table 153 Incidence of Adverse Events by Ethnicity – Safety Grouping 5	277
Table 154 Incidence of Adverse Events by Baseline Renal Function – Safety Grouping 5	280
Table 155 Changes in Estimated Glomerular Filtration Rate by Baseline Estimated Glomerular Filtration Rate – Safety Grouping 5.....	281
Table 156 Incidence of Adverse Events by Degree of Baseline Renal Impairment – Study 1245.36.....	283
Table 157 Subjects with Pregnancy While on Study Medication.....	285

Table of Figures

Figure 1 Molecular Structure of Empagliflozin.....	26
Figure 2 Studies Supporting the NDA	34
Figure 3 Forest Plot of Mean Change in Hemoglobin A1c – 24 Weeks, Efficacy Grouping 2, Full Analysis Set, Last Observation Carried Forward	45
Figure 4 Mean Change in Hemoglobin A1c – Efficacy Grouping 2, Full Analysis Set, Last Observation Carried Forward	48
Figure 5 Change in Fasting Plasma Glucose (mg/dL) – Efficacy Grouping 2, Full Analysis Set, Last Observation Carried Forward.....	50
Figure 6 Change in Body Weight – Efficacy Grouping 2, Full Analysis Set, Last Observation Carried Forward	52
Figure 7 Hourly Systolic Blood Pressure Profile – Study 1245.48, Baseline, Full Analysis Set, Last Observation Carried Forward Following Change in Antihypertensive Therapy	56
Figure 8 Hourly Diastolic Blood Pressure Profile – Study 1245.48, Baseline, Full Analysis Set, Last Observation Carried Forward Following Change in Antihypertensive Therapy	56
Figure 9 Hourly Systolic Blood Pressure Profile – Study 1245.48, Week 12, Full Analysis Set, Last Observation Carried Forward Following Change in Antihypertensive Therapy	57
Figure 10 Hourly Diastolic Blood Pressure Profile – Study 1245.48, Week 12, Full Analysis Set, Last Observation Carried Forward Following Change in Antihypertensive Therapy	57
Figure 11 Forest Plot of Change in Hemoglobin A1c by Baseline Renal Function – Efficacy Grouping 2, 24 Weeks Full Analysis Set, Last Observation Carried Forward.....	64
Figure 12 Change in Hemoglobin A1c Over Time – Study 1245.33, Full Analysis Set, Observed Cases at 78 weeks	80
Figure 13 Change in Hemoglobin A1c Over Time – Study 1245.36, Mild Renal Impairment, Full Analysis Set, Last Observation Carried Forward	81
Figure 14 Change in Hemoglobin A1c Over Time – Study 1245.36, Moderate Renal Impairment, Full Analysis Set, Last Observation Carried Forward	81
Figure 15 Change in Hemoglobin A1c Over Time – Study 1245.36, Severe Renal Impairment, Full Analysis Set, Last Observation Carried Forward	82
Figure 16 Safety Groupings	91
Figure 17 Forest Plot of Hazard Ratios for Four-Point Major Adverse Cardiovascular Events – Cox Regression	169
Figure 18 Kaplan-Meier Plot for Nonfatal Stroke – Treated Set.....	171
Figure 19 Kaplan-Meier Plot for Fatal and Nonfatal Stroke – Treated Set	171
Figure 20 Kaplan-Meier Plot for Fatal and Nonfatal Stroke – Study 1245.25, Treated Set.....	172

Figure 21 Kaplan-Meier Plot for Four-Point Major Adverse Cardiovascular Events – Treated Set	172
Figure 22 Kaplan-Meier Plot for Four-Point Major Adverse Cardiovascular Events – Study 1245.25, Treated Set	173
Figure 23 Four-Point Major Adverse Cardiovascular Events and Fatal/Nonfatal Stroke in the First 180 Days – Cardiovascular Meta-Analysis Pool.....	174
Figure 24 Excerpt from Dr. Jennie Chang’s Consult Review	230
Figure 25 Summary of Corrected QT Interval Findings from Study 1245.16.....	269
Figure 26 Adverse Events of Special Interest Over the First 180 Days – Safety Grouping 5	272

Abbreviations

25-OH vitamin D	25-hydroxy cholecalciferol
ADA	American Diabetes Association
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the curve
BMI	Body mass index
CEC	Clinical events committee
CHF	Congestive heart failure
CI	Confidence interval
Cmax	Concentration maximum
CMQ	Customized MedDRA query
CV	Cardiovascular
CVOT	Cardiovascular outcomes trial
CTD	Common technical document
DARRTS	Document Archiving, Reporting and Regulatory Tracking System
DBP	Diastolic blood pressure
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DPP-4	Dipeptidyl peptidase-4
eCTD	Electronic Common Technical Document
EFF-1	Efficacy Grouping 1
EFF-2	Efficacy Grouping 2
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
Empa	Empagliflozin
FAS	Full analysis set
FAS (OC)	Full analysis set, observed cases
FAS (OC-IR)	Full analysis set, observed cases including values after rescue medication
FAS78-completers	Full analysis set of patients who did not prematurely discontinue prior to 78 weeks, completed minimum treatment duration, and

	had on-treatment HbA1c within 78 weeks window
FDA	Food and Drug Administration
FDC	Fixed dose combination
FPG	Fasting plasma glucose
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transpeptidase
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c/glycosylated hemoglobin
HDL	High density lipoprotein cholesterol
HLT	Medical Dictionary for Regulatory Activities High Level Term
ICH	International Conference on Harmonisation
ICH E3	International Conference on Harmonisation: Structure and content of clinical study reports
IND	Investigational new drug
iPTH	Intact parathyroid hormone
ISE	Integrated Summary of Efficacy (appendix to Summary of Clinical Efficacy)
ISS	Integrated Summary of Safety (appendix to Summary of Clinical Safety)
LDL	Low density lipoprotein cholesterol
LL	Lower limit
LLRR	Lower limit of the reference range
LOCF	Last observation carried forward
LOCF-H	Last observation carried forward following change in antihypertensive therapy
LVOT	Last value on treatment
MACE	Major adverse cardiovascular event
Mdn	Median
MDRD	Modification of diet in renal disease
MedDRA	Medical Dictionary for Regulatory activities
MI	Myocardial infarction
MMRM	Mixed-effects model repeated measures
NA	Not applicable
NCF	Noncompleters considered failure
NDA	New Drug Application
NEC	Not elsewhere classified
NOAEL	No observed adverse effect level
Non-HDL	Non-high density lipoprotein cholesterol

NR	Not reported
OLS	Open-label set
Per 100	Events per 100 patient-years
Per 1000	Events per 1000 patient-years
PG	Plasma glucose
PI	Principal investigator
PK	Pharmacokinetics
PPS	Per-protocol set
PT	Medical Dictionary for Regulatory Activities Preferred Term
Q1	First quartile
Q3	Third quartile
SAE	Serious adverse event
SAF-3	Safety Grouping 3
SAF-5	Safety Grouping 5
SBP	Systolic blood pressure
SCE	Summary of clinical efficacy
SCS	Summary of clinical safety
SD	Standard deviation
SE	Standard error
SGLT2	Sodium-dependent glucose co-transporter-2
SMQ	Standardized Medical Dictionary for Regulatory Activities Query
SOC	Medical Dictionary for Regulatory Activities System Organ Class
Sub-I	Sub-investigator
T2DM	Type 2 diabetes mellitus
TG	Triglycerides
TIA	Transient ischemic attack
TS	Treated set
TS actual	Treated set- actual
TZD	Thiazolidinedione
U NTX: Cr	Urine N-telopeptide: creatinine ratio
UL	Upper limit
ULRR	Upper limit of reference range
WRR	Within the reference range

1. Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

I recommend approval of empagliflozin for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM) at both the 10 mg and 25 mg dose. While the Applicant has only requested approval of the 25 mg dose, I feel that there is support for approval of the 10 mg dose as well. For patients suitable for empagliflozin, treatment should be started at 10 mg once daily. The dose can be increased to 25 mg once daily, but should be done cautiously in elderly patients and in patients with moderate renal impairment.

1.2 Risk Benefit Assessment

While there are a number of therapeutic products available for use in treating T2DM, there remains a need for new therapies. To evaluate the benefits of empagliflozin versus the risks of empagliflozin, it is first necessary to discuss the expected benefits and the potential risks.

The Applicant has shown empagliflozin to be effective in reducing glycosylated hemoglobin (HbA1c) as monotherapy and as add-on to a variety of antidiabetic regimens (including metformin, metformin + sulfonylureas, pioglitazone, and basal insulin). In the pivotal phase 3 studies, the mean placebo-adjusted change in HbA1c ranged from -0.48% to -0.73% with empagliflozin 10 mg and from -0.59 to -0.84% with empagliflozin 25 mg. This translates to improved glycemic control which should lead to a reduction in diabetic complications, based on the likely benefits of glycemic control demonstrated in such trials as the Diabetes Control and Complications Trial¹ and the United Kingdom Prospective Diabetes Study². Empagliflozin also showed a mean reduction in body weight compared to placebo, which is an important difference compared to antidiabetic agents from some other classes. While the 25 mg dose demonstrated a numerically greater reduction in HbA1c than the 10 mg dose, the difference between the two doses is of questionable statistical and clinical significance.

There were adverse events seen with a greater incidence in the empagliflozin-treated patients compared to the placebo/comparator-treated patients. There was an increased incidence of

¹ Nathan DM, et al. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005; 353 (25): 2643-2653.

² Holman RR, et al. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; 359 (15): 1577-1589.

genitourinary infections, particularly mycotic infections, with empagliflozin treatment. These were treatable with standard therapies in the development program. Additional adverse events (AEs) seen more frequently with empagliflozin included dry mouth, thirst, and increased urination. Increased age appears to be a factor which increases the risk for these AEs, particularly with the 25 mg dose. Decreases in renal function were seen with empagliflozin therapy, particularly in patients of increased age or with moderate renal impairment at baseline. The observed changes in renal function with empagliflozin treatment appear to be reversible following cessation of therapy. I feel that these issues are primarily tolerability issues, and they do not generate sufficient concern to offset the expected benefit from improved glycemic control. In considering the dose for approval, it is notable that the 10 mg dose demonstrated a lower incidence for some of these events compared to the 25 mg dose, particularly in patients of increased age and/or with renal impairment at baseline.

Additional safety concerns that were considered during this review include the effect of empagliflozin on the liver, and on the development of malignancies.

While there was no evident imbalance in the reported liver adverse events, an imbalance in the number of patients with liver enzyme elevations between empagliflozin and placebo/comparator was seen in the development program. More patients receiving empagliflozin met the biochemical criteria for Hy's law¹, but all of these cases could be plausibly explained as a result of an alternative etiology. There does not appear to be a risk of severe, acute drug-induced liver injury with empagliflozin based on the clinical data presented.

A small imbalance in certain malignancy events was seen in the development program. There were more cases of lung cancer and more cases of melanoma occurring after 6 months of treatment in the empagliflozin-treated patients than in the placebo/comparator-treated patients. The initial imbalance was concerning as zero patients reported these events in the comparator arms, but further review of the cases assuaged my concern for potential carcinogenicity with empagliflozin. Most of the cases had pre-existing risk factors for these malignancies. There is also no mechanistic basis for the development of lung cancer or melanoma with empagliflozin. There does not appear to be a clear risk of carcinogenicity with empagliflozin based on the data presented.

¹Hy's law: (1) the drug causes hepatocellular injury, generally shown by more frequent $\geq 3x$ elevation above the upper limit of the reference range (ULRR) in alanine aminotransferase or aspartate aminotransferase, (2) Subjects with transaminases $> 3x$ ULRR also show elevation of total bilirubin $> 2x$ ULRR without findings of cholestasis (i.e. alkaline phosphatase $< 2x$ ULN), and (3) no other reason can be found to explain the laboratory abnormalities

Cardiovascular safety is discussed in more detail in a separate section from the main review, due to inclusion of interim data from an ongoing cardiovascular outcomes trial and the need to protect the integrity of that trial. A preplanned meta-analysis of major adverse cardiovascular events, which includes interim data from the ongoing cardiovascular safety study, excluded an upper bound of 1.8 for the 95% confidence interval.

Hypoglycemia is a concern with any antidiabetic therapy. In the empagliflozin development program, there was no increased risk for hypoglycemia when empagliflozin was used as monotherapy. There was an increased incidence in hypoglycemia when empagliflozin was added to antidiabetic agents with hypoglycemic potential (i.e. sulfonylureas). Adjustment to sulfonylurea and/or insulin doses should be considered when adding empagliflozin to either of these agents, to mitigate this risk.

Some changes in laboratory tests were seen with empagliflozin treatment. There was an increase in low density lipoprotein cholesterol (LDL), total cholesterol (TC) and high density lipoprotein cholesterol (HDL). Increases in hematocrit were also seen. Other laboratory test changes included increases in serum phosphate and serum lipase, and decreases in serum bicarbonate. There was no evident clinical effect from these changes.

Based on review of the available data, I feel that empagliflozin should be approved. The expected benefit from improved glycemic control exceeds the potential risks of therapy. Though only the 25 mg dose is proposed by the Applicant, I feel that both of the studied doses (i.e. 10 mg and 25 mg) should be approved.

For the 10 mg dose, the Applicant has demonstrated proven efficacy in reducing HbA1c, and a safety profile that does not suggest serious risks that would exceed the expected benefit with therapy. Though the difference in HbA1c reduction of the 25 mg dose compared to the 10 mg dose does not achieve statistical significance, it is important to note that this is based on a mean and that there will be some patients who could have further clinically significant reduction in HbA1c with this dose. The greater percentage of patients achieving the target HbA1c of < 7.0% also supports approval of the 25 mg dose. Though there is an increase in the incidence of some AEs with the 25 mg dose, these appear to be more issues of tolerability and not serious safety concerns. Limiting the 25 mg dose to patients who are not elderly or do not have renal impairment may mitigate some of the observed increases in adverse events with the 25 mg dose.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I do not recommend a risk evaluation and mitigation strategy for this therapeutic agent. An enhanced pharmacovigilance plan could be considered, with a particular focus on hepatic injury, and malignancy events.

1.4 Recommendations for Postmarket Requirements and Commitments

Postmarketing requirements that I would propose include further study of the 10 mg dose in patients with moderate renal impairment, studies in pediatric patients, and completion of the ongoing CVOT (Study 1245.25). Safety and efficacy have not been demonstrated in patients with hepatic impairment, and would require further study if the Applicant wishes to include labeling for this population. Additionally, further study on the safety and efficacy of empagliflozin in Black patients may be needed.

2. Introduction and Regulatory Background

2.1 Product Information

Empagliflozin is a sodium-dependent glucose co-transporter-2 (SGLT2) inhibitor developed for use in the treatment of T2DM. Type 2 diabetes mellitus is a disease of impaired glucose regulation due to impaired insulin action and insulin resistance. Management of T2DM focuses on glycemic control, and involves lifestyle changes (diet and exercise) as well as use of currently available antidiabetic drugs (see 2.2). Sodium-dependent glucose co-transporter-2 is a transporter found in the proximal renal tubule, and is responsible for renal glucose reabsorption. Inhibition of this transporter increases glucosuria which in turn should result in improved glycemic control.

2.2 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 (TZDs)
- Meglitinides

- Dipeptidyl peptidase-4 (DPP-4) inhibitors
- Glucagon-like peptide-1 (GLP-1) analogues
- SGLT2 inhibitor
- Alpha-glucosidase inhibitors
- Amylin-mimetics
- Dopamine agonist (i.e. bromocriptine)
- Insulin and insulin analogues
- Bile acid sequestrant (i.e. colestevam hydrochloride)

2.3 Availability of Proposed Active Ingredient in the United States

As of October 25, 2013, empagliflozin is not approved for marketing in the United States or in any other country. It is only available through participation in clinical studies.

2.4 Important Safety Issues with Consideration to Related Drugs

Two other SGLT2-inhibitors have been reviewed as New Drug Applications: dapagliflozin and canagliflozin.

A Complete Response was issued for dapagliflozin on January 17, 2012 due to concerns of malignancy (specifically bladder cancer) and liver toxicity. Dapagliflozin was approved in Australia on October 5, 2012 and by the European Medicines Agency (EMA) on November 12, 2012.

Canagliflozin was approved by the FDA on March 29, 2013. Issues discussed at the Advisory Committee for canagliflozin included reduced efficacy with impaired renal function, development of decreased renal function and renal adverse events (including hyperkalemia), volume depletion events, changes in bone turnover markers, an imbalance in fractures (especially in upper limb fractures), increased risk of genital mycotic infections, effects on lipids (i.e. increases in low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), and non-HDL), and an imbalance in early cardiovascular (CV) events. Post-marketing requirements for canagliflozin include a cardiovascular outcomes study, pediatric studies, a bone safety study, and an enhanced pharmacovigilance program.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Table 1 Summary of Presubmission Regulatory Activity

April 10, 2008	IND-102145 submitted to the Food and Drug Administration
May 4, 2010	End-of-Phase 2 meeting <ul style="list-style-type: none">- Main topics of discussion were bridging of phase 2 and phase 3 clinical supplies, the adequacy of the proposed clinical pharmacology program (particularly drug-drug interactions), adequacy of nonclinical data, the design of the proposed phase 3 clinical trials, and plans to address potential safety issues
July 10, 2012	Agreement on plan for cardiovascular safety meta-analysis
November 27, 2012	Pre-NDA meeting <ul style="list-style-type: none">- Main topics of discussion were proposed content and format of modules 3 to 5, content of the 4 month safety update, and proposed pediatric studies.
March 5, 2013	NDA-204629 submitted to the Food and Drug Administration

2.6 Other Relevant Background Information

None.

3. Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

No single investigator enrolled large numbers of patients compared to other sites. Two study sites were terminated for possible serious noncompliance. The Applicant reports that data from these two sites did not impact conclusions on efficacy or safety. One site closure was reported for failure to adhere to Good Clinical Practice after submission of the NDA. A total of fifteen sites were selected for inspection, covering six of the phase 3 studies (Studies 1245.19, 1245.20, 1245.23_{met}, 1245.23_{met+SU}, 1245.28, 1245.33, 1245.36). No violations that might affect the integrity of the development program were reported at the time this review was completed.

3.2 Compliance with Good Clinical Practices

The Applicant states that all clinical studies followed the International Conference on Harmonisation (ICH) Harmonised Tripartite Guidelines for Good Clinical Practice (GCP), and conformed to the Declaration of Helsinki.

As part of the Applicant's monitoring and quality assurance activities, the Applicant identified two study sites in the United States with possible serious noncompliance. One site participated in Study 1245.23 and the extension Study 1245.31. The other site participated in Study 1245.25. Study activities were terminated at both sites. The Applicant reports that data from these two sites did not impact conclusions on the efficacy or safety of empagliflozin.

3.3 Financial Disclosures

The clinical studies covered by the submitted financial disclosure certification are Studies: 1245.19, 1245.20, 1245.23, 1245.25, 1245.28, 1245.31, 1245.33, 1245.36, and 1245.48.

The Applicant has submitted a list of investigators for whom they have certified that: (1) they have not entered into any financial arrangement whereby the value of compensation to the investigator could be affected by the outcome of the study, (2) that the listed clinical investigators did not have proprietary interest in the product or significant equity in the Applicant, and (3) that no listed investigator was the recipient of significant payments.

Also included in this submission is a listing of investigators for which the Applicant cannot provide certification of the above. The majority of these are due to either no patients being enrolled, the study not being initiated by the investigator, or inability to contact the investigator as they are no longer at the site or on an extended leave of absence. A small number have incomplete financial disclosure questionnaires which were pending completion at the time of NDA submission.

A list of seven investigators with financial interests requiring disclosure is also submitted (Table 2). Included for these seven investigators are additional details of the financial disclosures. All of these investigators participated in large multinational studies, and each was responsible for only a small number of patients in a given study. The small contribution from each investigator minimizes the potential for bias, as does the use of a central adjudication committee for evaluation of MACE, the double-blind nature of the studies involved, and the use of a central laboratory for measurement of HbA1c (the primary endpoint).

Table 2 Investigators with Financial Disclosures

Investigator Name	Role	Study	Reason
(b) (6)	PI	(b) (6)	Lilly Advisory Board payments made to Institution > \$25K
	Sub-I		Spouse employed by Eli Lilly and has company stock > \$50K
	PI		Boehringer Ingelheim speaker honoraria > \$25K
	PI		Speaker honoraria > \$25K
	PI		Speaker honoraria > \$25K
	PI		Anticipated honoraria > \$25K, but did not receive honoraria > \$25K
	PI		Amount > \$25K

PI = principal investigator; Sub-I = sub-investigator

Source: Financial Certification and Disclosure submitted to Module 1.3.4 of the Electronic Common Technical Document

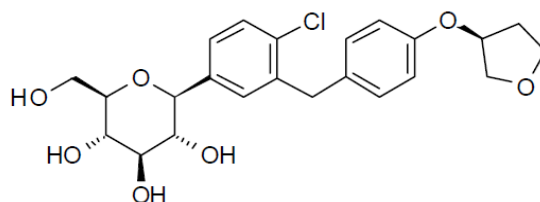
4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

For detailed review of the Chemistry, Manufacturing, and Controls refer to the review by Joseph Leginus.

Empagliflozin is a selective inhibitor of SGLT2, and is a new chemical entity (Figure 1). The molecular formula is $C_{23}H_{27}ClO_7$ and the molecular weight is 450.91 g/mol.

Figure 1 Molecular Structure of Empagliflozin



Source: Figure 1 (Quality Overall Summary)

Synthesis of empagliflozin is

(b) (4)

Stability of empagliflozin film-coated tablets in the proposed container closure system has been demonstrated in tests of 24-month long-term stability, 6-month accelerated stability, and stress stability.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

For detailed review of the Preclinical Pharmacology/Toxicology refer to the review by Mukesh Summan.

Primary toxicological species used in the toxicology studies were rats and dogs as empagliflozin is pharmacologically active in these species and the metabolic pattern of humans is represented in these species. Based on single dose studies in rodents, the acute toxicity in rats was low as indicated by a lethal dose of > 2000 mg/kg. Exposures achieved in chronic studies in mice, rats, and dogs were up to 62x, 35x, and 240x (respectively) of those seen with the maximum recommended human dose of 25 mg once daily.

Across the different species, toxicity was consistent with the mechanism of action. In addition to the expected urinary glucose loss, other findings included polyuria, decreased body weight/fat, increased food consumption, diarrhea, dehydration, decreased serum glucose, electrolyte imbalances, and increases in parameters reflecting increased protein catabolism and gluconeogenesis. Changes were consistently observed in the kidneys, and included tubular karyomegaly, cell necrosis, cystic hyperplasia/hypertrophy, renal mineralization, and tubular nephropathy and interstitial nephritis. Based on toxicology studies in male mice, male rats, and dogs, the no observed adverse effect level (NOAEL) for systemic toxicity was 47x, 10x, and 18x (respectively) the exposure expected to be seen with a daily therapeutic dose of 25 mg once daily.

Two-year carcinogenicity studies were performed in CD-1 mice and Wistar (Han) rats. In female CD-1 mice, there was no evidence of carcinogenic potential at doses up to 100 mg/kg/day (62x the clinical exposures in humans at 25 mg once daily). In male CD-1 mice, empagliflozin-related renal adenoma/carcinoma occurred at doses of 1000 mg/kg/day but not at doses of 300 mg/kg/day (11x the clinical exposures in humans at 25 mg once daily). In female Wistar rats, the evidence of carcinogenicity was seen at doses up to 700 mg/kg/day (72x the clinical exposures in humans at 25 mg once daily). In male Wistar rats, benign vascular tumors

(hemangiomas) of the mesenteric lymph nodes were seen at doses of 700 mg/kg/day, but this was not seen at 300 mg/kg/day (26x the clinical exposures in humans at 25 mg once daily). It is noted that these tumors are common in the male Wistar rat, and the relevance of this finding is unclear. Benign testicular interstitial cell tumors were observed in the male rats at doses of 300 and 700 mg/kg/day, but the incidence was not dose-related and there was no associated hyperplasia. The applicant postulates that these tumors are secondary to severe body weight loss. Similar findings were seen in the canagliflozin development program.

Developmental and reproductive toxicity was studied in rats and rabbits. There were no effects on fertility or early embryonic development in rats at exposures ≥ 155 x the clinical exposures in humans at 25 mg once daily. Teratogenicity was not seen with empagliflozin in rats or rabbits at exposures > 48 x the clinical exposures in humans at 25 mg once daily. The pre- and post-natal development toxicity study showed the NOAEL for maternal systemic toxicity and for growth of the F1 generation was 16x and 1x the clinical exposures in humans at 25 mg once daily. Empagliflozin has not been found to be a dermal sensitizer, dermal irritant, or ocular irritant. No potential for phototoxicity was seen.

Evaluation of impurities did not identify any genotoxic potential. No immunotoxic potential has been seen for empagliflozin.

4.4 Clinical Pharmacology

For detailed review of the Clinical Pharmacology refer to the review by Manoj Khurana.

4.4.1 Mechanism of Action

Approximately 90% of renally filtered glucose is reabsorbed via SGLT2 in the proximal tubule. Inhibiting SGLT2 decreases renal reabsorption of glucose leading to increased urinary glucose excretion and, as a result, reduced blood glucose levels. Empagliflozin is an oral, selective SGLT2 inhibitor developed to utilize this pathway in the treatment of patients with T2DM. The action of empagliflozin is independent of β -cell function and insulin.

4.4.2 Pharmacodynamics

Urinary glucose excretion was increased in a dose-dependent manner in patients with T2DM who were given empagliflozin, and the average renal glucose threshold decreased in a dose-dependent manner (Table 3). With this increase in urinary glucose excretion, there was an increase in mean urine volume, and an increase in urinary frequency (one to two voids per day).

Table 3 Dose-Dependent Changes in Renal Glucose Handling

Dose (mg)	Glucose Reabsorption Inhibition (%)	Average Renal Glucose Threshold (mg/dL)
Placebo	NA	230
1	NR	100.5
2.5	39	NR
10	46	43.8
25	58	33.1
100	64	26.0

NA = not applicable; NR = not reported

Source: Section 1.4 (Summary of Clinical Pharmacology)

Plasma glucose was reduced in empagliflozin-treated groups compared to placebo. Fasting plasma glucose (FPG) decreased after a single dose, and this was maintained over the treatment period.

Studies of the QT interval did not demonstrate QT(c) interval prolongation following single oral doses of empagliflozin (therapeutic (25 mg) and supra-therapeutic (200 mg)). This is further discussed in Section 7.4.4.

4.4.3 Pharmacokinetics

Following oral administration in healthy volunteers and in patients with T2DM, empagliflozin is rapidly absorbed and reaches peak plasma concentrations (C_{max}) at 1.5 hours after the dose. With a 25 mg dose given once daily, mean steady state plasma area under the curve (AUC) was 4740 nmol*h/L with a C_{max} of 687 nmol/L. Administration following a high-fat, high-calorie meal resulted in slightly lower exposures (AUC -16%, C_{max} -37% compared to administration in the fasting state).

No major metabolites of empagliflozin were detected in human plasma. The most abundant metabolites were glucuronide conjugates (2-O, 3-O, and 6-O glucuronide). Exposure to each metabolite was < 10% of the total drug-related material. The primary route of metabolism is glucuronidation by uridine 5'-diphospho-glucuronosyltransferases.

The elimination half-life of empagliflozin is 12.4 hours with an oral clearance of 10.6 L/h. Steady state plasma concentrations are reached by the 5th dose with once daily dosing.

Renal function affects plasma levels of empagliflozin. The AUC of empagliflozin increased by 18%, 20%, 66%, and 48% when administered to patients with mild renal impairment (estimated glomerular filtration rate (eGFR) < 90 ml/min/1.73 m²), moderate renal impairment (eGFR < 60 ml/min/1.73 m²), severe renal impairment (eGFR < 30 ml/min/1.73 m²), and end-stage renal disease, respectively. From population pharmacokinetic (PK) analysis, oral clearance of empagliflozin decreases with eGFR which results in increased drug exposure (AUC increased by 18.5%, 49.2%, and 88.1% in patients with eGFR of 60, 30, and 15 ml/min/1.73 m², respectively).

Hepatic function also affects plasma levels of empagliflozin. In a single-dose study in subjects with varying degree of hepatic impairment (i.e. Study 1245.13), the AUC of empagliflozin increased by 23%, 47%, and 75% while C_{max} increased by 4%, 23%, and 48% with mild, moderate, and severe hepatic impairment (by Child-Pugh classification), respectively. Notably, the increases in AUC did not correlate with increases in urinary glucose excretion. The Applicant does not feel that these changes are meaningful and recommends no dose adjustment in liver disease.

Other intrinsic factors studied include gender, age, race, and body mass index (BMI). None of the observed changes with any of these factors was felt to be clinically meaningful by the Applicant.

Drug-drug interaction studies showed similar PK profiles for empagliflozin when given with or without metformin, glimepiride, pioglitazone, sitagliptin, linagliptin, simvastatin, warfarin, verapamil, ramipril, hydrochlorothiazide, and torsemide. Small increases in overall clinical exposure were noted when empagliflozin was coadministered with gemfibrozil, rifampin, and probenecid. No clinically relevant effect was seen on PK profile for metformin, glimepiride, sitagliptin, linagliptin, simvastatin, warfarin, ramipril, digoxin, hydrochlorothiazide, torsemide, or oral contraceptives when coadministered with empagliflozin. Mixed results were seen for the PK profile of pioglitazone when coadministered with empagliflozin. One of two studies showed an increase in the overall exposure of pioglitazone and its metabolites when coadministered with empagliflozin 50 mg. The second study showed no clinically relevant effect of empagliflozin (10, 25, or 50 mg) coadministered with pioglitazone on the PK profile of pioglitazone and its metabolites.

5. Sources of Clinical Data

5.1 Tables of Studies/Clinical Studies

Table 4 is a listing of all the clinical studies performed by the Applicant to support the NDA. Some of these studies are not pertinent to this review and they will not be discussed. They are included for completeness. The studies which the Applicant feels are essential to support the NDA are presented in Figure 2.

Table 4 Listing of Clinical Studies

Study Number	Study Objective
Bioavailability Studies:	
1245.3	To investigate the effect of food on the bioavailability and pharmacokinetics of empagliflozin
1245.79	To investigate the effect of food on the bioavailability of empagliflozin and to assess the dose proportionality of empagliflozin 10 mg and 25 mg tablets under fasting conditions
Bioequivalence Studies:	
1245.51	To determine the bioequivalence of the study formulation and final formulation
1275.3	To determine the relative bioavailability of 2 formulations of empagliflozin 25 mg/linagliptin 5 mg FDC compared with coadministration of the individual tablets, and to assess the effect of food on the bioavailability of the FDC
1276.5	To determine the relative bioavailability of empagliflozin 12.5 mg/metformin 1000 mg FDC compared with coadministration of the individual tablets, and to assess the effect of food on the availability of the FDC
1276.9	To investigate the influence of different dosage regimens on the steady state pharmacokinetics and pharmacodynamics of empagliflozin administered orally
Pharmacokinetic Studies:	
1245.1	To investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of empagliflozin
1245.2	To investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of empagliflozin after multiple doses
1245.5	To evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of single rising doses of empagliflozin
1245.6	To investigate possible drug-drug interactions between empagliflozin and metformin after coadministration of multiple oral doses
1245.7	To investigate possible drug-drug interactions between empagliflozin and glimepiride after coadministration of multiple oral doses
1245.8	To determine the pharmacokinetics and total radioactivity of empagliflozin, including excretion mass balance, excretion pathways, and metabolism after oral administration of a [¹⁴ C] empagliflozin solution
1245.12	To assess the effect of kidney function in patients with type 2 diabetes on pharmacokinetics, pharmacodynamics and safety of empagliflozin

Study Number	Study Objective
1245.13	To assess the effect of liver function in patients with type 2 diabetes on pharmacokinetics, pharmacodynamics and safety of empagliflozin
1245.17	To investigate possible drug-drug interactions between empagliflozin and pioglitazone after coadministration of multiple oral doses
1245.18	To investigate a possible drug-drug interaction between empagliflozin and warfarin when coadministered
1245.27	To investigate possible drug-drug interactions between empagliflozin and sitagliptin after coadministration of multiple oral doses
1245.30	To investigate possible drug-drug interactions between empagliflozin and linagliptin after coadministration of multiple oral doses
1245.40	To evaluate the effect of multiple doses of empagliflozin on the single dose pharmacokinetics of digoxin (model P-gp substrate)
1245.41	To evaluate the effect of multiple oral doses of empagliflozin on the steady state pharmacokinetics of ethinyl estradiol and levonorgestrel
1245.42	The effect of empagliflozin given alone and with hydrochlorothiazide or torsemide on electrolytes, water balance, activation of the renin-angiotensin-aldosterone system, acid-base balance, glucose metabolism, bone metabolism, and body weight. The effect of empagliflozin on micturition frequency and muscle sympathetic nerve activity
1245.43	To investigate a possible drug-drug interaction between empagliflozin and the model P-gp inhibitor verapamil when coadministered as a single oral dose
1245.44 ¹	To investigate the pharmacokinetics, pharmacodynamics, safety, and tolerability of empagliflozin as single dose or multiple doses in Chinese patients with type 2 diabetes mellitus - China-specific study
1245.45	To investigate possible drug-drug interactions between empagliflozin and ramipril when coadministered as multiple oral doses
1245.50	To investigate the effect of different doses of empagliflozin on the bioavailability of pioglitazone after multiple oral doses of both drugs
1245.58	To investigate possible drug-drug interaction between empagliflozin and gemfibrozil when coadministered
1245.63	To investigate a possible drug-drug interaction between empagliflozin and simvastatin
1245.83	To investigate a possible drug-drug interaction between single dose of empagliflozin and single dose of rifampicin and multiple doses of probenecid
Pharmacodynamic Studies:	
1245.4	To investigate the safety, tolerability, pharmacokinetics and pharmacodynamics of empagliflozin for 28 days
1245.16	To demonstrate that empagliflozin does not prolong the QT(c) interval compared to placebo
Efficacy and Safety Studies:	
1245.9	To evaluate the efficacy, safety, and pharmacokinetics of 3 different doses of empagliflozin in patients with type 2 diabetes and insufficient glycemic control
1245.10	To evaluate the efficacy, safety, and pharmacokinetics of 5 different doses of empagliflozin in patients with type 2 diabetes, insufficient glycemic control, and metformin background medication
1245.15 ¹	To evaluate the pharmacokinetics, pharmacodynamics, safety, and tolerability of empagliflozin administered for 28 days in Japanese patients with type 2 diabetes - Japan-specific study

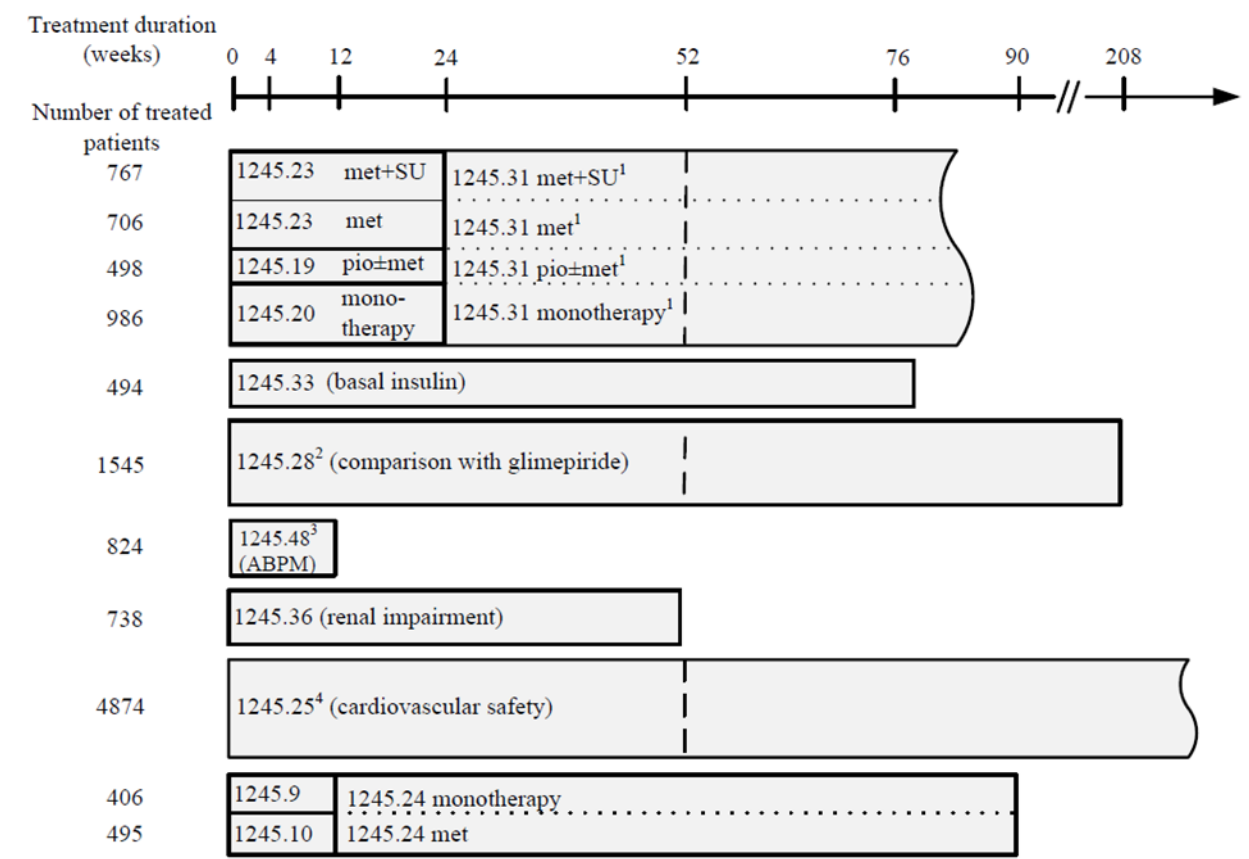
Study Number	Study Objective
1245.19 ²	To investigate the efficacy, safety, and tolerability of empagliflozin given for 24 weeks as add-on therapy to pioglitazone alone or pioglitazone in combination with metformin in patients with type 2 diabetes with insufficient glycemic control
1245.20 ²	To investigate the efficacy, safety and tolerability of empagliflozin compared with placebo and sitagliptin given for 24 weeks as monotherapy in drug-naïve patients with type 2 diabetes and insufficient glycemic control To assess through an open-label arm the efficacy and safety of empagliflozin in patients with type 2 diabetes and very poor glycemic control (HbA1c > 10%)
1245.23 ^{2,3}	To investigate the efficacy, safety and tolerability of empagliflozin compared with placebo given for 24 weeks as add-on therapy with metformin in patients with type 2 diabetes and insufficient glycemic control To investigate the efficacy, safety and tolerability of empagliflozin compared with placebo given for 24 weeks as add-on therapy with metformin plus sulfonylurea in patients with type 2 diabetes and insufficient glycemic control To assess through an open-label arm the efficacy and safety of empagliflozin in patients with type 2 diabetes and very poor glycemic control (HbA1c > 10%)
1245.24	To investigate the safety of empagliflozin during open-label long-term treatment and the efficacy of empagliflozin as monotherapy and add-on therapy to metformin
1245.28	To investigate the efficacy, safety and tolerability of empagliflozin compared with glimepiride administered over 52 and 104 weeks as add-on therapy to immediate release metformin with a 104 week extension period in patients with type 2 diabetes and insufficient control despite treatment with metformin
1245.31	To investigate the long-term efficacy, safety and tolerability of empagliflozin in patients with type 2 diabetes compared with sitagliptin or placebo as monotherapy (see Study 1245.20), with placebo on a background of pioglitazone (see Study 1245.19), and with placebo on a background of metformin +/- sulfonylurea (see Study 1245.23)
1245.33	To investigate the safety, efficacy, tolerability, and pharmacokinetics of empagliflozin given for 78 weeks in combination with background basal insulin therapy
1245.36	To investigate the efficacy, safety and tolerability of empagliflozin as add-on to pre-existing antidiabetic therapy compared with placebo in patients with type 2 diabetes, insufficient glycemic control, and different degrees of renal impairment over 52 weeks
1245.38 ¹	To investigate the efficacy and safety of empagliflozin administered for 12 weeks as monotherapy To evaluate the long-term safety of empagliflozin in a 40 week extension study by rerandomizing patients previously treated with 5 mg or 50 mg of empagliflozin or placebo in the first 12 weeks to empagliflozin 10 mg or 25 mg - Japan-specific study
1245.48	To investigate the efficacy, safety and tolerability of empagliflozin compared with placebo in patients with type 2 diabetes and hypertension over 12 weeks
Safety Studies:	
1245.25	To demonstrate non-inferiority for empagliflozin compared with placebo with respect to first occurrence of the adjudicated components of the composite MACE endpoint in patients with type 2 diabetes and increased cardiovascular risk

¹Study enrolling only non-U.S. patients; ²Denoted by the Applicant as a pivotal study; ³Study 1245.23 is considered as two studies (1245.23_{met} and 1245.23_{met+SU})

FDC = fixed-dose combination; HbA1c = hemoglobin A1c; MACE = major adverse cardiovascular event

Source: Table 1.1.1: 1 (Summary of Clinical Safety)

Figure 2 Studies Supporting the NDA



ABPM = ambulatory blood pressure monitoring, met = metformin, SU = sulphonylurea, pio = pioglitazone
The total numbers of patients treated with trial medication and included in the evaluation of safety are provided.
For trials 1245.31, 1245.28, and 1245.25, all data up to the respective interim database lock (see below) were used for safety analyses; for efficacy, analyses are presented for up to 52 weeks of treatment (i.e. including the treatment in the trials preceding 1245.31) as indicated by the dashed vertical lines.
¹ Trials 1245.31: interim database lock on 29 May 2012. The wavy line indicates that the planned treatment duration is flexible; it is planned to be at least 52 weeks in the extension trial (plus the 24 weeks from the initial trial).
² Trial 1245.28: interim database lock on 31 August 2012. The planned treatment duration is 104 weeks plus a 104-week extension treatment period.
³ Trial 1245.48 was conducted in patients with diabetes and hypertension.
⁴ Trial 1245.25: interim database lock on 31 August 2012. The wavy line indicates that the planned treatment duration is flexible (about 6 to 8 years) and dependent on the number of cardiovascular events accrued. Recruitment for this trial is still ongoing.

Source: Figure 1.3.2: 1 (Clinical Overview)

5.2 Review Strategy

Review of this NDA was initially guided by the information presented in the submitted clinical overview, summary of clinical efficacy (SCE), and summary of clinical safety (SCS). The appendices to the SCE and SCS (i.e. the integrated summary of efficacy (ISE) and integrated summary of safety (ISS)) were referenced as needed. Issues and concerns identified from the clinical summaries were addressed by in-depth review of the submitted study reports, narratives and datasets. The efficacy data from the pivotal phase 3 trials were reviewed individually and as a pool. Safety findings from the pooled pivotal phase 3 trials and from the larger pool of all patients with T2DM were reviewed.

All of the submitted narratives for deaths and nonfatal serious adverse events (SAEs) were reviewed. For adjudicated cardiovascular events, cases were randomly selected for review to evaluate the adjudication process. For review of the incidence of adverse events, the submitted AE datasets (AE.xpt files) and demographic datasets (DM.xpt files) were merged and reviewed.

5.3 Discussion of Individual Studies/Clinical Studies

The Applicant identifies four studies as pivotal studies: 1245.19, 1245.20, 1245.23_{met}, and 1245.23_{met+SU}. These studies were 24-week, randomized, double-blind, placebo-controlled studies with change in HbA1c as the primary endpoint. Two doses were studied in these studies (10 mg and 25 mg). Study 1245.19 compared empagliflozin with placebo as add-on to pioglitazone (with or without metformin). Study 1245.20 compared empagliflozin with placebo as monotherapy. Study 1245.23_{met} compared empagliflozin with placebo as add-on to metformin. Study 1245.23_{met+SU} compared empagliflozin with placebo as add-on to metformin plus a sulfonylurea. While Studies 1245.23_{met} and 1245.23_{met+SU} were performed under one protocol and study number and the results were submitted as a single study report, the Applicant considers them independent, individual studies for the purpose of the NDA. Study 1245.31 is a long-term extension of these 4 studies and provides additional supportive, long-term information. Aside from the differences in background therapy, the inclusion/exclusion criteria were similar for the four pivotal phase 3 studies.

Inclusion criteria included:

- Diagnosis of T2DM
- Age ≥ 18 years (≥ 20 for Japan)
- HbA1c $\geq 7.0\%$ and $\leq 10.0\%$
- Body Mass Index (BMI) $\leq 45 \text{ kg/m}^2$

Exclusion criteria included:

- Uncontrolled hyperglycemia (FPG > 240 mg/dL on two separate measurements)
- Myocardial infarction (MI), stroke, or transient ischemic attack (TIA) within 3 months prior to informed consent
- Liver disease (defined as alanine aminotransferase (ALT), aspartate aminotransferase (AST), or alkaline phosphatase > 3x upper limit of reference range (ULRR))
- eGFR < 30 ml/min
- Bariatric or other gastrointestinal surgeries that result in chronic malabsorption within two years prior to informed consent
- Blood dyscrasias
- History of cancer (except for basal cell carcinoma) and/or treatment for cancer within five years
- Antiobesity drugs or any other treatment leading to unstable body weight
- Systemic steroids at time of informed consent
- Change in dosage of thyroid hormones within six weeks prior to informed consent
- Any other uncontrolled endocrine disorder (except T2DM)
- Alcohol or drug abuse in the three months prior to informed consent

In addition to these studies, data from five supportive phase 3/phase 3-equivalent studies are submitted: 1245.25 (cardiovascular outcomes study, 10 mg and 25 mg), 1245.28 (empagliflozin vs. glimepiride, 25 mg only), 1245.33 (add-on to basal insulin, 10 mg and 25 mg), 1245.36 (empagliflozin in patients with varying degrees of renal impairment, 10 mg and 25 mg), and 1245.48 (empagliflozin in patients with hypertension, 10 mg and 25 mg). Supportive data are also provided by two phase 2 studies (1245.9 – 12 week double-blind, placebo controlled, monotherapy study (5 mg, 10 mg, and 25 mg), 1245.10 – 12 week double-blind, placebo controlled, add-on to metformin study (1 mg, 5 mg, 10 mg, 25 mg, and 50 mg)) and their open-label extension (1245.24, 10 mg and 25 mg). Three of the studies included in the NDA submission only have interim data: Studies 1245.25, 1245.28, and 1245.31.

The proposed label presents the efficacy results from Studies 1245.19, 1245.20, 1245.23_{met}, 1245.23_{met+SU}, 1245.36, and 1245.33. Results from the ongoing extension study (1245.31) at 52 weeks are also included, as are the efficacy results at 26 and 52 weeks for the ongoing active controlled study (1245.28), and results from a subpopulation of the ongoing CVOT (1245.25) with baseline therapy of a DPP-4 inhibitor (alone or in combination with metformin).

Safety findings are presented in the proposed label from an aggregated population composed of patients from Studies 1245.19, 1245.20, 1245.23_{met}, and 1245.23_{met+SU} at 24 weeks, and from Study 1245.33 at 18 weeks. Hypoglycemia results are presented separately for Study 1245.33 at 18 and 78 weeks, and for Studies 1245.19, 1245.20, 1245.23_{met}, and 1245.23_{met+SU} at 24 weeks. While these groupings are a subset of the larger safety grouping SAF-5, the overall findings are similar to that seen for the larger pool.

6. Review of Efficacy

Efficacy Summary

The Applicant has demonstrated that empagliflozin has greater efficacy in reducing HbA1c compared to placebo at both the 10 mg dose and the 25 mg dose. In the pivotal phase 3 studies, the mean placebo-adjusted change in HbA1c ranged from -0.48% to -0.73% with empagliflozin 10 mg and from -0.59 to -0.84% with empagliflozin 25 mg. While there were only slight differences between the 10 mg and 25 mg dose on the reduction in HbA1c, there are sufficient supportive findings of efficacy to support approval of both doses. In particular, treatment with the 25 mg dose resulted in a greater percentage of patients achieving an HbA1c < 7.0% compared to the 10 mg dose, and there was a reduced need for rescue medication with the 25 mg dose. Additional outcome measures assessed in the clinical studies included change in fasting plasma glucose, change in body weight, and change in blood pressure parameters. Greater reductions compared to placebo were seen for all of these endpoints with empagliflozin treatment.

6.1 Indication

Empagliflozin is proposed for use as an adjunct to diet and exercise to improve glycemic control in adults with T2DM either as monotherapy or as add-on to other antidiabetic treatments. The standard indication for drugs to treat T2DM does not specifically indicate use as monotherapy or as add-on therapy.

6.1.1 Methods

The clinical studies supporting the NDA were grouped into two efficacy groupings by the Applicant (Table 5). Efficacy Grouping 1 (EFF-1) is the pool of Studies 1245.19, 1245.20, and 1245.23_{met} up to 24 weeks. This grouping corresponds to the safety grouping SAF-2 (see Figure 16). Exclusion of data from Study 1245.23_{met+SU} was done to allow for risk-benefit assessment of patients not taking sulfonylureas, as this population was expected to have a higher risk for

hypoglycemia. Efficacy Grouping 2 (EFF-2) is the larger pool, and includes Studies 1245.19, 1245.20, 1245.23_{met}, and 1245.23_{met+SU} along with the extension Study 1245.31. This grouping corresponds to the safety grouping SAF-3. Additional studies considered individually in the evaluation of efficacy were Study 1245.24 (open-label extension of Study 1245.9 - monotherapy, and Study 1245.10 – add-on to metformin), Study 1245.25 (in patients at high risk for CV events), Study 1245.28 (vs. glimepiride), Study 1245.33 (add-on to basal insulin), Study 1245.36 (in patients with renal impairment), and Study 1245.48 (in patients with diabetes mellitus and hypertension, included ambulatory blood pressure monitoring).

Table 5 Grouping of Studies for Evaluation of Efficacy

Grouping	Study/Studies	Description	Analysis Timepoint(s)
EFF-1	1245.19 1245.20 1245.23 _{met}	Pivotal studies excluding patients receiving sulfonylurea as background therapy	24 weeks
EFF-2	1245.19 1245.20 1245.23 _{met} 1245.23 _{met+SU}	Pivotal studies, including all patients and extension	24 weeks ¹ 52 weeks
	1245.28	Compared to glimepiride active control	52 weeks
	1245.33	Basal insulin background therapy	18 weeks ¹ 78 weeks
	1245.48	Patients with hypertension (included ambulatory blood pressure monitoring)	12 weeks
	1245.36	Subjects with varying degrees of renal impairment	24 weeks ¹ 52 weeks
	1245.25	Subjects with increased cardiovascular risk	12 weeks 28 weeks 52 weeks
	1245.24	Open-label extension of Studies 1245.9 and 1245.10	90 weeks

¹Timepoint of primary analysis

EFF-1 = Efficacy Grouping 1; EFF-2 = Efficacy Grouping 2

Source: Table 1.3.2: 1 (Summary of Clinical Efficacy)

Primary efficacy analyses followed the intent-to-treat principle and were based on the full analysis set (FAS) which included all randomized patients who received at least one dose of study medication and had a baseline HbA1c measurement. A per-protocol set (PPS) was defined at the study level, but in general comprised all patients from the FAS who did not have any important protocol violations. The main analyses of efficacy used analysis of covariance (ANCOVA) models and a last observation carried forward (LOCF) method for imputation of missing data. Baseline HbA1c was a covariate, while treatment, renal function, geographical region, and study number were fixed effects. For categorical responder analyses, missing data were imputed using the noncompleters considered failure (NCF) approach. Sensitivity analyses

included evaluation of the PPS with LOCF, a full analysis set – observed cases (FAS (OC)) and full analysis set – observed cases, including values after rescue medication (FAS (OC-IR)) using the mixed-effects model repeated measures (MMRM) approach.

This review will focus on the efficacy results of the four pivotal studies and the efficacy grouping, EFF-2. There is additional discussion of other studies submitted in support of the NDA where appropriate. For a detailed review of efficacy see the review by Dongmei Liu.

6.1.2 Demographics

In the efficacy groupings EFF-1 and EFF-2, there were a total of 1,811 and 2,477 patients, respectively, treated with randomized study medication (Table 6).

Table 6 Subjects in Pivotal Studies – Full Analysis Set

	Empa 10	Empa 25	Placebo	Total
EFF-1				
1245.19	165	168	165	498
1245.20	224	224	228	676
1245.23 _{met}	217	213	207	637
Total	606	605	600	1,811
EFF-2				
1245.19	165	168	165	498
1245.20	224	224	228	676
1245.23 _{met}	217	213	207	637
1245.23 _{met+SU}	225	216	225	666
Total	831	821	825	2,477

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; EFF-1 = Efficacy Grouping 1; EFF-2 = Efficacy Grouping 2
Source: Tables 1.3 and 1.4 (Integrated Summary of Efficacy)

Baseline demographics were balanced in each individual pivotal study, as well as for the pooled efficacy groups (Table 7). Study 1245.20 also included an active comparator arm using sitagliptin. Baseline demographics for this group were similar to the empagliflozin- and placebo-treated patients in this study (not shown. See Table 11.2.1: 1 of the study report for Study 1245.20). Between the different pivotal studies, small differences in baseline demographics were observed. There were more patients with a longer duration of disease in the add-on studies (1245.19, 1245.23_{met}, and 1245.23_{met+SU}). This was likely due to differences in the eligibility criteria for each study. There was a higher percentage of males in Study 1245.20 than in other studies. There was also a higher percentage of Asian patients in Study 1245.20 than in other studies. There were more White patients in Study 1245.23_{met} than in other studies. These differences are unlikely to significantly impact the efficacy findings. Notably, the overall

number of Black patients was small (for the individual pivotal studies and for the efficacy groupings). As a result, interpretation of efficacy in this racial group may be limited.

Table 7 Baseline Demographics for Pivotal Studies and Efficacy Groupings – Full Analysis Set

	Empa 10		Empa 25		Placebo	
Study 1245.19						
N	165		168		165	
BMI (kg/m ² , SD)	54.7	9.9	54.2	8.9	54.6	10.5
Age (yrs, SD)	29.5	5.6	29.1	5.5	29.3	5.4
Male (N, %)	83	50.3	85	50.6	73	44.2
White (N, %)	69	41.8	68	40.5	60	36.4
Black (N, %)	4	2.4	6	3.6	1	0.6
Asian (N, %)	91	55.2	94	56.0	103	62.4
Diagnosis > 5 yrs (N, %)	76	46.1	75	44.6	68	41.2
Study 1245.20						
N	224		224		228	
BMI (kg/m ² , SD)	28.3	5.5	28.2	5.5	28.7	6.2
Age (yrs, SD)	56.2	11.6	53.8	11.6	54.9	10.9
Male (N, %)	142	63.4	145	64.7	123	53.9
White (N, %)	77	34.4	73	32.6	76	33.3
Black (N, %)	3	1.3	7	3.1	6	2.6
Asian (N, %)	143	63.8	144	64.3	146	64.0
Diagnosis > 5 yrs (N, %)	45	20.1	50	22.3	52	22.8
Study 1245.23 _{met}						
N	217		213		207	
BMI (kg/m ² , SD)	29.1	5.5	29.7	5.7	28.7	5.2
Age (yrs, SD)	55.5	9.9	55.6	10.2	56	9.7
Male (N, %)	125	57.6	120	56.3	116	56.0
White (N, %)	112	51.6	113	53.1	113	54.6
Black (N, %)	4	1.8	0	0.0	2	1.0
Asian (N, %)	99	45.6	98	46	92	44.4
Diagnosis > 5 yrs (N, %)	119	54.8	125	58.7	105	50.7
Study 1245.23 _{met+SU}						
N	225		216		225	
BMI (kg/m ² , SD)	28.3	5.4	28.3	5.5	27.9	4.9
Age (yrs, SD)	57	9.2	57.4	9.3	56.9	9.2
Male (N, %)	113	50.2	114	52.8	112	49.8
White (N, %)	89	39.6	85	39.4	88	39.1
Black (N, %)	3	1.3	3	1.4	7	3.1
Asian (N, %)	129	57.3	125	57.9	127	56.4
Diagnosis > 5 yrs (N, %)	163	72.4	166	76.9	187	83.1

	Empa 10		Empa 25		Placebo	
EFF-1						
N	606		605		600	
BMI (kg/m ² , SD)	28.8	5.5	29	5.6	28.9	5.6
Age (yrs, SD)	55.5	10.6	54.6	10.4	55.2	10.4
Male (N, %)	350	57.8	350	57.9	312	52.0
White (N, %)	258	42.6	254	42.0	249	41.5
Black (N, %)	11	1.8	13	2.1	9	1.5
Asian (N, %)	333	55.0	336	55.5	341	56.8
Diagnosis > 5 yrs (N, %)	240	39.6	250	41.3	225	37.5
EFF-2						
N	831		821		825	
BMI (kg/m ² , SD)	28.7	5.5	28.8	5.6	28.6	5.5
Age (yrs, SD)	55.9	10.2	55.3	10.2	55.7	10.1
Male (N, %)	463	55.7	464	56.5	424	51.4
White (N, %)	347	41.8	339	41.3	337	40.8
Black (N, %)	14	1.7	16	1.9	16	1.9
Asian (N, %)	462	55.6	461	56.2	468	56.7
Diagnosis > 5 yrs (N, %)	403	48.5	416	50.7	412	49.9

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg. BMI = body mass index; SD = standard deviation; yrs = years; EFF-1 = Efficacy Grouping 1; EFF-2 = Efficacy Grouping 2

Source: Table 3.1.2.1.1: 1 (Summary of Clinical Efficacy)

6.1.3 Subject Disposition

Of the 4,634 screened patients for the pivotal studies, 2,964 were randomized to blinded treatment or assigned open-label treatment. At least one dose of randomized study treatment was given to 2,700 patients. In each of the pivotal studies and in the two efficacy groupings (EFF-1 and EFF-2), premature discontinuation was more common in the placebo-treated patients (Table 8). The most common reason for premature discontinuation was not continuing on to the extension study. The most common reason for not continuing on to the extension study was reported as “Other” (Table 9). Discontinuation due to an AE was the next most common reason for premature discontinuation. This was more common in the placebo group (with the exception of Study 1245.23_{met+SU} where the 25 mg dose had a higher incidence of discontinuation due to AE). Between the two doses of empagliflozin, premature discontinuation due to an adverse event occurred with the Empa 25 group at an incidence greater or equal to that seen in the Empa 10 group for all of the individual studies and the efficacy groupings, EFF-1 and EFF-2.

Table 8 Subject Disposition

		Prematurely Discontinued									
	Tx'd	Total		Due to AE		Lack of Efficacy		Did Not Continue in Extension		Other ¹	
	N	N	%	N	%	N	%	N	%	N	%
Study 1245.19											
Placebo	165	77	46.7	5	3.0	0	0.0	54	32.7	18	10.9
Empa 10	165	65	39.4	2	1.2	0	0.0	48	29.1	15	9.1
Empa 25	168	65	38.7	5	3.0	0	0.0	50	29.8	10	6.0
Study 1245.20											
Placebo	228	103	45.2	12	5.3	2	0.9	51	22.4	38	16.7
Empa 10	224	72	32.1	7	3.1	0	0.0	41	18.3	24	10.7
Empa 25	224	77	34.4	7	3.1	0	0.0	45	20.1	25	11.2
Sitagliptin	223	78	35.0	6	2.7	0	0.0	51	22.9	21	9.4
Study 1245.23 _{met}											
Placebo	207	80	38.6	8	3.9	0	0.0	48	23.2	24	11.6
Empa 10	217	54	24.9	6	2.8	0	0.0	36	16.6	12	5.5
Empa 25	213	72	33.8	8	3.8	0	0.0	44	20.7	20	9.4
Study 1245.23 _{met+SU}											
Placebo	225	90	40.0	10	4.4	2	0.9	56	24.9	22	9.8
Empa 10	225	69	30.7	9	4.0	0	0.0	45	20.0	15	6.7
Empa 25	216	64	29.6	14	6.5	1	0.5	34	15.7	15	6.9
EFF-1											
Placebo	601	80	13.3	19	3.2	1	0.2	233	38.8	60	10.0
Empa 10	606	37	6.1	6	1.0	0	0.0	162	26.7	31	5.1
Empa 25	605	49	8.1	14	2.3	0	0.0	188	31.1	35	5.8
Sitagliptin	223	17	7.6	6	2.7	0	0.0	68	30.5	11	4.9
EFF-2											
Placebo	825	350	42.4	35	4.2	4	0.5	209	25.3	102	12.4
Empa 10	831	260	31.3	24	2.9	0	0.0	170	20.5	66	7.9
Empa 25	821	278	33.9	34	4.1	1	0.1	173	21.1	70	8.5
Sitagliptin	223	78	35.0	6	2.7	0	0.0	51	22.9	21	9.4

¹includes patients discontinued prematurely for noncompliance with protocol, patients lost to follow-up, patients refusing to continue not due to an AE, patients who stopped study drug with the reason missing

AE = adverse event; Tx'd = treated; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; EFF-1 = Efficacy

Grouping 1; EFF-2 = Efficacy Grouping 2

Source: Tables 2.1.1.1 through 2.1.2.5 (Integrated Summary of Efficacy)

Table 9 Reasons for Not Continuing in Extension Study 1245.31

	Treated	Total		Ineligible		Tolerability Issues		Other reason ¹	
		N	%	N	%	N	%	N	%
Study 1245.19									
Placebo	165	72	43.6	8	4.8	0	0.0	64	38.8
Empa 10	165	59	35.8	1	0.6	0	0.0	58	35.2
Empa 25	168	62	36.9	2	1.2	1	0.6	59	35.1
Study 1245.20									
Placebo	228	92	40.4	12	5.3	4	1.8	76	33.3
Empa 10	224	59	26.3	5	2.2	2	0.9	52	23.2
Empa 25	224	65	29.0	6	2.7	3	1.3	56	25.0
Sitagliptin	223	68	30.5	5	2.2	0	0.0	63	28.3
Study 1245.23									
Placebo	432	149	34.5	13	3.0	5	1.2	131	30.3
Empa 10	442	106	24.0	3	0.7	0	0.0	103	23.3
Empa 25	429	112	26.1	8	1.9	8	1.9	96	22.4

[†] includes study site not participating in extension, extension study not approved at study site at time of eligibility for extension, patient lost to follow-up, patient with personal reasons (moving, travel, etc.)

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg

Source: Table 10.1: 3 (Study 1245.19 study report), Table 10.1: 3 (Study 1245.20 study report), Table 10.1 (Study 1245.23 study report)

6.1.4 Analysis of Primary Endpoint(s)

The primary endpoint across all of the efficacy studies was change from baseline in HbA1c. Hemoglobin A1c was assayed in central laboratories with a National Glycohemoglobin Standardization Program Level I certificate. All of the pivotal studies and the aggregated efficacy groupings EFF-1 and EFF-2 demonstrated a greater reduction in HbA1c from baseline at 24 weeks with empagliflozin treatment compared to placebo (Table 10).

The greatest efficacy was seen in the monotherapy study (1245.20) with a placebo-adjusted reduction in HbA1c of -0.73% and -0.84% for the 10 mg and 25 mg dose, respectively. Lesser reductions in HbA1c from baseline were seen in the add-on studies (Study 1245.19 – add-on to pioglitazone +/- metformin, -0.48% for 10 mg and -0.61% for 25 mg; Study 1245.23_{met} – add-on to metformin, -0.58% for 10 mg and -0.64% for 25 mg; Study 1245.23_{met+SU} – add-on to metformin + sulfonylurea, -0.64% for 10 mg and -0.59% for 25 mg). For the efficacy groupings, placebo-adjusted HbA1c reductions were seen of -0.65% and -0.64% (EFF-1, 10 mg and 25 mg respectively), and -0.64% and -0.70% (EFF-2, 10 mg and 25 mg respectively).

Though the confidence intervals overlapped, the patients treated with empagliflozin 25 mg had a numerically greater mean reduction in HbA1c compared to the patients treated with

empagliflozin 10 mg in every study except Study 1245.23_{met+SU} (Figure 3). Further discussion of dose and efficacy can be found in 6.1.8.

Analysis of the PPS produced similar findings (Table 11). Additional analyses were performed using an MMRM model with the FAS (OC) (Table 12) and FAS (OC-IR) (Table 13). The findings of these sensitivity analyses were consistent with the primary analysis which was performed using ANCOVA and LOCF.

The full effect of treatment on HbA1c was seen at twelve weeks after initiation of treatment. Only a minimal change was seen in HbA1c from twelve weeks to 24 weeks and to 52 weeks (Figure 4).

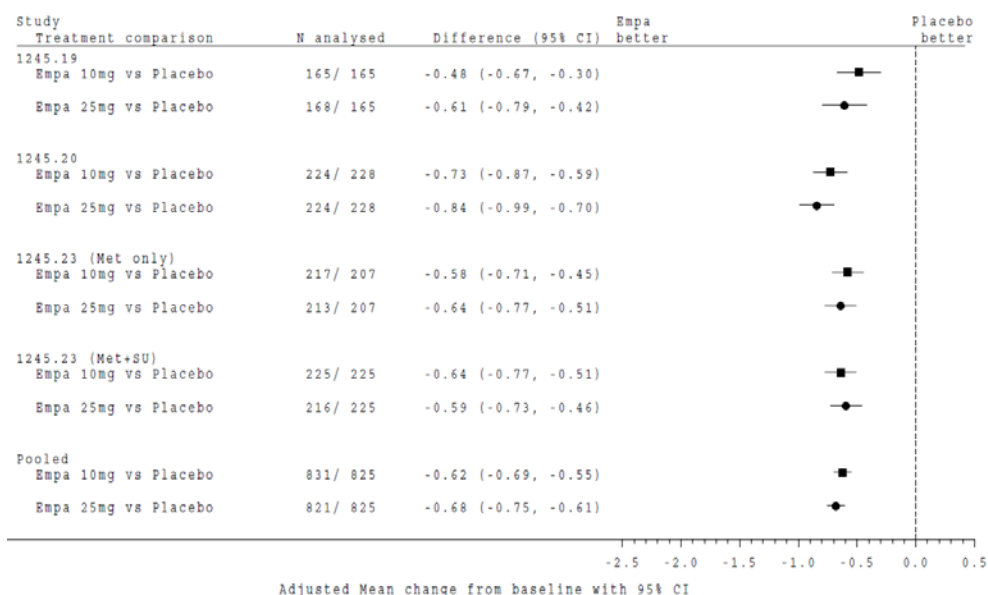
Table 10 Change in Hemoglobin A1c – 24 weeks, Full Analysis Set, Last Observation Carried Forward, Analysis of Covariance Model

		Baseline		Change from Baseline				Difference from Placebo				
	N	Mean	SE	Mean	SE	Adj. Mean	SE	Adj. Mean	SE	95% CI		p-value
										LL	UL	
Study 1245.19												
Placebo	165	8.16	0.07	-0.13	0.08	-0.11	0.07					
Empa 10	165	8.07	0.07	-0.58	0.07	-0.59	0.07	-0.48	0.09	-0.67	-0.30	< 0.0001
Empa 25	168	8.06	0.06	-0.70	0.07	-0.71	0.07	-0.61	0.09	-0.79	-0.42	< 0.0001
Study 1245.20												
Placebo	228	7.91	0.05	0.06	0.05	0.07	0.05					
Empa 10	224	7.87	0.06	-0.66	0.06	-0.66	0.05	-0.73	0.07	-0.87	-0.59	< 0.0001
Empa 25	224	7.86	0.06	-0.77	0.06	-0.78	0.05	-0.84	0.07	-0.99	-0.70	< 0.0001
Study 1245.23 _{met}												
Placebo	207	7.90	0.06	-0.13	0.05	-0.13	0.05					
Empa 10	217	7.94	0.05	-0.73	0.05	-0.71	0.05	-0.58	0.07	-0.71	-0.45	< 0.0001
Empa 25	213	7.86	0.06	-0.75	0.06	-0.77	0.05	-0.64	0.07	-0.77	-0.51	< 0.0001
Study 1245.23 _{met+SU}												
Placebo	225	8.15	0.06	-0.19	0.05	-0.18	0.05					
Empa 10	225	8.07	0.05	-0.80	0.05	-0.82	0.05	-0.64	0.07	-0.77	-0.51	< 0.0001
Empa 25	216	8.10	0.06	-0.77	0.05	-0.77	0.05	-0.59	0.07	-0.73	-0.46	< 0.0001
EFF-1												
Placebo	600	7.98	0.04	-0.06	0.03	-0.05	0.03					
Empa 10	606	7.95	0.03	-0.66	0.03	-0.66	0.03	-0.61	0.04	-0.70	-0.52	< 0.0001
Empa 25	605	7.91	0.03	-0.74	0.03	-0.76	0.03	-0.71	0.04	-0.80	-0.62	< 0.0001

		Baseline		Change from Baseline				Difference from Placebo				
	N	Mean	SE	Mean	SE	Adj. Mean	SE	Adj. Mean	SE	95% CI		p-value
										LL	UL	
EFF-2												
Placebo	825	8.02	0.03	-0.10	0.03	-0.08	0.03					
Empa 10	831	7.98	0.03	-0.70	0.03	-0.70	0.03	-0.62	0.04	-0.69	-0.55	< 0.0001
Empa 25	821	7.96	0.03	-0.75	0.03	-0.76	0.03	-0.68	0.04	-0.75	-0.61	< 0.0001

SE = standard error; Adj. Mean = adjusted mean; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; EFF-1 = Efficacy Grouping 1; EFF-2 = Efficacy Grouping 2
Source: Table 3.2.1.1: 1 (Summary of Clinical Efficacy)

Figure 3 Forest Plot of Mean Change in Hemoglobin A1c – 24 Weeks, Efficacy Grouping 2, Full Analysis Set, Last Observation Carried Forward



Source: Figure 4.1.2.1.3 (Integrated Summary of Efficacy)

Table 11 Change in Hemoglobin A1c – 24 Weeks, Per-Protocol Set, Last Observation Carried Forward, Analysis of Covariance Model

		Baseline		Change from Baseline				Difference from Placebo				
	N	Mean	SE	Mean	SE	Adj. Mean	SE	Adj. Mean	SE	95% CI		p-value
										LL	UL	
Study 1245.19												
Placebo	152	8.19	0.08	-0.12	0.09	-0.08	0.07					
Empa 10	153	8.06	0.07	-0.62	0.07	-0.65	0.07	-0.57	0.10	-0.87	-0.48	< 0.0001
Empa 25	155	8.09	0.07	-0.75	0.07	-0.76	0.07	-0.68	0.10	-0.87	-0.48	< 0.0001

		Baseline		Change from Baseline				Difference from Placebo				
	N	Mean	SE	Mean	SE	Adj. Mean	SE	Adj. Mean	SE	95% CI		p-value
										LL	UL	
Study 1245.20												
Placebo	202	7.90	0.05	0.05	0.06	0.06	0.05					
Empa 10	206	7.87	0.06	-0.68	0.06	-0.68	0.05	-0.74	0.08	-0.89	-0.59	< 0.0001
Empa 25	212	7.85	0.06	-0.77	0.06	-0.78	0.05	-0.84	0.08	-0.99	-0.69	< 0.0001
Study 1245.23_{met}												
Placebo	181	7.89	0.07	-0.16	0.06	-0.16	0.05					
Empa 10	202	7.93	0.06	-0.74	0.05	-0.72	0.05	-0.56	0.07	-0.70	-0.42	< 0.0001
Empa 25	197	7.87	0.06	-0.77	0.06	-0.79	0.05	-0.63	0.07	-0.77	-0.49	< 0.0001
Study 1245.23_{met+SU}												
Placebo	196	8.16	0.06	-0.19	0.06	-0.17	0.05					
Empa 10	203	8.06	0.06	-0.81	0.05	-0.82	0.05	-0.65	0.07	-0.79	-0.51	< 0.0001
Empa 25	191	8.08	0.06	-0.81	0.06	-0.82	0.05	-0.64	0.07	-0.79	-0.50	< 0.0001
EFF-2												
Placebo	731	8.03	0.03	-0.10	0.03	-0.08	0.03					
Empa 10	764	7.98	0.03	-0.72	0.03	-0.72	0.03	-0.64	0.04	-0.72	-0.56	< 0.0001
Empa 25	755	7.96	0.03	-0.78	0.03	-0.79	0.03	-0.70	0.04	-0.78	-0.63	< 0.0001

SE = standard error; Adj. Mean = adjusted mean; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; EFF-2 = Efficacy Grouping 2

Source: Table 4.1.2.2.1 (Integrated Summary of Efficacy)

Table 12 Change in Hemoglobin A1c – 24 Weeks, Full Analysis Set (Observed Cases), Mixed-Effects Model Repeated Measures

		Baseline		Change from Baseline				Difference from Placebo				
	N	Mean	SE	Mean	SE	Adj. Mean	SE	Adj. Mean	SE	95% CI		p-value
										LL	UL	
Study 1245.19												
Placebo	131	8.16	0.07	-0.16	0.10	-0.12	0.07					
Empa 10	147	8.07	0.07	-0.66	0.07	-0.62	0.07	-0.50	0.10	-0.70	-0.30	< 0.0001
Empa 25	156	8.06	0.06	-0.73	0.07	-0.72	0.07	-0.60	0.10	-0.80	-0.41	< 0.0001
Study 1245.20												
Placebo	159	7.91	0.05	-0.08	0.06	0.08	0.06					
Empa 10	203	7.87	0.06	-0.71	0.06	-0.69	0.06	-0.77	0.08	-0.93	-0.61	< 0.0001
Empa 25	203	7.86	0.06	-0.80	0.06	-0.79	0.06	-0.87	0.08	-1.03	-0.71	< 0.0001
Study 1245.23_{met}												
Placebo	156	7.90	0.06	-0.24	0.06	-0.15	0.05					
Empa 10	198	7.94	0.05	-0.77	0.05	-0.71	0.05	-0.56	0.07	-0.70	-0.42	< 0.0001
Empa 25	186	7.86	0.06	-0.83	0.06	-0.79	0.05	-0.64	0.07	-0.78	-0.50	< 0.0001
Study 1245.23_{met+SU}												
Placebo	168	8.15	0.06	-0.31	0.06	-0.21	0.05					
Empa 10	186	8.07	0.05	-0.87	0.06	-0.86	0.05	-0.65	0.07	-0.79	-0.50	< 0.0001
Empa 25	185	8.10	0.06	-0.86	0.06	-0.84	0.05	-0.63	0.07	-0.77	-0.48	< 0.0001

		Baseline		Change from Baseline				Difference from Placebo				
	N	Mean	SE	Mean	SE	Adj. Mean	SE	Adj. Mean	SE	95% CI		p-value
										LL	UL	
EFF-2												
Placebo	614	8.02	0.03	-0.20	0.03	-0.10	0.03					
Empa 10	734	7.98	0.03	-0.76	0.03	-0.73	0.03	-0.62	0.04	-0.70	-0.54	< 0.0001
Empa 25	730	7.96	0.03	-0.81	0.03	-0.79	0.03	-0.69	0.04	-0.77	-0.61	< 0.0001

SE = standard error; Adj. Mean = adjusted mean; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; EFF-2 = Efficacy Grouping 2

Source: Table 4.1.2.5.4 (Integrated Summary of Efficacy)

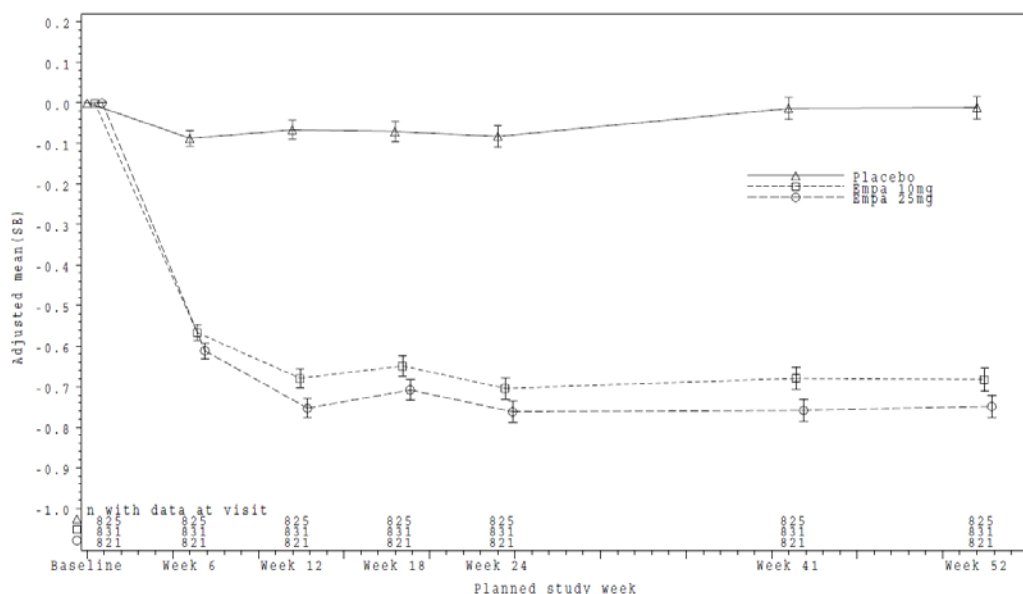
Table 13 Change in Hemoglobin A1c – 24 Weeks, Full Analysis Set, Observed Cases Including Values After Rescue Medication, Mixed-Effects Model Repeated Measures

		Baseline		Change from Baseline				Difference from placebo				
	N	Mean	SE	Mean	SE	Adj. mean	SE	Adj. mean	SE	95% CI		p-value
										LL	UL	
Study 1245.19												
Placebo	147	8.16	0.07	-0.16	0.09	-0.13	0.07					
Empa 10	152	8.07	0.07	-0.64	0.07	-0.64	0.07	-0.50	0.10	-0.70	-0.31	< 0.0001
Empa 25	157	8.06	0.06	-0.72	0.07	-0.72	0.07	-0.59	0.10	-0.78	-0.39	< 0.0001
Study 1245.20												
Placebo	187	7.91	0.05	-0.16	0.06	-0.12	0.06					
Empa 10	206	7.87	0.06	-0.71	0.06	-0.70	0.05	-0.58	0.08	-0.73	-0.42	< 0.0001
Empa 25	205	7.86	0.06	-0.80	0.06	-0.81	0.05	-0.69	0.08	-0.84	-0.54	< 0.0001
Study 1245.23_{met}												
Placebo	183	7.90	0.06	-0.26	0.06	-0.24	0.05					
Empa 10	209	7.94	0.05	-0.76	0.05	-0.74	0.05	-0.50	0.07	-0.64	-0.37	< 0.0001
Empa 25	196	7.86	0.06	-0.81	0.06	-0.81	0.05	-0.58	0.07	-0.71	-0.44	< 0.0001
Study 1245.23_{met+SU}												
Placebo	200	8.15	0.06	-0.30	0.06	-0.28	0.05					
Empa 10	207	8.07	0.05	-0.87	0.05	-0.88	0.05	-0.60	0.07	-0.73	-0.46	< 0.0001
Empa 25	199	8.10	0.06	-0.84	0.06	-0.84	0.05	-0.56	0.07	-0.70	-0.42	< 0.0001
EFF-2												
Placebo	717	8.02	0.03	-0.22	0.03	-0.20	0.03					
Empa 10	774	7.98	0.03	-0.75	0.03	-0.75	0.03	-0.55	0.04	-0.63	-0.47	< 0.0001
Empa 25	757	7.96	0.03	-0.80	0.03	-0.80	0.03	-0.60	0.04	-0.68	-0.53	< 0.0001

SE = standard error; Adj. Mean = adjusted mean; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; EFF-2 = Efficacy Grouping 2

Source: Table 4.1.2.5.1 (Integrated Summary of Efficacy)

Figure 4 Mean Change in Hemoglobin A1c – Efficacy Grouping 2, Full Analysis Set, Last Observation Carried Forward



Source: Figure 4.1.2.3.4 (Integrated Summary of Efficacy)

A subset of patients taking metformin + a DPP-4 inhibitor as background from the ongoing CVOT was also analyzed for this endpoint. The addition of empagliflozin showed a placebo-adjusted reduction in HbA1c of -0.51% and -0.50% (10 mg and 25 mg at 28 weeks, respectively) (Table 14).

Table 14 Change in Hemoglobin A1c – Study 1245.25, Dipeptidyl Peptidase-4 Inhibitor +/- Metformin, Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline				Difference from placebo				
	N	Mean	SE	Mean	SE	Adj. mean	SE	Adj. mean	SE	95% CI		
										LL	UL	
12 weeks												
Placebo	96	7.99	0.08	-0.09	0.06	-0.10	0.06					
Empa 10	87	8.06	0.08	-0.54	0.06	-0.53	0.06	-0.43	0.09	-0.59	-0.26	< 0.0001
Empa 25	64	7.92	0.10	-0.52	0.08	-0.52	0.07	-0.42	0.09	-0.61	-0.24	< 0.0001
28 weeks												
Placebo	96	7.99	0.08	-0.02	0.07	-0.02	0.07					
Empa 10	87	8.06	0.08	-0.55	0.07	-0.54	0.07	-0.51	0.10	-0.70	-0.32	< 0.0001
Empa 25	64	7.92	0.10	-0.50	0.09	-0.52	0.08	-0.50	0.11	-0.71	-0.29	< 0.0001

SE = standard error; Adj. Mean = adjusted mean; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg

Source: Table 3.2.1.2: 2 (Summary of Clinical Efficacy)

6.1.5 Analysis of Secondary Endpoints(s)

6.1.5.1 Change from Baseline in Fasting Plasma Glucose

For the pool of studies identified as EFF-2, a decrease in FPG of approximately 30 mg/dL compared to placebo was seen with empagliflozin treatment (Table 15). As was the case with HbA1c, greater reductions were seen in the monotherapy study (1245.20) than in the add-on studies. There was a slightly greater reduction with the 25 mg dose than with the 10 mg dose (Table 15).

Table 15 Change in Fasting Plasma Glucose (mg/dL) – 24 Weeks, Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline				Difference from placebo				
	N	Mean	SE	Mean	SE	Adj. mean	SE	Adj. mean	SE	95% CI		p-value
										LL	UL	
Study 1245.19												
Placebo	165	151.9	3.1	6.6	3.2	6.7	2.6					
Empa 10	163	152.0	3.0	-17.3	3.2	-17.1	2.6	-23.8	3.7	-31.0	-16.5	< 0.0001
Empa 25	168	151.9	2.9	-22.1	2.4	-22.3	2.6	-29.0	3.7	-36.2	-21.7	< 0.0001
Study 1245.20												
Placebo	226	154.7	2.4	10.3	2.3	10.9	1.9					
Empa 10	223	152.8	2.2	-20.2	2.1	-20.3	1.9	-31.1	2.7	-36.4	-25.9	< 0.0001
Empa 25	223	152.6	2.3	-24.8	2.1	-25.3	1.9	-36.1	2.7	-41.4	-30.8	< 0.0001
Study 1245.23 _{met}												
Placebo	207	156.0	2.3	4.5	2.5	6.3	1.8					
Empa 10	216	154.6	2.4	-20.4	2.1	-19.8	1.7	-26.2	2.5	-31.1	-21.3	< 0.0001
Empa 25	213	149.4	2.1	-20.0	1.9	-22.3	1.8	-28.6	2.5	-33.6	-23.7	< 0.0001
Study 1245.23 _{met+SU}												
Placebo	224	151.7	2.4	6.6	2.5	5.5	1.9					
Empa 10	225	151.0	2.2	-22.4	2.2	-23.1	1.9	-28.7	2.7	-34.0	-23.3	< 0.0001
Empa 25	215	156.5	2.3	-25.3	2.0	-23.4	2.0	-28.9	2.8	-34.3	-23.4	< 0.0001
EFF-1												
Placebo	598	154.4	1.5	7.3	1.5	8.1	1.2					
Empa 10	602	153.2	1.4	-19.5	1.4	-19.4	1.2	-27.5	1.7	-30.8	-24.2	< 0.0001
Empa 25	604	151.3	1.4	-22.3	1.2	-23.2	1.2	-31.3	1.7	-34.6	-28.0	< 0.0001
EFF-2												
Placebo	822	153.7	1.3	7.1	1.3	7.4	1.0					
Empa 10	827	152.6	1.2	-20.3	1.2	-20.4	1.0	-27.8	1.4	-30.6	-25.0	< 0.0001
Empa 25	819	152.6	1.2	-23.1	1.0	-23.2	1.0	-30.6	1.4	-33.5	-27.8	< 0.0001

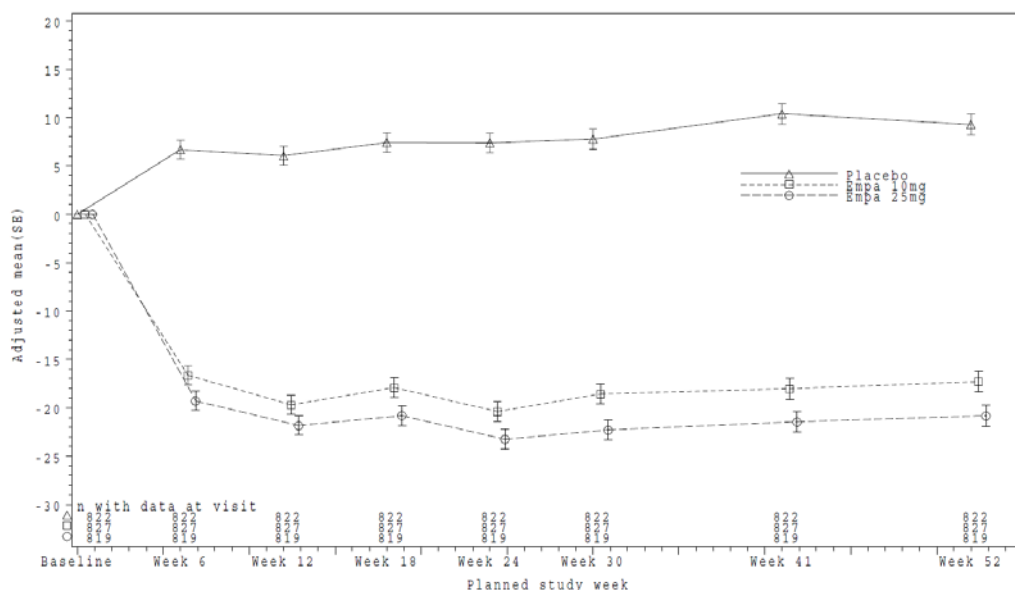
SE = standard error; Adj. Mean = adjusted mean; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg

Source: Table 3.2.2.1: 1 (Summary of Clinical Efficacy)

Additional sensitivity analyses as were performed for the primary endpoint produced similar findings (not shown, see Sections 1.4.2.1.2, 1.4.2.1.3, 1.4.2.2.2, and 1.4.2.2.5 of the Integrated Summary of Efficacy).

The change in FPG from baseline over time was analyzed using an MMRM model. For the pooled efficacy grouping EFF-2, the full treatment effect appeared to be reached by six weeks (Figure 5), though no values were measured between initiation of treatment and six weeks. After six weeks, only minimal change was noted to 24 weeks and 52 weeks.

Figure 5 Change in Fasting Plasma Glucose (mg/dL) – Efficacy Grouping 2, Full Analysis Set, Last Observation Carried Forward



Source: Figure 4.2.2.3.4 (Integrated Summary of Efficacy)

6.1.5.2 Change from Baseline in Body Weight

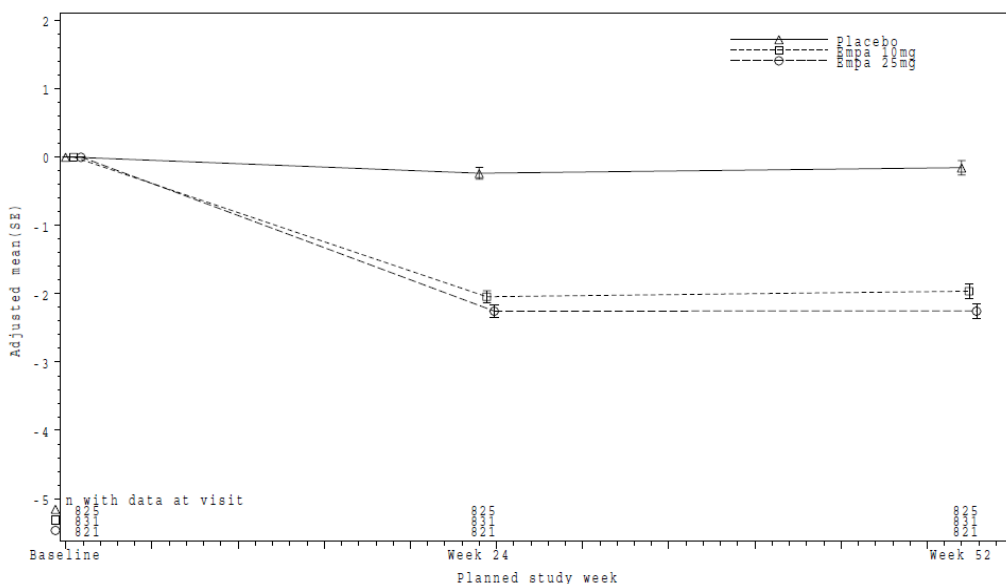
In all of the pivotal studies and the efficacy pools, treatment with empagliflozin resulted in a greater decrease in body weight from baseline than did treatment with placebo (Table 16). The magnitude of this placebo-corrected change was in the range of one to two kg. Additional sensitivity analyses of this endpoint produced similar findings (not shown, see Sections 1.4.3.1 and 1.4.3.2 of the Integrated Summary of Efficacy). The change in body weight appeared to be stable from week 24 to week 52 (Figure 6).

Table 16 Change in Body Weight (kg) – 24 Weeks, Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline				Difference from placebo				
	N	Mean	SE	Mean	SE	Adj. mean	SE	Adj. mean	SE	95% CI		p-value
										LL	UL	
Study 1245.19												
Placebo	165	78.10	1.57	0.35	0.22	0.33	0.21					
Empa 10	165	77.97	1.49	-1.58	0.23	-1.60	0.21	-1.93	0.30	-2.52	-1.47	< 0.0001
Empa 25	168	78.93	1.54	-1.49	0.20	-1.46	0.21	-1.79	0.30	-2.38	-1.68	< 0.0001
Study 1245.20												
Placebo	228	78.23	1.32	-0.33	0.15	-0.33	0.17					
Empa 10	224	78.35	1.25	-2.27	0.19	-2.27	0.17	-1.94	0.24	-2.41	-1.13	< 0.0001
Empa 25	224	77.80	1.20	-2.48	0.18	-2.48	0.17	-2.15	0.24	-2.63	-1.53	< 0.0001
Study 1245.23 _{met}												
Placebo	207	79.73	1.29	-0.41	0.15	-0.45	0.17					
Empa 10	217	81.59	1.26	-2.06	0.18	-2.06	0.17	-1.61	0.24	-2.08	-1.35	< 0.0001
Empa 25	213	82.21	1.32	-2.50	0.19	-2.46	0.17	-2.00	0.24	-2.48	-1.58	< 0.0001
Study 1245.23 _{met+SU}												
Placebo	225	76.23	1.13	-0.36	0.13	-0.39	0.15					
Empa 10	225	77.08	1.22	-2.16	0.18	-2.16	0.15	-1.77	0.22	-2.20	-1.33	< 0.0001
Empa 25	216	77.50	1.28	-2.42	0.15	-2.42	0.15	-2.02	0.22	-2.45	-1.20	< 0.0001
EFF-1												
Placebo	600	78.71	0.80	-0.17	0.10	-0.19	0.11					
Empa 10	606	79.41	0.76	-2.02	0.12	-2.01	0.11	-1.82	0.15	-2.12	-1.53	< 0.0001
Empa 25	605	79.67	0.77	-2.21	0.11	-2.20	0.11	-2.01	0.15	-2.30	-1.71	< 0.0001
EFF-2												
Placebo	825	78.03	0.66	-0.22	0.08	-0.24	0.09					
Empa 10	831	78.77	0.65	-2.05	0.10	-2.04	0.09	-1.80	0.12	-2.05	-1.56	< 0.0001
Empa 25	821	79.10	0.66	-2.27	0.09	-2.26	0.09	-2.02	0.12	-2.26	-1.77	< 0.0001

SE = standard error; Adj. mean = adjusted mean; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; EFF-1 = Efficacy Grouping 1; EFF-2 = Efficacy Grouping 2
Source: Table 3.2.3.1: 1 (Summary of Clinical Efficacy)

Figure 6 Change in Body Weight – Efficacy Grouping 2, Full Analysis Set, Last Observation Carried Forward



Source: Figure 4.3.2.3.4 (Integrated Summary of Efficacy)

6.1.5.3 Change from Baseline in Blood Pressure (Systolic and Diastolic)

A decrease from baseline in systolic (Table 17) and diastolic blood pressure (Table 18) was seen for empagliflozin-treated patients compared to placebo. The placebo-adjusted differences were small, < 5 mmHg for systolic blood pressure and < 3 mm Hg for diastolic blood pressure. These findings are of unclear clinical significance.

Table 17 Change in Systolic Blood Pressure (mmHg) – 24 Weeks, Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline				Difference from placebo				
	N	Mean	SE	Mean	SE	Adj. mean	SE	Adj. mean	SE	95% CI		p-value
										LL	UL	
Study 1245.19												
Placebo	165	125.7	0.9	0.8	1.0	0.8	0.8					
Empa 10	165	126.5	1.1	-3.2	1.0	-3.2	0.8	-4.0	1.2	-6.3	-1.7	0.0075
Empa 25	168	125.9	1.1	-4.1	0.9	-4.1	0.8	-4.9	1.2	-7.2	-2.6	0.0004
Study 1245.20												
Placebo	228	130.4	1.1	-0.3	0.8	-0.6	0.8					
Empa 10	224	133.0	1.1	-4.4	1.0	-3.6	0.8	-3.0	1.1	-5.3	-0.8	< 0.0001
Empa 25	224	129.9	1.2	-4.0	0.9	-4.6	0.8	-4.0	1.1	-6.2	-1.8	< 0.0001
Study 1245.23 _{met}												
Placebo	207	128.6	1.0	-0.1	0.8	-0.3	0.7					
Empa 10	217	129.6	1.0	-4.6	0.8	-4.5	0.7	-4.2	1.0	-6.3	-2.1	0.0043
Empa 25	213	130.0	1.0	-5.4	0.8	-5.2	0.7	-4.9	1.1	-6.9	-2.8	0.0271
Study 1245.23 _{met+SU}												
Placebo	225	128.8	1.0	-1.3	0.8	-1.4	0.7					
Empa 10	225	128.7	1.0	-4.0	0.7	-4.1	0.7	-2.7	1.0	-4.6	-0.9	0.0007
Empa 25	216	129.3	1.0	-3.7	0.8	-3.5	0.7	-2.1	1.0	-4.0	-0.2	< 0.0001
EFF-1												
Placebo	600	128.5	0.6	0.1	0.5	-0.1	0.5					
Empa 10	606	130.0	0.6	-4.1	0.5	-3.8	0.5	-3.6	0.6	-4.9	-2.4	< 0.0001
Empa 25	605	128.8	0.6	-4.5	0.5	-4.6	0.5	-4.5	0.6	-5.7	-3.2	< 0.0001
EFF-2												
Placebo	825	128.6	0.5	-0.3	0.4	-0.5	0.4					
Empa 10	831	129.6	0.5	-4.1	0.4	-3.9	0.4	-3.4	0.5	-4.4	-2.3	< 0.0001
Empa 25	821	129.0	0.5	-4.3	0.4	-4.3	0.4	-3.8	0.5	-4.9	-2.8	< 0.0001

SE = standard error; Adj. mean = adjusted mean; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; EFF-1 = Efficacy Grouping 1; EFF-2 = Efficacy Grouping 2
Source: Table 3.2.4.1.1: 1 (Summary of Clinical Efficacy)

Table 18 Change in Diastolic Blood Pressure (mmHg) – 24 Weeks, Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline				Difference from placebo				
	N	Mean	SE	Mean	SE	Adj. mean	SE	Adj. mean	SE	95% CI		p-value
										LL	UL	
Study 1245.19												
Placebo	165	76.3	0.7	0.5	0.6	0.3	0.5					
Empa 10	165	77.2	0.7	-1.6	0.6	-1.5	0.5	-1.8	0.7	-3.2	-0.4	0.0116
Empa 25	168	77.2	0.6	-2.3	0.5	-2.2	0.5	-2.5	0.7	-3.9	-1.1	0.0005
Study 1245.20												
Placebo	228	78.9	0.6	-0.5	0.5	-0.5	0.5					
Empa 10	224	79.2	0.6	-1.6	0.6	-1.4	0.5	-0.9	0.7	-2.3	0.4	0.1683
Empa 25	224	78.3	0.6	-2.0	0.6	-2.2	0.5	-1.7	0.7	-3.0	-0.4	0.012
Study 1245.23 _{met}												
Placebo	207	78.1	0.6	0.2	0.6	0.0	0.5					
Empa 10	217	79.6	0.5	-2.3	0.5	-2.0	0.5	-2.0	0.7	-3.3	-0.6	0.005
Empa 25	213	78.4	0.6	-1.5	0.5	-1.6	0.5	-1.6	0.7	-2.9	-0.2	0.0247
Study 1245.23 _{met+SU}												
Placebo	225	78.3	0.6	-1.6	0.5	-1.7	0.4					
Empa 10	225	78.4	0.6	-2.1	0.5	-2.2	0.4	-0.5	0.6	-1.7	0.7	0.4137
Empa 25	216	79.0	0.6	-2.3	0.5	-2.2	0.4	-0.5	0.6	-1.7	0.7	0.434
EFF-1												
Placebo	600	77.9	0.4	0.0	0.3	-0.1	0.3					
Empa 10	606	78.8	0.4	-1.8	0.3	-1.6	0.3	-1.5	0.4	-2.3	-0.4	0.0001
Empa 25	605	78.0	0.4	-1.9	0.3	-2.0	0.3	-1.9	0.4	-2.7	-1.1	< 0.0001
EFF-2												
Placebo	825	78.0	0.3	-0.4	0.3	-0.5	0.2					
Empa 10	831	78.7	0.3	-1.9	0.3	-1.8	0.2	-1.3	0.3	-1.9	-0.6	0.0002
Empa 25	821	78.3	0.3	-2.0	0.3	-2.0	0.2	-1.5	0.3	-2.2	-0.8	< 0.0001

SE = standard error; Adj. mean = adjusted mean; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; EFF-1 = Efficacy Grouping 1; EFF-2 = Efficacy Grouping 2
Source: Table 3.2.4.2.1: 1 (Summary of Clinical Efficacy)

In addition to the pivotal studies and efficacy groupings discussed above, Study 1245.48 was designed to examine the effects of treatment with empagliflozin on blood pressure in patients with diabetes mellitus and hypertension. As part of this study, ambulatory blood pressure monitoring was performed. Co-primary endpoints for this study were change from baseline in HbA1c after twelve weeks, and change from baseline in 24 hour systolic blood pressure after twelve weeks. Change from baseline in 24 hour diastolic blood pressure after twelve weeks was a key secondary endpoint.

Analysis of the data from the study was performed using an ANCOVA model with the last observation carried forward without values following a change in antihypertensive therapy (LOCF-H). For the co-primary endpoint of mean change in 24 hour systolic blood pressure, empagliflozin-treated patients demonstrated a greater reduction in 24 hour systolic blood pressure compared to placebo (Table 19). Similar findings were seen for mean change in 24 hour diastolic blood pressure, though with a smaller absolute value for change. As was seen in the larger efficacy grouping (i.e. EFF-2) the placebo-adjusted difference was a decrease of < 5 mmHg for systolic blood pressure and < 3 mmHg for diastolic blood pressure. The clinical significance of this change is unclear.

Table 19 Change in 24-hour Blood Pressure – Study 1245.48, Week 12, Full Analysis Set, Last Observation Carried Forward Following Change in Antihypertensive Therapy

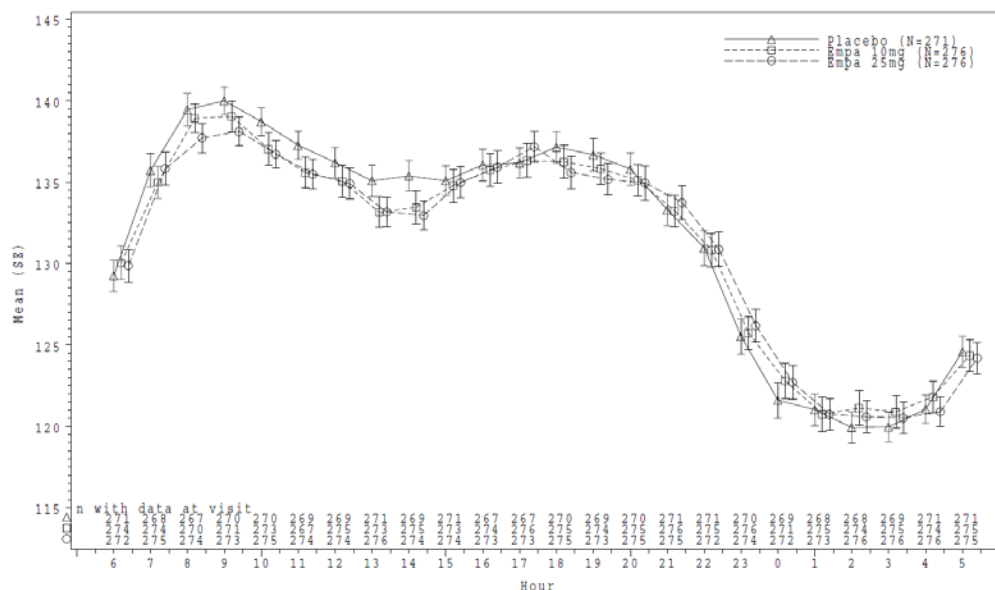
	N	Baseline		Change from Baseline				Difference from placebo				
		Mean	SE	Mean	SE	Adj. Mean	SE	Adj. Mean	SE	95% CI		p-value
										LL	UL	
Systolic												
Placebo	271	131.72	0.72	0.42	0.50	0.48	0.49					
Empa 10	276	131.34	0.78	-2.99	0.53	-2.95	0.48	-3.44	0.69	-4.78	-2.09	< 0.0001
Empa 25	276	131.18	0.73	-3.59	0.56	-3.68	0.48	-4.16	0.68	-5.50	-2.83	< 0.0001
Diastolic												
Placebo	271	75.16	0.45	0.30	0.31	0.32	0.29					
Empa 10	276	75.13	0.50	-1.10	0.30	-1.04	0.28	-1.36	0.40	-2.15	-0.56	0.0008
Empa 25	276	74.64	0.45	-1.32	0.30	-1.40	0.28	-1.72	0.40	-2.51	-0.93	< 0.0001

SE = standard error; Adj. Mean = adjusted mean; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg

Source: Tables 11.4.1.1.1: 2 and 11.4.1.2.1: 1 (Study 1245.48 study report)

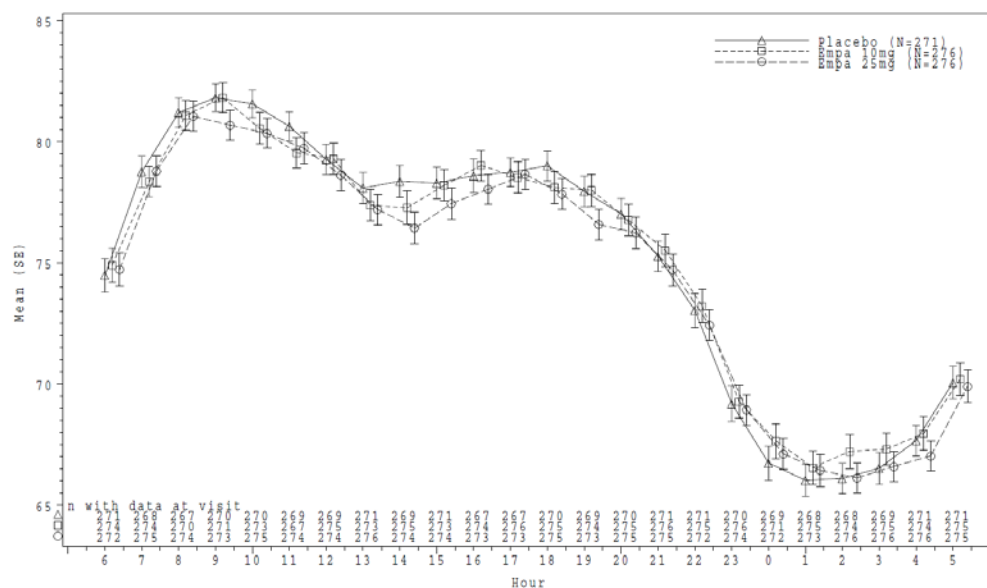
In addition to examining the mean blood pressure, the use of 24 hour ambulatory blood pressure monitoring in this study allowed for comparison of the hourly blood pressure profiles. At baseline, patients had very similar profiles at baseline with the expected decrease in the night time hours (defined by the Applicant as from 10PM until 6AM) (Figure 7, Figure 8). By twelve weeks, a noticeable difference in blood pressure profiles was seen for systolic blood pressure, primarily during the day time hours (Figure 9). A difference in diastolic blood pressure profiles was less apparent (Figure 10). Night time blood pressures appeared to be essentially unchanged.

Figure 7 Hourly Systolic Blood Pressure Profile – Study 1245.48, Baseline, Full Analysis Set, Last Observation Carried Forward Following Change in Antihypertensive Therapy



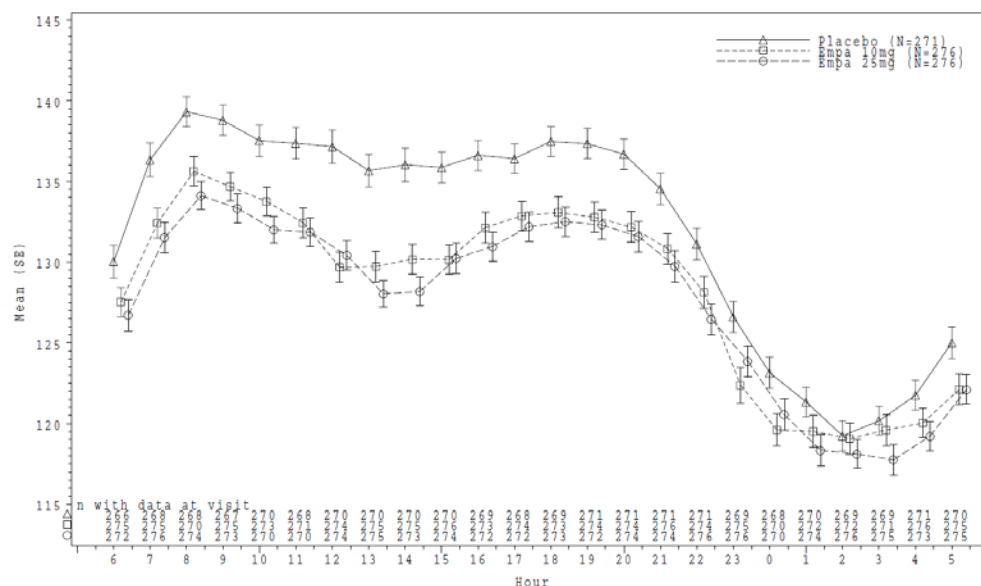
Source: Figure 15.2.4.5.5: 1 (Study 1245.48 study report)

Figure 8 Hourly Diastolic Blood Pressure Profile – Study 1245.48, Baseline, Full Analysis Set, Last Observation Carried Forward Following Change in Antihypertensive Therapy



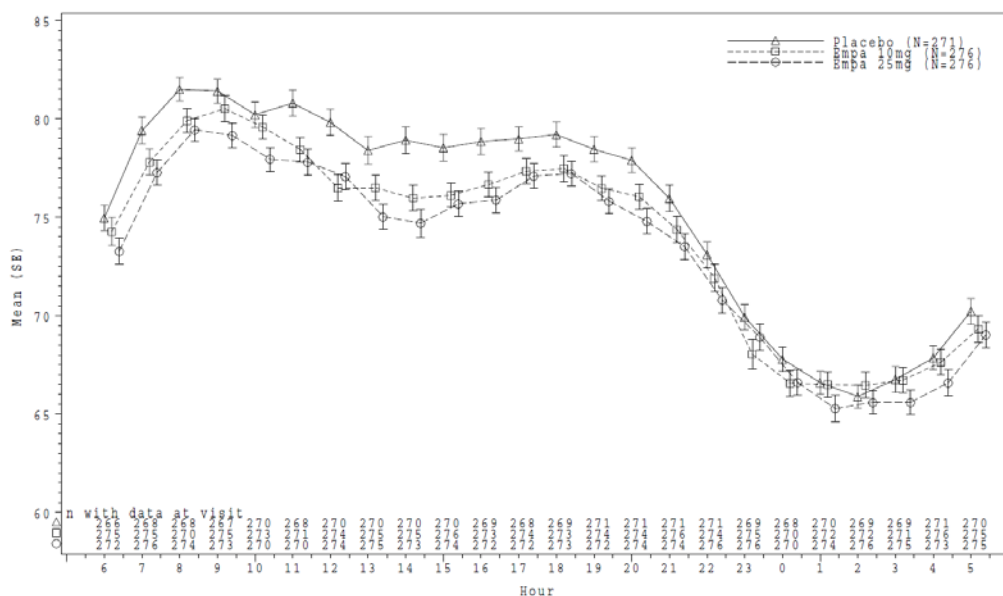
Source: Figure 15.2.4.5.6: 1 (Study 1245.48 study report)

Figure 9 Hourly Systolic Blood Pressure Profile – Study 1245.48, Week 12, Full Analysis Set, Last Observation Carried Forward Following Change in Antihypertensive Therapy



Source: Figure 15.2.4.5.5: 2 (Study 1245.48 study report)

Figure 10 Hourly Diastolic Blood Pressure Profile – Study 1245.48, Week 12, Full Analysis Set, Last Observation Carried Forward Following Change in Antihypertensive Therapy



Source: Figure 15.2.4.5.6: 2 (Study 1245.48 study report)

6.1.6 Other Endpoints

6.1.6.1 Percentage of Patients Achieving Hemoglobin A1c < 7.0%

A greater percentage of empagliflozin-treated patients with a baseline HbA1c $\geq 7.0\%$ was able to achieve an HbA1c < 7.0% at 24 weeks (Table 20). Odds ratios were > 1.0 for all studies, and slightly higher for the 25 mg dose than the 10 mg dose. This was true for the individual studies, as well as for the efficacy groupings.

Table 20 Percentage of Patients Achieving Hemoglobin A1c < 7.0% - 24 Weeks, Full Analysis Set, Noncompleters Considered Failure

– For patients with baseline Hemoglobin A1c $\geq 7.0\%$

	N	n	%	OR	95% CI		p-value
					LL	UL	
Study 1245.19							
Placebo	155	12	7.7				
Empa 10	151	36	23.8	3.889	1.882	8.034	0.0002
Empa 25	160	49	30.6	5.286	2.607	10.719	< 0.0001
Study 1245.20							
Placebo	208	25	12.0				
Empa 10	204	72	35.3	4.089	2.425	6.896	< 0.0001
Empa 25	202	88	43.6	6.054	3.601	10.179	< 0.0001
Study 1245.23 _{met}							
Placebo	184	23	12.5				
Empa 10	199	76	38.2	4.830	2.811	8.301	< 0.0001
Empa 25	191	77	40.3	5.033	2.924	8.661	< 0.0001
Study 1245.23 _{met+SU}							
Placebo	216	20	9.3				
Empa 10	209	56	26.8	3.976	2.235	7.074	< 0.0001
Empa 25	202	67	33.2	5.513	3.115	9.756	< 0.0001
EFF-1							
Placebo	547	60	11.0				
Empa 10	554	183	33.0	4.297	3.080	5.995	< 0.0001
Empa 25	553	210	38.0	5.316	3.820	7.399	< 0.0001
EFF-2							
Placebo	763	80	10.5				
Empa 10	763	240	31.5	4.227	3.170	5.636	< 0.0001
Empa 25	755	281	37.2	5.503	4.136	7.322	< 0.0001

OR = odds ratio; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; EFF-1 = Efficacy Grouping 1; EFF-2 = Efficacy Grouping 2

Source: Table 3.2.1.1.1: 2 (Summary of Clinical Efficacy)

6.1.6.2 Percentage of Patients Achieving Blood Pressure < 130/80 mmHg

The current American Diabetes Association (ADA) Standards of Medical Care in Diabetes Position Statement¹ proposes treatment targets for systolic blood pressure of < 140 mmHg for people with diabetes and hypertension, and a target of < 130 mmHg for some individuals if it can be achieved without undue burden. The proposed treatment target for diastolic blood pressure is < 80 mmHg. In line with these recommendations, the Applicant examined the ability of empagliflozin to assist patients in reaching a blood pressure of < 130/80.

For patients who had a baseline blood pressure \geq 130/80, empagliflozin treatment resulted in a greater percentage achieving blood pressure < 130/80 after 24 weeks of treatment (Table 21). This was true for the individual pivotal studies as well as for the efficacy groupings. Of note, statistical significance for this endpoint was not seen for some of the individual studies, and the 25 mg dose did not appear to be more efficacious than the 10 mg dose for this endpoint.

Table 21 Percentage of Patients Achieving Blood Pressure < 130/80 mmHg – 24 Weeks, Full Analysis Set, Noncompleters Considered Failure

– For patients with baseline blood pressure \geq 130/80 mmHg

	N	n	%	OR	95% CI		p-value
					LL	UL	
Study 1245.19							
Placebo	97	21	21.6				
Empa 10	89	34	38.2	2.335	1.210	4.505	0.0087
Empa 25	91	30	33.0	1.897	0.976	3.687	0.0002
Study 1245.20							
Placebo	130	19	14.6				
Empa 10	146	41	28.1	2.281	1.232	4.222	< 0.0001
Empa 25	133	46	34.6	3.194	1.730	5.899	0.0006
Study 1245.23_{met}							
Placebo	136	18	13.2				
Empa 10	142	51	35.9	3.758	2.041	6.921	0.167
Empa 25	138	42	30.4	2.953	1.586	5.499	0.2918
Study 1245.23_{met+SU}							
Placebo	138	35	25.4				
Empa 10	140	46	32.9	1.447	0.856	2.448	0.114
Empa 25	144	45	31.3	1.326	0.785	2.239	0.0591

¹American Diabetes Association Position Statement: Standards of Medical Care in Diabetes – 2013. Diabetes Care 2013; 36 (suppl 1): S11-S66.

	N	n	%	OR	95% CI		p-value
					LL	UL	
EFF-1							
Placebo	363	58	16.0				
Empa 10	377	126	33.4	2.712	1.896	3.879	< 0.0001
Empa 25	362	118	32.6	2.651	1.847	3.805	< 0.0001
EFF-2							
Placebo	501	93	18.6				
Empa 10	517	172	33.3	2.224	1.659	2.981	< 0.0001
Empa 25	506	163	32.2	2.126	1.582	2.856	< 0.0001

OR = odds ratio; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; EFF-1 = Efficacy Grouping 1; EFF-2 = Efficacy Grouping 2

Source: Table 3.2.4.3.1: 1 (Summary of Clinical Efficacy)

6.1.6.3 Percentage of Patients With > 5% Reduction in Body Weight

The percentage of patients able to achieve a reduction in body weight from baseline of more than 5% was analyzed for each pivotal study and for the pooled efficacy groupings. A greater percentage of the empagliflozin-treated patients were able to achieve a > 5% reduction of body weight from baseline compared to placebo-treated patients (Table 22). The odds ratio for achieving this endpoint was similar for both doses in the aggregated efficacy groupings. Interestingly, the 10 mg dose appeared better at achieving this target in Studies 1245.19 and 1245.23_{met+SU}, while the 25 mg dose appeared better in Study 1245.20. No difference between the two doses was seen in EFF-1 or EFF-2.

Table 22 Percentage of Patients Achieving > 5% Body Weight Reduction – 24 Weeks, Full Analysis Set, Noncompleters Considered Failure

	N	n	%	OR	95% CI		p-value
					LL	UL	
Study 1245.19							
Placebo	165	9	5.5				
Empa 10	165	31	18.8	4.052	1.852	8.865	< 0.0001
Empa 25	168	23	13.7	2.685	1.195	8.821	< 0.0001
Study 1245.20							
Placebo	228	10	4.4				
Empa 10	224	51	22.8	6.498	3.194	13.221	< 0.0001
Empa 25	224	65	29.0	9.075	4.503	18.293	< 0.0001
Study 1245.23_{met}							
Placebo	207	10	4.8				
Empa 10	217	46	21.2	5.367	2.623	10.982	< 0.0001
Empa 25	213	49	23.0	5.882	2.884	11.997	< 0.0001

	N	n	%	OR	95% CI		p-value
					LL	UL	
Study 1245.23_{met+SU}							
Placebo	225	13	5.8				
Empa 10	225	62	27.9	6.186	3.278	11.662	< 0.0001
Empa 25	216	51	23.6	5.042	2.646	9.605	< 0.0001
EFF-1							
Placebo	600	29	4.8				
Empa 10	606	128	21.1	5.315	3.485	8.865	< 0.0001
Empa 25	605	137	22.6	5.796	3.808	6.032	< 0.0001
EFF-2							
Placebo	825	42	5.1				
Empa 10	831	190	22.9	5.565	3.918	8.105	< 0.0001
Empa 25	821	188	22.9	5.580	3.926	8.821	< 0.0001

OR = odds ratio; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; EFF-1 = Efficacy Grouping 1; EFF-2 = Efficacy Grouping 2

Source: Table 3.2.3.1.3: 1 (Summary of Clinical Efficacy)

6.1.6.4 Percentage of Patients Requiring Rescue Medication

For patients who met predefined rescue criteria, rescue medication was permitted. The need for rescue medication was defined for the integrated analysis of efficacy by either an increase in the dose of background antidiabetic medication above baseline for seven days or more, or the use of additional antidiabetic medication for seven days or more. Patients who prematurely discontinued due to lack of efficacy and increased background medication dose or started additional antidiabetic medication were also counted as requiring rescue medication. The need for rescue medication can be viewed as evidence of poor glycemic control and, as an extension of this, decreased efficacy.

More patients in the placebo groups required rescue medication. This was true for the individual studies, and for the efficacy groupings (Table 23). Notably, the patients receiving the 10 mg dose appeared more likely to require rescue medication compared to the 25 mg dose.

Table 23 Percentage of Patients Requiring Rescue Medication – 24 Weeks, Full Analysis Set

	N	n	%	OR	95% CI		p-value
					LL	UL	
Study 1245.19							
Placebo	165	20	12.1				
Empa 10	165	7	4.2	0.329	0.133	0.811	0.0158
Empa 25	168	3	1.8	0.138	0.040	0.479	0.0018
Study 1245.20							
Placebo	228	40	17.5				
Empa 10	224	7	3.1	0.119	0.049	0.288	< 0.0001
Empa 25	224	4	1.8	0.067	0.022	0.201	< 0.0001
Study 1245.23_{met}							
Placebo	207	38	18.4				
Empa 10	217	12	5.5	0.237	0.117	0.480	< 0.0001
Empa 25	213	9	4.2	0.174	0.079	0.387	< 0.0001
Study 1245.23_{met+SU}							
Placebo	225	32	14.2				
Empa 10	225	8	3.6	0.223	0.099	0.506	0.0003
Empa 25	216	4	1.9	0.104	0.035	0.308	< 0.0001
EFF-1							
Placebo	600	77	12.8				
Empa 10	606	20	3.3	0.210	0.124	0.355	< 0.0001
Empa 25	605	11	1.8	0.112	0.058	0.219	< 0.0001
EFF-2							
Placebo	825	130	15.8				
Empa 10	831	34	4.1	0.210	0.140	0.315	< 0.0001
Empa 25	821	20	2.4	0.120	0.073	0.198	< 0.0001

OR = odds ratio; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; EFF-1 = Efficacy Grouping 1; EFF-2 = Efficacy Grouping 2

Source: Table 3.2.6.1: 1 (Summary of Clinical Efficacy)

6.1.7 Subpopulations

6.1.7.1 By Baseline Renal Function

Given the mechanism of action for empagliflozin, renal impairment could conceivably have an impact on efficacy. To facilitate analysis of efficacy by baseline renal function, eGFR calculated by the Modification of Diet in Renal Disease (MDRD) formula¹ was used to group patients. Normal renal function was defined as eGFR ≥ 90 ml/min/1.73 m², mild renal impairment was defined as 60 to < 90 ml/min/1.73 m², moderate renal impairment was defined as 30 to < 60

¹eGFR (mL/min/1.73 m²) = $175 \times [\text{serum creatinine } (\mu\text{mol/L})/88.4]^{-1.154} \times [\text{age}]^{-0.203} \times [0.742 \text{ if patient is female}] \times [1.212 \text{ if patient is of African origin}]$

ml/min/1.73 m², and severe renal impairment was defined as < 30 ml/min/1.73 m². Moderate renal impairment was further divided in to moderate A (45 to < 60 ml/min/1.73 m²) and moderate B (30 to < 45 ml/min/1.73 m²).

Analysis of change in HbA1c by baseline renal function for patients in EFF-2 showed reduced efficacy of empagliflozin in patients with greater degrees of renal impairment (Table 24, Figure 11). While patients with mild renal impairment continued to show a statistically significant reduction in HbA1c compared to placebo, the magnitude was less than that seen in the normal renal function patients. Further reductions in efficacy were seen in patients with moderate renal insufficiency. Results from the moderate A group were essentially the same as that seen for the whole moderate renal impairment group, likely due to the small number of patients in the moderate B group. There were too few patients in the moderate B group to make any meaningful conclusions for patients with an eGFR < 45 ml/min/1.73 m².

Study 1245.36 was specifically designed to explore the efficacy and safety of empagliflozin in patients with renal impairment. As was seen with EFF-2, efficacy waned with worsening baseline renal impairment (Table 25). Only a single dose (empagliflozin 25 mg) was studied in moderate and severe renal impairment, limiting the available information with regards to the 10 mg dose. Detailed analysis for patients with severe renal impairment was not performed, but there was no apparent treatment effect for empagliflozin in these patients.

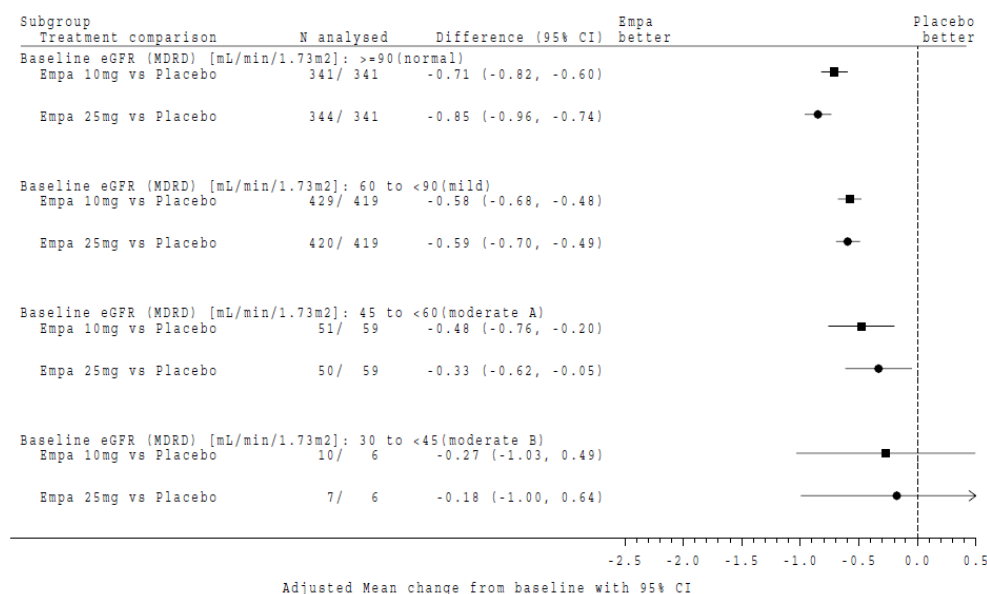
Table 24 Change in Hemoglobin A1c by Baseline Renal Function – Efficacy Grouping 2, 24 Weeks, Full Analysis Set, Last Observation Carried Forward

	N	Baseline		Change from Baseline		Difference from placebo				
		Mean	SE	Adj Mean	SE	Adj Mean	SE	95% CI		p-value
								UL	LL	
eGFR ≥ 90										
Placebo	341	8.08	0.05	-0.05	0.04					
Empa 10	341	8.04	0.05	-0.76	0.04	-0.71	0.06	-0.82	-0.60	< 0.0001
Empa 25	344	8.02	0.05	-0.90	0.04	-0.85	0.06	-0.96	-0.74	< 0.0001
eGFR 60 to < 90										
Placebo	419	8.01	0.04	-0.10	0.04					
Empa 10	429	7.94	0.04	-0.68	0.04	-0.58	0.05	-0.68	-0.48	< 0.0001
Empa 25	420	7.93	0.04	-0.70	0.04	-0.59	0.05	-0.70	-0.49	< 0.0001
eGFR 30 to < 60										
Placebo	65	7.88	0.09	-0.13	0.09					
Empa 10	61	7.93	0.11	-0.57	0.10	-0.44	0.13	-0.70	-0.17	0.0011
Empa 25	57	7.84	0.10	-0.44	0.10	-0.31	0.14	-0.58	-0.04	0.0231

		Baseline		Change from Baseline		Difference from placebo				
	N	Mean	SE	Adj Mean	SE	Adj Mean	SE	95% CI		p-value
								UL	LL	
eGFR 45 to < 60										
Placebo	59	7.87	0.09	-0.14	0.10					
Empa 10	51	7.95	0.13	-0.62	0.11	-0.48	0.14	-0.76	-0.20	0.0009
Empa 25	50	7.85	0.10	-0.47	0.11	-0.33	0.14	-0.62	-0.05	0.0218
eGFR 30 to < 45										
Placebo	6	7.92	0.39	-0.05	0.31					
Empa 10	10	7.84	0.23	-0.32	0.24	-0.27	0.39	-1.03	0.49	0.4861
Empa 25	7	7.74	0.37	-0.23	0.28	-0.18	0.42	-1.00	0.64	0.6729

SE = standard error; Adj. Mean = adjusted mean; CI = confidence interval; UL = upper limit; LL = lower limit; eGFR = estimated glomerular filtration rate; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg
Source: Table 3.3.1.10: 1 (Summary of Clinical Efficacy)

Figure 11 Forest Plot of Change in Hemoglobin A1c by Baseline Renal Function – Efficacy Grouping 2, 24 Weeks Full Analysis Set, Last Observation Carried Forward



Source: Figure 4.1.3.9.6 (Integrated Summary of Efficacy)

Table 25 Change in Hemoglobin A1c by Baseline Renal Function – Study 1245.36, 24 Weeks, Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline		Difference from Placebo				
	N	Mean	SE	Adj Mean	SE	Adj Mean	SE	95% CI		p-value
								UL	LL	
eGFR 60 to < 90										
Placebo	95	8.09	0.08	0.06	0.07					
Empa 10	98	8.02	0.09	-0.46	0.07	-0.52	0.10	-0.72	-0.32	< 0.0001
Empa 25	97	7.96	0.07	-0.63	0.07	-0.68	0.10	-0.88	-0.49	< 0.0001
eGFR 30 to < 60										
Placebo	187	8.04	0.06	0.05	0.05					
Empa 25	187	8.03	0.06	-0.37	0.05	-0.42	0.07	-0.56	-0.28	< 0.0001
eGFR 45 to < 60										
Placebo	89	8.08	0.09	-0.08	0.08					
Empa 25	91	8.12	0.09	-0.54	0.07	-0.46	0.10	-0.56	-0.28	< 0.0001
eGFR 30 to < 45										
Placebo	98	8.01	0.08	0.17	0.07					
Empa 25	96	7.95	0.08	-0.21	0.07	-0.39	0.10	-0.58	-0.19	0.0001
eGFR 15 to < 30										
Placebo	37	8.16	0.16							
Empa 25	37	8.06	0.17							

SE = standard error; Adj. Mean = adjusted mean; CI = confidence interval; UL = upper limit; LL = lower limit; eGFR = estimated glomerular filtration rate; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg
Source: Table 15.2.1.2.1.2: 1 (Study 1245.36 study report)

6.1.7.2 By Age

Subjects were divided into age groups to allow for analysis of the effect of age (Table 26). While reductions in HbA1c from baseline were seen for all age groups, it is notable that efficacy was reduced as age increased. This reduced efficacy was most notable in patients > 75 years old, although there were few patients in this age group. This decrease in efficacy with age was also seen in the analysis of the interim data from the ongoing cardiovascular outcomes study (Table 27).

As renal function typically declines with age, the effect of changes in renal function in this subgroup must be considered with respect to its effect on efficacy. A post-hoc subgroup analysis performed on the interim data for Study 1245.25 examining the impact of renal function on the efficacy of empagliflozin in patients ≥ 75 years of age suggested that the decreased efficacy seen with increasing age was due (at least in part) to decreases in renal function (Table 28).

Table 26 Change in Hemoglobin A1c by Age – Efficacy Grouping 2, 24 Weeks, Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline		Difference from placebo				
	N	Mean	SE	Adj. mean	SE	Adj. mean	SE	95% CI		p-value
								LL	UL	
< 50 years old										
Placebo	222	8.10	0.06	-0.03	0.05					
Empa 10	224	8.03	0.06	-0.78	0.05	-0.75	0.07	-0.89	-0.61	< 0.0001
Empa 25	240	8.01	0.06	-0.91	0.05	-0.87	0.07	-1.01	-0.74	< 0.0001
50 to < 65 years old										
Placebo	459	8.04	0.04	-0.08	0.04					
Empa 10	439	7.99	0.04	-0.66	0.04	-0.58	0.05	-0.68	-0.48	< 0.0001
Empa 25	432	8.00	0.04	-0.07	0.04	-0.63	0.05	-0.73	-0.53	< 0.0001
65 to < 75 years old										
Placebo	119	7.91	0.07	-0.01	0.07					
Empa 10	144	7.91	0.07	-0.73	0.06	-0.60	0.09	-0.78	-0.42	< 0.0001
Empa 25	132	7.77	0.06	-0.67	0.07	-0.54	0.10	-0.73	-0.36	< 0.0001
≥ 75 years old										
Placebo	25	7.70	0.14	-0.50	0.15					
Empa 10	24	7.89	0.16	-0.55	0.15	-0.21	0.22	-0.63	0.22	0.3369
Empa 25	17	7.81	0.18	-0.67	0.18	-0.33	0.24	-0.79	0.14	0.1684

SE = standard error; Adj. Mean = adjusted mean; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg

Source: Table 3.3.1.1: 1 (Summary of Clinical Efficacy)

Table 27 Change in Hemoglobin A1c by Age – Study 1245.25, Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline		Difference from placebo				
	N	Mean	SE	Adj. mean	SE	Adj. mean	SE	95% CI		p-value
								LL	UL	
12 weeks										
< 50 years old										
Placebo	88	8.37	0.09	0.17	0.07					
Empa 10	105	8.24	0.08	-0.47	0.07	-0.64	0.10	-0.83	-0.45	< 0.0001
Empa 25	104	8.18	0.09	-0.75	0.07	-0.92	0.10	-1.11	-0.73	< 0.0001
50 to < 65 years old										
Placebo	759	8.13	0.03	-0.10	0.02					
Empa 10	741	8.12	0.03	-0.49	0.02	-0.39	0.03	-0.46	-0.32	< 0.0001
Empa 25	739	8.15	0.03	-0.59	0.02	-0.49	0.03	-0.56	-0.43	< 0.0001
65 to < 75 years old										
Placebo	505	8.03	0.04	-0.14	0.03					
Empa 10	506	8.02	0.04	-0.54	0.03	-0.40	0.04	-0.48	-0.32	< 0.0001
Empa 25	534	8.01	0.04	-0.51	0.03	-0.37	0.04	-0.46	-0.29	< 0.0001

		Baseline		Change from Baseline		Difference from placebo				
	N	Mean	SE	Adj. mean	SE	Adj. mean	SE	95% CI		p-value
								LL	UL	
≥ 75 years old										
Placebo	142	7.96	0.06	-0.13	0.06					
Empa 10	139	8.10	0.07	-0.42	0.06	-0.29	0.08	-0.45	-0.14	0.0002
Empa 25	122	7.96	0.07	-0.48	0.06	-0.35	0.08	-0.51	-0.19	< 0.0001
28 weeks										
< 50 years old										
Placebo	88	8.37	0.09	0.24	0.08					
Empa 10	105	8.24	0.08	-0.41	0.07	-0.66	0.11	-0.87	-0.44	< 0.0001
Empa 25	104	8.18	0.09	-0.77	0.07	-1.01	0.11	-1.23	-0.80	< 0.0001
50 to < 65 years old										
Placebo	759	8.13	0.03	-0.02	0.03					
Empa 10	741	8.12	0.03	-0.45	0.03	-0.43	0.04	-0.51	-0.35	< 0.0001
Empa 25	739	8.15	0.03	-0.57	0.03	-0.55	0.04	-0.62	-0.47	< 0.0001
65 to < 75 years old										
Placebo	505	8.03	0.04	-0.12	0.03					
Empa 10	506	8.02	0.04	-0.52	0.03	-0.40	0.05	-0.49	-0.31	< 0.0001
Empa 25	534	8.01	0.04	-0.50	0.03	-0.38	0.05	-0.47	-0.29	< 0.0001
≥ 75 years old										
Placebo	142	7.96	0.06	-0.20	0.06					
Empa 10	139	8.10	0.07	-0.40	0.06	-0.20	0.09	-0.37	-0.02	0.0290
Empa 25	122	7.96	0.07	-0.50	0.07	-0.30	0.09	-0.48	-0.11	0.0014

SE = standard error; Adj. Mean = adjusted mean; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg

Source: Tables 4.1.4.1.2.1 and 4.1.4.1.2.4 (Integrated Summary of Efficacy)

Table 28 Change in Hemoglobin A1c for Patients ≥ 75 Years Old by Estimated Glomerular Filtration Rate – Study 1245.25, Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline		Difference from Placebo				
	N	Mean	SE	Adj. mean	SE	Adj. mean	SE	95% CI		p-value
								LL	UL	
12 weeks										
eGFR ≥ 60										
Placebo	70	7.98	0.09	-0.05	0.08					
Empa 10	71	8.00	0.11	-0.44	0.08	-0.38	0.11	-0.61	-0.16	0.0008
Empa 25	62	7.96	0.10	-0.61	0.09	-0.55	0.12	-0.79	-0.32	< 0.0001
eGFR < 60										
Placebo	72	7.94	0.09	-0.08	0.08					
Empa 10	68	8.20	0.10	-0.29	0.08	-0.20	0.12	-0.43	0.02	0.0800
Empa 25	60	7.96	0.10	-0.21	0.09	-0.13	0.12	-0.36	0.10	0.2751

		Baseline		Change from Baseline		Difference from Placebo				
	N	Mean	SE	Adj. mean	SE	Adj. mean	SE	95% CI		p-value
								LL	UL	
28 weeks										
eGFR ≥ 60										
Placebo	70	7.98	0.09	-0.09	0.09					
Empa 10	71	8.00	0.11	-0.42	0.09	-0.33	0.12	-0.57	-0.08	0.0084
Empa 25	62	7.96	0.10	-0.57	0.09	-0.48	0.13	-0.73	-0.23	0.0002
eGFR < 60										
Placebo	72	7.94	0.09	-0.17	0.09					
Empa 10	68	8.20	0.10	-0.21	0.09	-0.04	0.13	-0.29	0.21	0.7685
Empa 25	60	7.96	0.10	-0.28	0.09	-0.10	0.13	-0.35	0.15	0.4267

SE = standard error; Adj. Mean = adjusted mean; CI = confidence interval; LL = lower limit; UL = upper limit, eGFR = estimated glomerular filtration rate in ml/min/1.73 m²; Empa 10 = empagliflozin 10 mg; Empag 25 = empagliflozin 25 mg
Source: Tables 4.1.4.1.3.1 and 4.1.4.1.3.2 (Integrated Summary of Efficacy)

6.1.7.3 By Baseline Hemoglobin A1c

Subgroup analysis by baseline HbA1c was performed by dividing patients into the following categories: < 8.0%, 8.0 to < 9.0%, and ≥ 9.0%. The upper limit for HbA1c for inclusion was 10.0%. Subjects with a baseline HbA1c > 10.0% were allowed to enroll in an open-label arm. The results of this population will not be discussed. A statistically significant reduction in HbA1c was seen for both doses of empagliflozin compared to placebo for all categories (Table 29). As baseline HbA1c increased, so too did the magnitude of the reduction in HbA1c. The reductions were similar for both doses.

Table 29 Change in Hemoglobin A1c by Baseline Hemoglobin A1c – 24 Weeks, Efficacy Grouping 2, Full Analysis Set, Last Observation Carried Forward

	Placebo		Empa 10		Empa 25	
HbA1c < 8.0%						
N	440		456		453	
Baseline (SE)	7.38	0.02	7.36	0.02	7.35	0.02
Adjusted mean change (SE)	0.00	0.04	-0.40	0.04	-0.47	0.04
Adjusted mean change vs. placebo (SE)			-0.40	0.05	-0.46	0.05
95% CI (LL, UL)			-0.50	-0.30	-0.57	-0.36
p-value			< 0.0001		< 0.0001	
HbA1c 8.0% to < 9.0%						
N	257		257		261	
Baseline (SE)	8.41	0.02	7.40	0.02	8.38	0.02
Adjusted mean change (SE)	-0.13	0.05	-0.87	0.05	-0.92	0.05
Adjusted mean change vs. placebo (SE)			-0.75	0.07	-0.79	0.07
95% CI (LL, UL)			-0.88	-0.61	-0.93	-0.66
p-value			< 0.0001		< 0.0001	

	Placebo		Empa 10		Empa 25	
HbA1c \geq 9.0%						
N	128		118		107	
Baseline (SE)	9.49	0.04	9.47	0.04	9.56	0.05
Adjusted mean change (SE)	-0.34	0.07	-1.48	0.07	-1.52	0.07
Adjusted mean change vs. placebo (SE)			-1.14	0.10	-1.18	0.10
95% CI (LL, UL)			-1.33	-0.94	-1.38	-0.98
p-value			< 0.0001		< 0.0001	

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; HbA1c = hemoglobin A1c; SE = standard error; CI = confidence interval; LL = lower limit; UL = upper limit
Source: Table 4.1.3.7.7 (Integrated Summary of Efficacy)

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Two doses were selected for study in the pivotal phase 3 studies supporting this NDA: 10 mg and 25 mg. There was a numerically greater decrease in HbA1c from baseline for the 25 mg dose compared to the 10 mg dose at 24 and 52 weeks (Table 30, Table 31). However, the difference between the two doses failed to reach statistical significance. In the CVOT, interim data were analyzed to evaluate change in HbA1c at twelve and 28 weeks (Table 32). A difference between the two doses was seen, with a p-value < 0.05. This difference, however, was < 0.1%.

The 25 mg dose was more efficacious in achieving certain categorical responses and patients in the 25 mg dose treatment arm less frequently required rescue medication. A greater percentage of patients in the 25 mg dose treatment arm with baseline HbA1c \geq 7% achieved an HbA1c < 7% with p-values < 0.05 for the pooled efficacy grouping EFF-2 at 24 and 52 weeks (Table 33), as well as for the CVOT at twelve and 28 weeks (Table 34). This was also the case for changes in fasting plasma glucose (Table 35 Table 36). There was no clinically or statistically significant difference between the two doses for changes in body weight (Table 37, Table 38), or blood pressure (systolic and diastolic) (Table 39, Table 40, Table 41, Table 42).

Overall, there does not appear to be a significant difference in efficacy between the two doses. Though the efficacy of the 25 mg dose in reducing HbA1c is numerically greater than the 10 mg dose, the differences between the two doses are small and rarely reach statistical significance. For those endpoints where a p-value < 0.05 is seen, the differences between the two doses is small and of unclear clinical significance.

Table 30 Comparison of Dose on Change in Hemoglobin A1c – 24 Weeks, Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline		Difference from Empa 10		95% CI		
	N	Mean	SE	Adj. mean	SE	Adj. mean	SE	LL	UL	p-value
Study 1245.19										
Empa 10	165	8.07	0.07	-0.59	0.07					
Empa 25	168	8.06	0.06	-0.71	0.07	-0.12	0.09	-0.31	0.06	0.1867
Study 1245.20										
Empa 10	224	7.87	0.06	-0.66	0.05					
Empa 25	224	7.86	0.06	-0.78	0.05	-0.12	0.07	-0.26	0.03	0.1113
Study 1245.23_{met}										
Empa 10	217	7.94	0.05	-0.71	0.05					
Empa 25	213	7.86	0.06	-0.77	0.05	-0.06	0.07	-0.19	0.07	0.3618
Study 1245.23_{met+SU}										
Empa 10	225	8.07	0.05	-0.82	0.05					
Empa 25	216	8.10	0.06	-0.77	0.05	0.04	0.07	-0.09	0.18	0.5068
EFF-2										
Empa 10	831	7.98	0.03	-0.70	0.03					
Empa 25	821	7.96	0.03	-0.76	0.03	-0.06	0.04	-0.13	0.01	0.1184

Empa 10 = empagliflozin 10 mg; CI = confidence interval; SE = standard error; Adj. Mean = adjusted mean; LL = lower limit; UL = upper limit; Empa 25 = empagliflozin 25 mg; EFF-2 = Efficacy Grouping 2
Source: Table 4.1.2.1.1 (Integrated Summary of Efficacy)

Table 31 Comparison of Dose on Change in Hemoglobin A1c – 52 Weeks, Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline		Difference from Empa 10		95% CI		
	N	Mean	SE	Adj. mean	SE	Adj. mean	SE	LL	UL	p-value
Study 1245.19										
Empa 10	165	8.07	0.07	-0.61	0.07					
Empa 25	168	8.06	0.06	-0.69	0.07	-0.09	0.10	-0.28	0.10	0.3761
Study 1245.20										
Empa 10	224	7.87	0.06	-0.67	0.05					
Empa 25	224	7.86	0.06	-0.82	0.05	-0.15	0.07	-0.30	-0.01	0.0400
Study 1245.23_{met}										
Empa 10	217	7.94	0.05	-0.68	0.05					
Empa 25	213	7.86	0.06	-0.76	0.05	-0.08	0.07	-0.21	0.06	0.2848
Study 1245.23_{met+SU}										
Empa 10	225	8.07	0.05	-0.74	0.06					
Empa 25	216	8.10	0.06	-0.70	0.05	0.04	0.08	-0.11	0.19	0.5700

		Baseline		Change from Baseline		Difference from Empa 10		95% CI		
	N	Mean	SE	Adj. mean	SE	Adj. mean	SE	LL	UL	p-value
EFF-2										
Empa 10	831	7.98	0.03	-0.68	0.03					
Empa 25	821	7.96	0.03	-0.75	0.03	-0.07	0.04	-0.14	0.01	0.0923

Empa 10 = empagliflozin 10 mg; CI = confidence interval; SE = standard error; Adj. Mean = adjusted mean; LL = lower limit; UL = upper limit; Empa 25 = empagliflozin 25 mg; EFF-2 = Efficacy Grouping 2

Source: Table 4.1.2.3.1 (Integrated Summary of Efficacy)

Table 32 Comparison of Dose on Change in Hemoglobin A1c from Baseline – Study 1245.25, Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline		Difference from Empa 10		95% CI		
	N	Mean	SE	Adj. mean	SE	Adj. mean	SE	LL	UL	p-value
12 weeks										
Empa 10	1491	8.09	0.02	-0.50	0.02					
Empa 25	1499	8.09	0.02	-0.56	0.02	-0.07	0.02	-0.12	-0.02	0.0058
28 weeks										
Empa 10	1491	8.09	0.02	-0.47	0.02					
Empa 25	1499	8.09	0.02	-0.55	0.02	-0.09	0.03	-0.14	-0.03	0.0022

Empa 10 = empagliflozin 10 mg; CI = confidence interval; SE = standard error; Adj. Mean = adjusted mean; LL = lower limit; UL = upper limit; Empa 25 = empagliflozin 25 mg

Source: Tables 4.1.4.1.1.1 and 4.1.4.1.1.4 (Integrated Summary of Efficacy)

Table 33 Comparison of Dose on Ability to Achieve Hemoglobin A1c < 7.0% –Full Analysis Set, Noncompleters Considered Failure, Logistic Regression

– For patients with baseline hemoglobin A1c $\geq 7.0\%$

		Achieving HbA1c < 7.0%				Odds Ratio vs. Empa 10				
				95% CI			95% CI			
	N	n	%	LL	UL		LL	UL		p-value
24 Weeks										
Study 1245.19										
Empa 10	151	36	23.8	17.3	31.4					
Empa 25	160	49	30.6	23.6	38.4	1.359	0.798	2.315		0.2585
Study 1245.20										
Empa 10	204	72	35.3	28.7	42.3					
Empa 25	202	88	43.6	36..6	50.7	1.481	0.971	2.256		0.0680
Study 1245.23_{met}										
Empa 10	199	76	38.2	31.4	45.3					
Empa 25	191	77	40.3	33.3	47.6	1.042	0.679	1.598		0.8506
Study 1245.23_{met+SU}										
Empa 10	209	56	26.8	20.9	33.3					
Empa 25	202	67	33.2	26.7	40.1	1.386	0.885	2.171		0.1534

		Achieving HbA1c < 7.0%				Odds Ratio vs. Empa 10			
				95% CI			95% CI		
	N	n	%	LL	UL		LL	UL	p-value
EFF-2									
Empa 10	763	240	31.5	28.2	34.9				
Empa 25	755	281	37.2	33.8	40.8	1.302	1.040	1.629	0.0212
52 Weeks									
Study 1245.19									
Empa 10	151	22	14.6	9.4	21.2				
Empa 25	160	38	23.8	17.4	31.1	1.770	0.959	3.266	0.0679
Study 1245.20									
Empa 10	204	65	31.9	25.5	38.7				
Empa 25	202	78	38.6	31.9	45.7	1.395	0.908	2.145	0.1291
Study 1245.23_{met}									
Empa 10	199	56	28.1	22.0	34.9				
Empa 25	191	59	10.9	24.4	38.0	1.064	0.675	1.679	0.7892
Study 1245.23_{met+SU}									
Empa 10	209	39	18.7	13.6	24.6				
Empa 25	202	42	20.8	15.4	27.0	1.140	0.688	1.891	0.6107
EFF-2									
Empa 10	763	182	23.9	20.9	27.0				
Empa 25	755	217	28.7	25.5	32.1	1.286	1.010	1.638	0.0414

HbA1c = hemoglobin A1c; Empa 10 = empagliflozin 10 mg; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 25 = empagliflozin 25 mg; EFF-2 = Efficacy Grouping 2

Source: Tables 4.6.1.2.1.6 and 4.6.1.2.2.6 (Integrated Summary of Efficacy)

Table 34 Comparison of Dose on Ability to Achieve Hemoglobin A1c < 7.0% - Study 1245.25, Full Analysis Set, Noncompleters Considered Failure, Logistic Regression

– For patients with baseline hemoglobin A1c \geq 7.0%

		Achieving HbA1c < 7.0%				Odds Ratio vs. Empa 10			
				95% CI			95% CI		
	N	n	%	LL	UL		LL	UL	p-value
12 weeks									
Empa 10	1398	279	20.0	17.9	22.2				
Empa 25	1407	337	24.0	21.7	26.3	1.317	1.081	1.605	0.0063
28 weeks									
Empa 10	1398	268	19.2	17.1	21.3				
Empa 25	1407	319	22.7	20.5	25.0	1.261	1.040	1.530	0.0183

HbA1c = hemoglobin A1c; Empa 10 = empagliflozin 10 mg; CI = confidence interval; LL = lower limit; UL = upper limit; Empa 25 = empagliflozin 25 mg

Source: Tables 4.6.1.3.1.4 and 4.6.1.3.1.5 (Integrated Summary of Efficacy)

Table 35 Comparison of Dose on Changes in Fasting Plasma Glucose (mg/dL) –Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline		Difference from Empa 10		95% CI		
	N	Mean	SE	Adj. Mean	SE	Adj. Mean	SE	LL	UL	p-value
24 Weeks										
Study 1245.19										
Empa 10	163	152.0	3.0	-17.1	2.6					
Empa 25	168	151.9	2.9	-22.3	2.6	-5.2	3.7	-12.4	2.0	0.1596
Study 1245.20										
Empa 10	223	152.8	2.2	-20.3	1.9					
Empa 25	223	152.6	2.3	-25.3	1.9	-5.0	2.7	-10.3	0.3	0.0650
Study 1245.23 _{met}										
Empa 10	216	154.6	2.4	-19.8	1.7					
Empa 25	215	156.5	2.3	-23.4	2.0	-2.5	2.5	-7.3	2.4	0.3190
Study 1245.23 _{met+SU}										
Empa 10	225	151.0	2.2	-23.1	1.9					
Empa 25	215	156.5	2.3	-23.4	2.0	-0.2	2.8	-5.7	5.2	0.9317
EFF-2										
Empa 10	827	152.6	1.2	-20.4	1.0					
Empa 25	819	152.6	1.2	-23.2	1.0	-2.8	1.4	-5.7	0.0	0.0474
52 Weeks										
Study 1245.19										
Empa 10	163	152.0	3.0	-16.0	2.8					
Empa 25	168	151.9	2.9	-22.2	2.7	-6.2	3.9	-13.9	1.4	0.1114
Study 1245.20										
Empa 10	223	152.8	2.2	-19.0	1.9					
Empa 25	223	152.6	2.3	-24.8	1.9	-5.9	2.7	-11.1	-0.6	0.0276
Study 1245.23 _{met}										
Empa 10	216	154.6	2.4	-16.2	2.0					
Empa 25	215	156.5	2.3	-19.2	2.0	-3.0	2.8	-8.5	2.5	0.2789
Study 1245.23 _{met+SU}										
Empa 10	225	151.0	2.2	-17.2	2.2					
Empa 25	215	156.5	2.3	-18.1	2.2	-0.8	3.1	-6.9	5.2	0.7859
EFF-2										
Empa 10	827	152.6	1.2	-17.3	1.1					
Empa 25	819	152.6	1.2	-20.8	1.1	-3.5	1.5	-6.6	-0.5	0.0209

Empa 10 = empagliflozin 10 mg; CI = confidence interval; SE = standard error; Adj. Mean = adjusted mean; LL = lower limit; UL = upper limit; Empa 25 = empagliflozin 25 mg; EFF-2 = Efficacy Grouping 2

Source: Tables 4.2.2.1.1 and 4.2.2.3.1 (Integrated Summary of Efficacy)

Table 36 Comparison of Dose on Changes in Fasting Plasma Glucose (mg/dL) – Study 1245.25, Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline		Difference from Empa 10		95% CI		
	N	Mean	SE	Adj. Mean	SE	Adj. Mean	SE	LL	UL	p-value
12 weeks										
Empa 10	1487	151.9	1.1	-14.0	0.9					
Empa 25	1498	151.4	1.1	-17.6	0.9	-3.6	1.3	-6.2	-1.0	0.0058
28 weeks										
Empa 10	1487	151.9	1.1	-13.1	1.0					
Empa 25	1498	151.4	1.1	-18.2	1.0	-5.1	1.4	-7.8	-2.4	0.0002

Empa 10 = empagliflozin 10 mg; CI = confidence interval; SE = standard error; Adj. Mean = adjusted mean; LL = lower limit; UL = upper limit; Empa 25 = empagliflozin 25 mg

Source: Tables 4.2.4.1.1.1 and 4.2.4.1.1.4 (Integrated Summary of Efficacy)

Table 37 Comparison of Dose on Change in Body Weight (kg) –Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline		Difference from Empa 10		95% CI		
	N	Mean	SE	Adj. Mean	SE	Adj. Mean	SE	LL	UL	p-value
Study 1245.19										
Empa 10	165	78.10	1.57	-1.60	0.21					
Empa 25	168	78.93	1.54	-1.46	0.21	0.13	0.30	-0.46	0.73	0.6548
Study 1245.20										
Empa 10	224	78.35	1.25	-2.27	0.17					
Empa 25	224	77.80	1.20	-2.48	0.17	-0.22	0.24	-0.69	0.26	0.3743
Study 1245.23_{met}										
Empa 10	217	81.59	1.26	-2.06	0.17					
Empa 25	213	82.21	1.32	-2.46	0.17	-0.40	0.24	-0.87	0.08	0.0996
Study 1245.23_{met+SU}										
Empa 10	225	77.08	1.22	-2.16	0.15					
Empa 25	216	77.50	1.28	-2.40	0.16	-0.24	0.22	-0.67	0.19	0.2658
EFF-2										
Empa 10	831	78.77	0.65	-2.04	0.90					
Empa 25	821	79.10	0.66	-2.26	0.09	-0.21	0.12	-0.45	0.03	0.0896
52 Weeks										
Study 1245.19										
Empa 10	165	78.10	1.57	-1.54	0.22					
Empa 25	168	78.93	1.54	-1.28	0.02	0.25	0.31	-0.35	0.86	0.4121
Study 1245.20										
Empa 10	224	78.35	1.25	-1.93	0.24					
Empa 25	224	77.80	1.20	-2.49	0.24	-0.56	0.34	-1.23	0.12	0.1047

		Baseline		Change from Baseline		Difference from Empa 10		95% CI		
	N	Mean	SE	Adj. Mean	SE	Adj. Mean	SE	LL	UL	p-value
Study 1245.23_{met}										
Empa 10	217	81.59	1.26	-2.07	0.19					
Empa 25	213	82.21	1.32	-2.66	0.19	-0.59	0.27	-1.13	-0.05	0.0316
Study 1245.23_{met+SU}										
Empa 10	225	77.08	1.22	-2.23	0.17					
Empa 25	216	77.50	1.28	-2.31	0.18	-0.09	0.25	-0.57	0.40	0.7307
EFF-2										
Empa 10	831	78.77	0.65	-1.96	0.11					
Empa 25	821	79.10	0.66	-2.25	0.11	-0.29	0.15	-0.58	0.00	0.0512

Empa 10 = empagliflozin 10 mg; CI = confidence interval; SE = standard error; Adj. Mean = adjusted mean; LL = lower limit; UL = upper limit; Empa 25 = empagliflozin 25 mg; EFF-2 = Efficacy Grouping 2

Source: Tables 4.3.2.1.1 and 4.3.2.3.1 (Integrated Summary of Efficacy)

Table 38 Comparison of Dose on Change in Body Weight (kg) – Study 1245.25, Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline		Difference from Empa 10		95% CI		
	N	Mean	SE	Adj. mean	SE	Adj. mean	SE	LL	UL	p-value
12 weeks										
Empa 10	1491	85.44	0.49	-1.07	0.08					
Empa 25	1499	86.06	0.49	-1.11	0.08	-0.04	0.12	-0.27	0.19	0.7388
28 weeks										
Empa 10	1491	85.44	0.49	-1.38	0.11					
Empa 25	1499	86.06	0.49	-1.54	0.11	-0.16	0.16	-0.48	0.16	0.3254

Empa 10 = empagliflozin 10 mg; CI = confidence interval; SE = standard error; Adj. Mean = adjusted mean; LL = lower limit; UL = upper limit; Empa 25 = empagliflozin 25 mg

Source: Tables 4.3.4.1.1.1 and 4.3.4.1.1.4 (Integrated Summary of Efficacy)

Table 39 Comparison of Dose on Change in Systolic Blood Pressure (mmHg) – Full Analysis Set, Last Observation Carried Forward

	N	Baseline		Change from Baseline		Difference from Empa 10		95% CI		
		Mean	SE	Adj. mean	SE	Adj. mean	SE	LL	UL	p-value
24 Weeks										
Study 1245.19										
Empa 10	165	126.5	1.1	-3.2	0.8					
Empa 25	168	125.9	1.1	-4.1	0.8	-0.9	1.2	-3.2	1.3	0.4241
Study 1245.20										
Empa 10	224	133	1.1	-3.6	0.8					
Empa 25	224	129.9	1.2	-4.6	0.8	-1	1.1	-3.2	1.2	0.3833
Study 1245.23_{met}										
Empa 10	217	129.6	0.9	-4.1	0.7					
Empa 25	216	129.3	1	-3.5	0.7	0.6	1	-1.3	2.5	0.5352

	N	Baseline		Change from Baseline		Difference from Empa 10		95% CI		p-value
		Mean	SE	Adj. mean	SE	Adj. mean	SE	LL	UL	
Study 1245.23_{met+SU}										
Empa 10	225	128.7	0.9	-4.1	0.7					
Empa 25	216	129.3	1	-3.5	0.7	0.6	1	-1.3	2.5	0.5352
EFF-2										
Empa 10	831	129.6	0.5	-3.9	0.4					
Empa 25	821	129	0.5	-4.3	0.4	-0.5	0.5	-1.5	0.6	0.3969
52 Weeks										
Study 1245.19										
Empa 10	165	126.5	1.1	-2.1	0.8					
Empa 25	168	125.9	1.1	-2.8	0.8	-0.7	1.2	-3.1	1.6	0.5361
Study 1245.20										
Empa 10	224	133	1.1	-4	0.8					
Empa 25	224	129.9	1.2	-3.9	0.8	0.1	1.1	-2	2.3	0.9077
Study 1245.23_{met}										
Empa 10	217	129.6	0.9	-3.7	0.7					
Empa 25	216	129.3	1	-4.4	0.8	-0.7	1.1	-2.8	1.4	0.5275
Study 1245.23_{met+SU}										
Empa 10	225	128.7	0.9	-2.9	0.7					
Empa 25	216	129.3	1	-2.8	0.7	0.1	1	-1.9	2.1	0.9201
EFF-2										
Empa 10	831	129.6	0.5	-3.2	0.4					
Empa 25	821	129	0.5	-3.5	0.4	-0.3	0.5	-1.3	0.8	0.6373

Empa 10 = empagliflozin 10 mg; CI = confidence interval; SE = standard error; Adj. Mean = adjusted mean; LL = lower limit; UL = upper limit; Empa 25 = empagliflozin 25 mg; EFF-2 = Efficacy Grouping 2
Source: Tables 4.4.2.1.1 and 4.4.2.3.1 (Integrated Summary of Efficacy)

Table 40 Comparison of Dose on Change in Systolic Blood Pressure (mmHg) – Study 1245.25, Full Analysis Set, Last Observation Carried Forward

	N	Baseline		Change from Baseline		Difference from Empa 10		95% CI		p-value
		Mean	SE	Adj. mean	SE	Adj. mean	SE	LL	UL	
12 weeks										
Empa 10	1491	134.2	0.4	-4.6	0.3					
Empa 25	1499	134.8	0.4	-4.6	0.3	-0.1	0.5	-1.0	0.8	0.8987
28 weeks										
Empa 10	1491	134.2	0.4	-3.9	0.3					
Empa 25	1499	134.8	0.4	-4.5	0.3	-0.6	0.5	-1.6	0.3	0.2056

Empa 10 = empagliflozin 10 mg; CI = confidence interval; SE = standard error; Adj. Mean = adjusted mean; LL = lower limit; UL = upper limit; Empa 25 = empagliflozin 25 mg; EFF-2 = Efficacy Grouping 2
Source: Tables 4.4.4.1.1.1 and 4.4.4.1.1.4 (ISE)

Table 41 Comparison of Dose on Change in Diastolic Blood Pressure (mmHg) – 24 Weeks, Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline		Difference from Empa 10		95% CI		
	N	Mean	SE	Adj. mean	SE	Adj. mean	SE	LL	UL	p-value
24 Weeks										
Study 1245.19										
Empa 10	165	77.2	0.7	-1.5	0.5					
Empa 25	168	77.2	0.6	-2.2	0.5	-0.7	0.7	-2.1	0.7	0.3421
Study 1245.20										
Empa 10	224	79.2	0.6	-1.4	0.5					
Empa 25	224	78.3	0.6	-2.2	0.5	-0.8	0.7	-2.1	0.6	0.257
Study 1245.23_{met}										
Empa 10	217	79.6	0.5	-2	0.5					
Empa 25	213	78.4	0.6	-1.6	0.5	0.4	0.7	-1	1.7	0.5712
Study 1245.23_{met+SU}										
Empa 10	225	78.4	0.6	-2.2	0.4					
Empa 25	216	79	0.6	-2.2	0.4	0	0.6	-1.2	1.3	0.9788
EFF-2										
Empa 10	831	78.7	0.3	-1.8	0.2					
Empa 25	821	78.3	0.3	-2	0.2	-0.2	0.3	-0.9	0.4	0.4621
52 Weeks										
Study 1245.19										
Empa 10	165	77.2	0.7	-1.4	0.5					
Empa 25	168	77.2	0.6	-1.9	0.5	-0.5	0.7	-1.9	0.9	0.4916
Study 1245.20										
Empa 10	224	79.2	0.6	-1.2	0.5					
Empa 25	224	78.3	0.6	-1.7	0.5	-0.6	0.7	-1.9	0.7	0.3905
Study 1245.23_{met}										
Empa 10	217	79.6	0.5	-2.1	0.5					
Empa 25	213	78.4	0.6	-1.8	0.5	0.3	0.7	-1.1	1.7	0.6833
Study 1245.23_{met+SU}										
Empa 10	225	78.4	0.6	-1.6	0.5					
Empa 25	216	79	0.6	-1.9	0.5	-0.3	0.6	-1.5	1	0.6695
EFF-2										
Empa 10	831	78.7	0.3	-1.6	0.2					
Empa 25	821	78.3	0.3	-1.8	0.2	-0.2	0.3	-0.9	0.4	0.4999

Empa 10 = empagliflozin 10 mg; CI = confidence interval; SE = standard error; Adj. Mean = adjusted mean; LL = lower limit; UL = upper limit; Empa 25 = empagliflozin 25 mg; EFF-2 = Efficacy Grouping 2
Source: Tables 4.5.2.1.1 and 4.5.2.3.1 (Integrated Summary of Efficacy)

Table 42 Comparison of Dose on Change in Diastolic Blood Pressure (mmHg) – Study 1245.25, Full Analysis Set, Last Observation Carried Forward

		Baseline		Change from Baseline		Difference from Empa 10		95% CI		
	N	Mean	SE	Adj. mean	SE	Adj. mean	SE	LL	UL	p-value
12 weeks										
Empa 10	1491	76.1	0.3	-1.8	0.2					
Empa 25	1499	76.1	0.2	-1.9	0.2	-0.1	0.3	-0.6	0.4	0.7675
28 weeks										
Empa 10	1491	76.1	0.3	-1.7	0.2					
Empa 25	1499	76.1	0.2	-1.9	0.2	-0.2	0.3	-0.7	0.4	0.5061

Empa 10 = empagliflozin 10 mg; CI = confidence interval; SE = standard error; Adj. Mean = adjusted mean; LL = lower limit; UL = upper limit; Empa 25 = empagliflozin 25 mg; EFF-2 = Efficacy Grouping 2
Source: Tables 4.5.4.1.1.1 and 4.5.4.1.1.4 (Integrated Summary of Efficacy)

Reviewer Comment on Dose Dependence for Efficacy:

Though there was a numerically greater reduction in HbA1c for the 25 mg dose compared to the 10 mg dose, the comparison of efficacy between the two doses demonstrated no statistical difference between them on the ability to reduce HbA1c. However, the 25 mg dose appears more effective in reducing HbA1c < 7% if it was ≥ 7% at baseline, and there was a statistically significant greater reduction in fasting plasma glucose (though the reduction is of questionable clinical relevance given the HbA1c findings). Subjects from the 25 mg dose treatment arm also required less rescue medication. While the Applicant has proposed the 25 mg dose only, I feel that the 10 mg dose has demonstrated clinical effectiveness and should be approved. There are some limitations with regard to the available data for the 10 mg dose, specifically the limited data for the 10 mg dose in the setting of moderate renal impairment. Given that there are some differences in the safety profiles of the 10 mg and 25 mg dose not favoring the 25 mg dose (discussed below); the lack of further HbA1c reduction with the 25 mg dose raises a question regarding the approvability of the 25 mg dose. However, I feel that the improvement in categorical response and decreased use of rescue medication with the 25 mg dose supports approval of the 25 mg dose as well.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Though the timepoint for the primary analysis was 24 weeks, additional efficacy data were collected at later time points. For the four pivotal studies, additional data were collected and analyzed at 52 weeks (Table 43). From these data, the reduction in HbA1c seen with empagliflozin treatment appears to persist for at least 52 weeks. As discussed in Section 6.1.4, only minimal fluctuations were seen in HbA1c from week twelve to week 52 (Figure 4).

Additional evidence of persistence of efficacy comes from the other phase 2/3 studies. Study 1245.33 (empagliflozin add-on to basal insulin) followed patients to 78 weeks, and empagliflozin remained efficacious in reducing HbA1c at 78 weeks (Table 48). In contrast to the results for EFF-2, the reduction in HbA1c appeared to wane slightly over time starting at week 42, particularly with the 10 mg dose (Figure 12). Study 1245.36 (empagliflozin in renal impairment) followed patients with different degrees of renal impairment for 52 weeks. In the mild renal impairment patients, the effect of treatment with empagliflozin on HbA1c persisted to 52 weeks (Figure 13). Similar findings were seen in the patients with moderate renal impairment (Figure 14). As noted above, no effect of empagliflozin was seen in patients with severe renal impairment, either at 24 or 52 weeks (Figure 15).

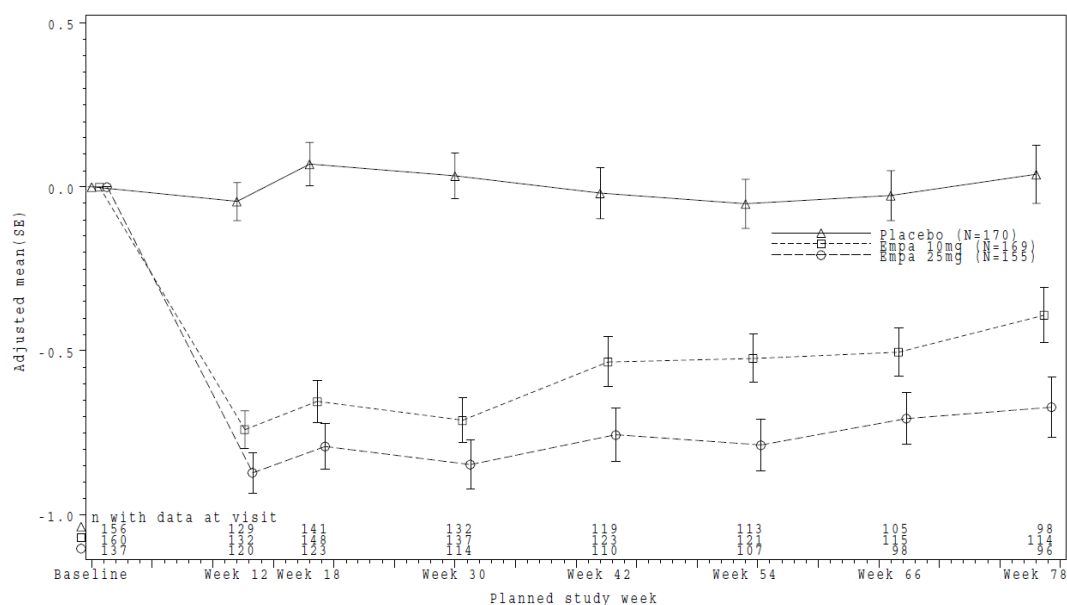
Table 43 Change in Hemoglobin A1c – 52 Weeks, Full Analysis Set, Last Observation Carried Forward

	Placebo		Empa 10		Empa 25	
Study 1245.19						
N	165		165		168	
Baseline (SE)	8.16	0.07	8.07	0.07	8.06	0.06
Adjusted mean change (SE)	-0.06	0.07	-0.61	0.01	-0.69	0.07
Adjusted mean change vs. placebo (SE)			-0.54	0.10	-0.63	0.10
95% CI (LL, UL)			-0.73	-0.35	-0.82	-0.44
p-value			< 0.0001		< 0.0001	
Study 1245.20						
N	228		224		224	
Baseline (SE)	7.91	0.05	7.87	0.06	7.86	0.06
Adjusted mean change (SE)	0.09	0.05	-0.67	0.05	-0.82	0.05
Adjusted mean change vs. placebo (SE)			-0.76	0.07	-0.91	0.07
95% CI (LL, UL)			-0.90	-0.61	-10.60	-0.76
p-value			< 0.0001		< 0.0001	
Study 1245.23 _{met}						
N	207		217		213	
Baseline (SE)	7.90	0.06	7.94	0.05	7.86	0.06
Adjusted mean change (SE)	-0.06	0.05	-0.68	0.05	-0.76	0.05
Adjusted mean change vs. placebo (SE)			-0.62	0.07	-0.70	0.07
95% CI (LL, UL)			-0.76	-0.48	-0.84	-0.56
p-value			< 0.0001		< 0.0001	
Study 1245.23 _{met+SU}						
N	225		225		216	
Baseline (SE)	8.15	0.06	8.07	0.05	8.10	0.06
Adjusted mean change (SE)	-0.04	0.05	-0.75	0.05	-0.70	0.05
Adjusted mean change vs. placebo (SE)			-0.71	0.07	-0.67	0.08
95% CI (LL, UL)			-0.86	-0.56	-0.82	-0.52
p-value			< 0.0001		< 0.0001	

	Placebo		Empa 10		Empa 25	
EFF-2						
N	825		831		821	
Baseline (SE)	8.02	0.03	7.98	0.03	7.96	0.03
Adjusted mean change (SE)	-0.01	0.03	-0.68	0.03	-0.75	0.03
Adjusted mean change vs. placebo (SE)			-0.67	0.04	-0.74	0.04
95% CI (LL, UL)			-0.75	-0.59	-0.81	-0.66
p-value			< 0.0001		< 0.0001	

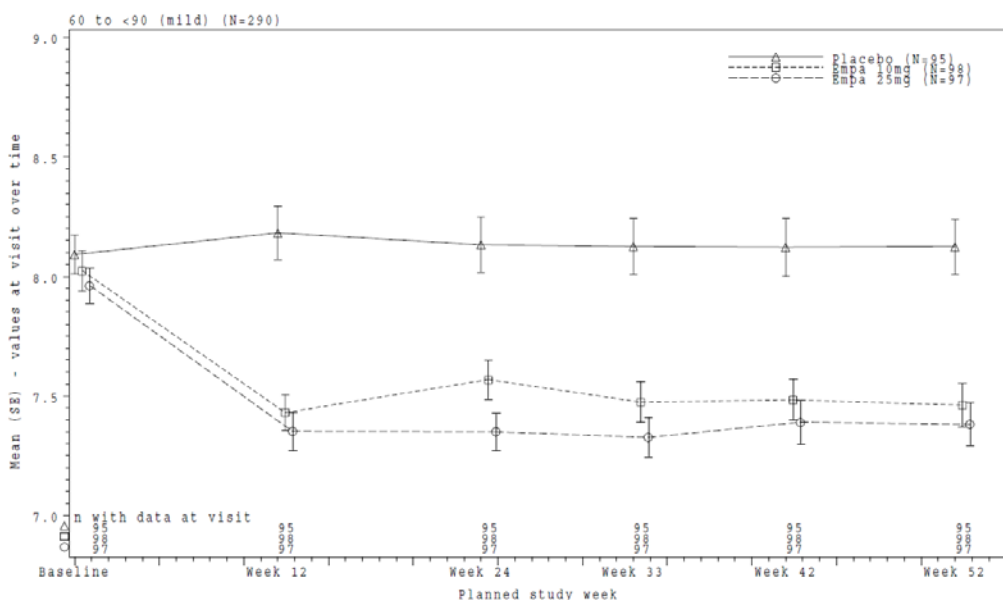
Source: 4.1.2.3.1 (ISE)

Figure 12 Change in Hemoglobin A1c Over Time – Study 1245.33, Full Analysis Set, Observed Cases at 78 weeks



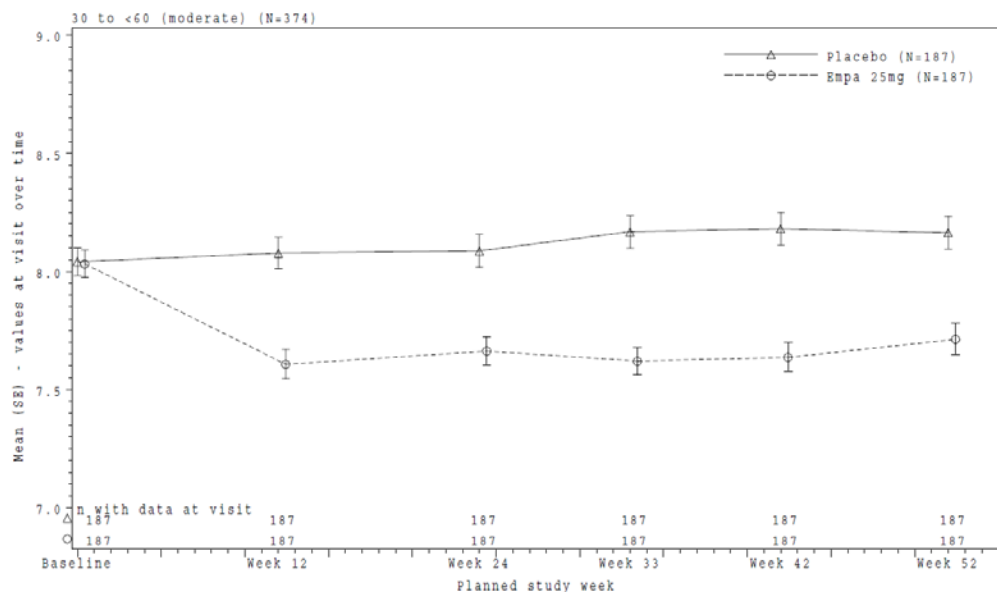
Source: Figure 15.2.2.2.2: 1 (Study 1245.33 study report)

Figure 13 Change in Hemoglobin A1c Over Time – Study 1245.36, Mild Renal Impairment, Full Analysis Set, Last Observation Carried Forward



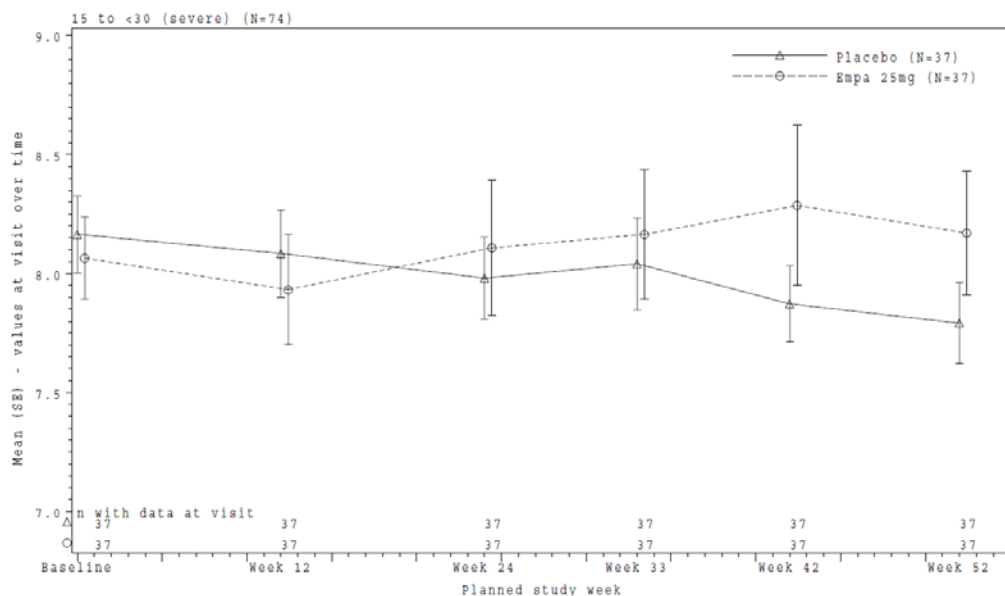
Source: Figure 15.2.1.2.3.3: 1 (Study 1245.36 study report)

Figure 14 Change in Hemoglobin A1c Over Time – Study 1245.36, Moderate Renal Impairment, Full Analysis Set, Last Observation Carried Forward



Source: Figure 15.2.1.2.3.3: 1 (Study 1245.36 study report)

Figure 15 Change in Hemoglobin A1c Over Time – Study 1245.36, Severe Renal Impairment, Full Analysis Set, Last Observation Carried Forward



Source: Figure 15.2.1.2.3.3: 1 (Study 1245.36 study report)

6.1.10 Additional Efficacy Issues/Analyses

To facilitate review of the proposed label, efficacy results from Studies 1245.19, 1245.20, 1245.23_{met}, 1245.23_{met+SU}, 1245.33, and 1245.36 will be briefly discussed below, as will the efficacy findings from the prespecified interim analysis of the ongoing active-controlled study (1245.28), and the comparison of empagliflozin vs. placebo as add-on to a DPP-4 inhibitor (+/- metformin) background from the interim analysis of the ongoing CVOT (Study 1245.25).

Study 1245.19:

Study 1245.19 was a randomized, double-blind, placebo-controlled, parallel group study of empagliflozin on a background of pioglitazone (alone or in combination with metformin). The primary endpoint was change in HbA1c from baseline to 24 weeks. Subjects were stratified by baseline HbA1c, renal function, and background medication. Efficacy endpoints were analyzed using a full analysis set with imputation of missing data by last observation carried forward (Table 44).

Table 44 Summary of Efficacy Results from Study 1245.19 – 24 Weeks, Full Analysis Set, Last Observation Carried Forward

	Placebo		Empa 10		Empa 25	
N	165		165		168	
HbA1c (%) – pioglitazone +/- metformin						
Baseline (SE)	8.16	0.07	8.07	0.07	8.06	0.06
Adjusted mean change (SE)	-0.11	0.07	-0.59	0.07	-0.72	0.07
Adjusted mean change vs. placebo (SE)			-0.48	0.09	-0.61	0.09
95% CI (LL,UL)			-0.66	-0.29	-0.82	-0.40
p-value			< 0.0001		< 0.0001	
HbA1c (%) – pioglitazone + metformin						
Baseline (SE)	8.15	0.08	8.07	0.08	8.10	0.07
Adjusted mean change (SE)	-0.11	0.08	-0.55	0.08	-0.70	0.07
Adjusted mean change vs. placebo (SE)			-0.45	0.11	-0.60	0.11
95% CI (LL,UL)			-0.66	-0.24	-0.83	-0.36
p-value			< 0.0001		< 0.0001	
FPG (mg/dl)						
Baseline (SE)	151.93	3.14	152.01	2.99	151.86	2.86
Adjusted mean change (SE)	6.47	2.61	-17.00	2.63	-21.99	2.59
Adjusted mean change vs. placebo (SE)			-23.48	3.71	-28.46	3.68
95% CI (LL,UL)			-30.76	-16.20	-35.69	-21.24
p-value			< 0.0001		< 0.0001	
Body weight (kg)						
Baseline (SE)	78.10	1.57	77.97	1.49	78.93	1.54
Adjusted mean change (SE)	0.34	0.21	-1.62	0.21	-1.47	0.21
Adjusted mean change vs. placebo (SE)			-1.95	0.30	-1.81	0.30
95% CI (LL,UL)			-2.55	-1.36	-2.41	-1.22
p-value			< 0.0001		< 0.0001	

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; HbA1c = hemoglobin A1c; SE = standard error; CI = confidence interval; LL = upper limit; UL = lower limit; FPG = fasting plasma glucose

Source: Tables 15.2.1.1: 1, 15.2.1.2.1: 5, 15.2.2.1.1: 1, and 15.2.2.2.1: 1 (Study 1245.19 study report)

Study 1245.20:

Study 1245.20 was a randomized, double-blind active and placebo-controlled parallel group study of empagliflozin as monotherapy. An active control (sitagliptin 100 mg) was also used in this study. The primary endpoint was change in HbA1c from baseline to 24 weeks. Subjects were stratified by baseline HbA1c, and renal function. Efficacy endpoints were analyzed using a full analysis set with imputation of missing data by last observation carried forward (Table 45).

Table 45 Summary of Efficacy Results from Study 1245.20 – 24 Weeks, Full Analysis Set, Last Observation Carried Forward

	Placebo		Empa 10		Empa 25		Sita	
N	228		224		224		223	
HbA1c (%)								
Baseline (SE)	7.91	0.05	7.87	0.06	7.86	0.06	7.85	0.05
Adjusted mean change (SE)	0.08	0.05	-0.66	0.05	-0.78	0.05	-0.66	0.05
Adjusted mean change vs. placebo (SE)			-0.74	0.07	-0.85	0.07	-0.73	0.07
95% CI (LL,UL)			-0.88	-0.59	-0.99	-0.71	-0.88	-0.59
p-value			< 0.0001		< 0.0001		< 0.0001	
Adjusted mean change vs. Sitagliptin (SE)			0.00	0.07	-0.12	0.07		
95% CI (LL,UL)			-0.15	0.14	-0.26	0.03		
p-value			0.9697		0.1060			
FPG (mg/dl)								
Baseline (SE)	154.7	2.4	152.8	2.2	152.6	2.3	147.1	1.9
Adjusted mean change (SE)	11.8	2.0	-19.4	2.0	-24.5	2.0	-6.9	2.0
Adjusted mean change vs. placebo (SE)			-31.2	2.8	-36.2	2.8	-18.7	2.8
95% CI (LL,UL)			-36.6	-25.8	-41.7	-30.8	-24.2	-13.2
p-value			< 0.0001		< 0.0001		< 0.0001	
Adjusted mean change vs. Sitagliptin (SE)			-12.5	2.8	-17.5	2.8		
95% CI (LL,UL)			-18.0	-7.0	-23.0	-12.0		
p-value			< 0.0001		< 0.0001			
Body weight (kg)								
Baseline (SE)	78.23	1.32	78.35	1.25	77.8	1.20	79.31	1.37
Adjusted mean change (SE)	-0.33	0.17	-2.26	0.17	-2.48	0.17	0.18	0.17
Adjusted mean change vs. placebo (SE)			-1.93	0.24	-2.15	0.24	0.52	0.25
95% CI (LL,UL)			-2.41	-1.45	-2.63	-0.167	0.04	1.00
p-value			< 0.0001		< 0.0001		0.0355	
Adjusted mean change vs. Sitagliptin (SE)			-2.45	0.25	-2.67	0.25		
95% CI (LL,UL)			-2.93	-1.96	-3.15	-2.18		
p-value			< 0.0001		< 0.0001			

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; Sita = sitagliptin; HbA1c = hemoglobin A1c; SE = standard error; CI = confidence interval; LL = upper limit; UL = lower limit; FPG = fasting plasma glucose

Source: Tables 15.2.1.1: 1, 15.2.2.1.1: 1, and 15.2.3.1.1: 1 (Study 1245.20 study report)

Study 1245.23_{met}:

Study 1245.23_{met} was a randomized, double-blind placebo-controlled parallel group study of empagliflozin as add-on to metformin. The primary endpoint was change in HbA1c from baseline to 24 weeks. Subjects were stratified by baseline HbA1c, and renal function. Efficacy endpoints were analyzed using a full analysis set with imputation of missing data by last observation carried forward (Table 46).

Table 46 Summary of Efficacy Results from Study 1245.23_{met} – 24 Weeks, Full Analysis Set, Last Observation Carried Forward

	Placebo		Empa 10		Empa 25	
N	207		217		213	
HbA1c (%)						
Baseline (SE)	7.90	0.06	7.94	0.05	7.86	0.06
Adjusted mean change (SE)	-0.13	0.05	-0.7	0.05	-0.77	0.05
Adjusted mean change vs. placebo (SE)			-0.57	0.07	-0.64	0.07
95% CI (LL,UL)			-0.70	-0.43	-0.77	-0.50
p-value			< 0.0001		< 0.0001	
FPG (mg/dl)						
Baseline (SE)	156.02	2.26	154.58	2.41	149.42	2.10
Adjusted mean change (SE)	6.38	1.77	-20.04	1.73	-22.28	1.75
Adjusted mean change vs. placebo (SE)			-26.43	2.47	-28.67	2.49
95% CI (LL,UL)			-31.28	-21.6	-33.56	-23.78
p-value			< 0.0001		< 0.0001	
Body weight (kg)						
Baseline (SE)	79.73	1.29	81.59	1.26	82.21	1.32
Adjusted mean change (SE)	-0.45	0.17	-2.08	0.17	-2.46	0.17
Adjusted mean change vs. placebo (SE)			-1.63	0.24	-2.01	0.24
95% CI (LL,UL)			-2.17	-1.08	-2.56	-1.46
p-value			< 0.0001		< 0.0001	

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; HbA1c = hemoglobin A1c; SE = standard error; CI = confidence interval; LL = upper limit; UL = lower limit; FPG = fasting plasma glucose
Source: Tables 15.1.2.1.1: 1, 15.1.2.3.5: 1, and 15.1.2.2.1.1: 1 (Study 1245.23 study report)

Study 1245.23_{met+SU}:

Study 1245.23_{met+SU} was a randomized, double-blind placebo-controlled parallel group study of empagliflozin as add-on to metformin plus a sulfonylurea. The primary endpoint was change in HbA1c from baseline to 24 weeks. Subjects were stratified by baseline HbA1c, and renal function. Efficacy endpoints were analyzed using a full analysis set with imputation of missing data by last observation carried forward (Table 47).

Table 47 Summary of Efficacy Results from Study 1245.23_{met+SU} – 24 Weeks, Full Analysis Set, Last Observation Carried Forward

	Placebo		Empa 10		Empa 25	
N	224		225		215	
HbA1c (%)						
Baseline (SE)	8.15	0.06	8.07	0.05	8.10	0.06
Adjusted mean change (SE)	-0.17	0.05	-0.82	0.05	-0.77	0.05
Adjusted mean change vs. placebo (SE)			-0.64	0.07	-0.59	0.07
95% CI (LL,UL)			-0.77	-0.51	-0.73	-0.46
p-value			< 0.0001		< 0.0001	
FPG (mg/dl)						
Baseline (SE)	151.69	2.39	151.01	2.19	156.47	2.30
Adjusted mean change (SE)	5.52	1.96	-23.30	1.95	-23.27	2.00
Adjusted mean change vs. placebo (SE)			-28.82	2.76	-28.8	2.80
95% CI (LL,UL)			-34.25	-23.40	-34.29	-23.30
p-value			< 0.0001		< 0.0001	
Body weight (kg)						
Baseline (SE)	76.23	1.13	77.08	1.22	77.5	1.28
Adjusted mean change (SE)	-0.39	0.15	-2.16	0.15	-2.39	0.16
Adjusted mean change vs. placebo (SE)			-1.76	0.22	-1.99	0.22
95% CI (LL,UL)			-2.19	-1.34	-2.42	-1.56
p-value			< 0.0001		< 0.0001	

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; HbA1c = hemoglobin A1c; SE = standard error; CI = confidence interval; LL = upper limit; UL = lower limit; FPG = fasting plasma glucose
Source: Tables 15.2.2.1.1: 1, 15.2.2.3.5: 1, and 15.2.2.2.1.1: 1 (Study 1245.23 study report)

Study 1245.33:

Study 1245.33 was a randomized, double-blind, placebo-controlled parallel group study of empagliflozin as add-on to basal insulin with or without metformin and/or sulfonylurea. The primary endpoint was change in HbA1c from baseline to 18 weeks. Subjects were stratified by baseline HbA1c. The primary efficacy endpoint was analyzed using the full analysis set with imputation of missing data by last observation carried forward (Table 48).

Table 48 Summary of Efficacy Results from Study 1245.33 – 18 and 78 Weeks, Full Analysis Set, Last Observation Carried Forward

	Placebo		Empa 10		Empa 25	
18 weeks						
HbA1c (%) ¹						
N	125		132		117	
Baseline (SE)	8.10	0.07	8.26	0.07	8.34	0.08
Adjusted mean change (SE)	-0.01	0.07	-0.57	0.07	-0.71	0.07
Adjusted mean change vs. placebo (SE)			-0.56	0.10	-0.70	0.10
95% CI (LL,UL)			-0.75	-0.36	-0.90	-0.50
p-value			< 0.0001		< 0.0001	
FPG (mg/dl) ²						
N	135		138		120	
Mean adjusted baseline (SE)						
Adjusted mean change (SE)	11.15	3.30	-17.25	3.26	-23.06	3.49
Adjusted mean change vs. placebo (SE)			-28.40	4.65	-34.21	4.81
95% CI (LL,UL)			-37.54	-19.27	-43.67	-24.76
p-value			< 0.0001		< 0.0001	
Body weight (kg) ²						
N	141		148		125	
Adjusted mean baseline (SE)	91.32	0.68	89.28	0.66	90.45	0.72
Adjusted mean change (SE)	-0.05	0.68	-2.09	0.66	-0.92	0.72
Adjusted mean change vs. placebo (SE)			-2.04	0.95	-0.87	0.99
95% CI (LL,UL)			-3.90	-0.18	-2.81	1.08
p-value			0.0320		0.3818	
78 weeks						
HbA1c (%) ³						
N	112		127		110	
Baseline (SE)	8.09	0.07	8.27	0.07	8.29	0.08
Adjusted mean change (SE)	-0.02	0.09	-0.48	0.08	-0.64	0.09
Adjusted mean change vs. placebo (SE)			-0.46	0.12	-0.62	0.12
95% CI (LL,UL)			-0.70	-0.23	-0.87	-0.38
p-value			0.0001		< 0.0001	

	Placebo		Empa 10		Empa 25	
FPG (mg/dl)²						
N	92		104		92	
Adjusted mean change (SE)	-5.48	3.67	-10.51	3.49	-17.43	3.71
Adjusted mean change vs. placebo (SE)			-5.03	5.07	-11.95	5.23
95% CI (LL,UL)			-15.01	4.94	-22.24	-1.67
p-value			0.3216		0.0229	
Body weight (kg)²						
N	100		113		96	
Mean adjusted baseline (SE)	92.54	0.80	88.91	0.76	89.42	0.82
Adjusted mean change (SE)	1.16	0.80	-2.47	0.76	-1.96	0.82
Adjusted mean change vs. placebo (SE)			-3.63	1.10	-3.12	1.15
95% CI (LL,UL)			-5.81	-1.45	-5.39	-0.85
p-value			0.0012		0.0073	

¹Full analysis set, Last observation carried forward; ²Full analysis set, Observed cases, mixed-effects model repeated measures;

³Full analysis set – completers at 78 weeks, last observation carried forward

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; HbA1c = hemoglobin A1c; SE = standard error; CI = confidence interval; LL = upper limit; UL = lower limit; FPG = fasting plasma glucose

Source: Tables 15.2.1.1: 1, 15.2.3.4: 1, 15.2.3.5: 1, 15.2.2.2.1: 1 (Study 1245.33 study report)

Efficacy issues that will need further evaluation:

Efficacy of the 10 mg dose in moderate renal impairment has not been established. This will need to be addressed to inform labeling and prescribing recommendations. Efficacy in hepatic impairment has not been established. There are limited data on the use of empagliflozin administered with DPP-4 inhibitors and with GLP-1 agonists. Pediatric patients were not included in the development program, thus there is no evidence of efficacy in pediatric patients. Efficacy in this patient population will need to be established. Black patients made up a small percentage of the overall population. Additional study in Black patients may be warranted to evaluate for potential differences in efficacy due to race.

7. Review of Safety

Safety Summary

The overall safety profile for empagliflozin does not raise safety concerns that would preclude approval. While there is an increased incidence in some adverse events and laboratory changes with empagliflozin, the safety signals identified in the empagliflozin development program do not generate sufficient concern to outweigh the expected benefit from improved glycemic control.

Safety issues identified in the review of empagliflozin were an increase in genitourinary infections (particularly mycotic infections), increased urination, and increased thirst. For older patients (i.e. > 75 years old), there was an increase in volume depletion events and renal impairment. Hypoglycemia was not more frequent with empagliflozin compared to placebo when administered as monotherapy, or as add-on to metformin or pioglitazone. An increased incidence of hypoglycemic events was seen when empagliflozin was added to sulfonylurea therapy. These appear to be issues of tolerability rather than issues that would impede approval. The genital infections were treatable with standard therapies in the development program, and the changes in renal function were reversible with cessation of therapy.

Cardiovascular safety will be discussed separately from this summary due to inclusion of interim data from an ongoing cardiovascular outcomes trial, and the need to protect the integrity of that trial. A preplanned meta-analysis of major adverse cardiovascular events excluded an upper bound of 1.8 for the 95% confidence interval. This meta-analysis includes data from an interim analysis of a still-ongoing cardiovascular outcomes trial.

Two areas of questionable concern were identified during the review of empagliflozin. These are (1) drug-induced liver injury (DILI), and (2) malignancy events (specifically lung cancers and melanomas). For both of these, there was an imbalance in the number of empagliflozin-treated patients compared to placebo/comparators. Review of additional details for the individual cases provides reassurance that these imbalances are unlikely to be the result of treatment with empagliflozin.

7.1 Methods

Issues and concerns identified from the SCS were addressed by in-depth review of the submitted study reports, narratives and datasets. Particular detail was paid to the pool of patients comprising the pivotal phase 3 studies, and the pool of all patients with T2DM. All of the submitted narratives for deaths and nonfatal SAEs were reviewed. For adjudicated CV events, adjudicated cases were randomly selected for review to evaluate the adjudication process.

The submitted adverse event datasets (AE.xpt files) were combined with the corresponding demographic datasets (DM.xpt files) to provide demographic data and AE data for the individual studies. These combined datasets were concatenated to generate adverse event incidence tables for comparison with those provided by the Applicant. Additional examination of the submitted data was performed for studies as grouped in the proposed label

7.1.1 Studies/Clinical Studies Used to Evaluate Safety

Adverse event datasets have been submitted for the thirteen phase 2b/3 studies intended to support the NDA. The studies have been pooled into safety groups by the Applicant (Table 49, Figure 16) to allow for analysis of the empagliflozin safety profile. For the ongoing studies (1245.25, 1245.28, and 1245.31), safety data available at the prespecified cut-off date of August 31, 2012 are included in the integrated analysis.

Table 49 Safety Population Groupings

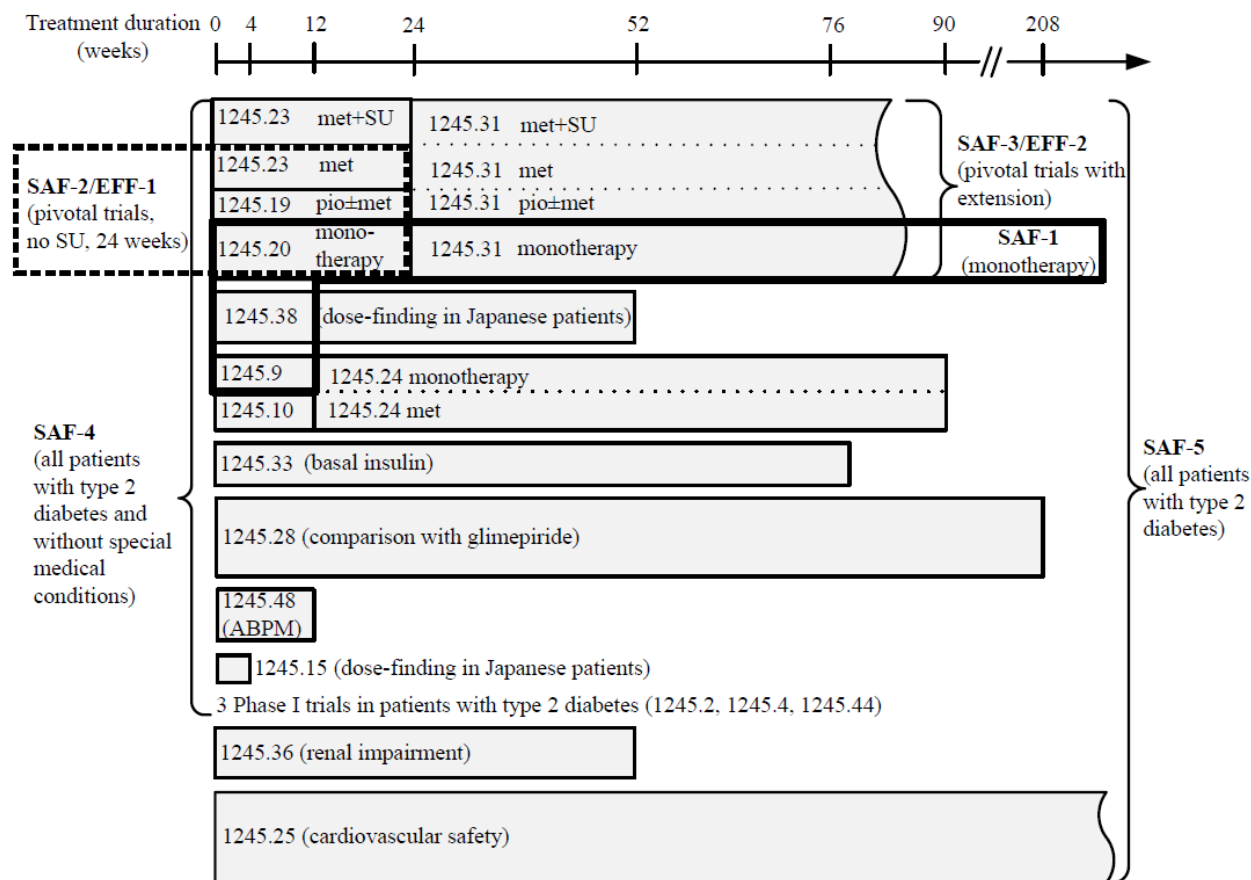
Grouping	Description	Studies
SAF-1	Studies with empagliflozin monotherapy (no background antidiabetic therapy)	1245.9, 1245.20, 1245.31 _{mono} , 1245.38
SAF-2	Pivotal studies, excluding patients receiving sulfonylurea background therapy (corresponds to grouping EFF-1)	1245.19, 1245.20, 1245.23 _{met}
SAF-3	Pivotal studies and extensions, including all patients (corresponds to grouping EFF-2)	1245.19, 1245.20, 1245.23 _{met} , 1245.23 _{met+SU} , 1245.31
SAF-4	All studies in patients with type 2 diabetes and without special medical conditions (i.e. renal impairment, cardiovascular risk)	1245.2, 1245.4, 1245.9, 1245.10, 1245.15, 1245.19, 1245.20, 1245.23 _{met} , 1245.23 _{met+SU} , 1245.28, 1245.31, 1245.33, 1245.38, 1245.44, 1245.48
SAF-5	All studies in patients with type 2 diabetes	1245.2, 1245.4, 1245.9, 1245.10, 1245.15, 1245.19, 1245.20, 1245.23 _{met} , 1245.23 _{met+SU} , 1245.24, 1245.25, 1245.28, 1245.31, 1245.33, 1245.36, 1245.38, 1245.44, 1245.48
SAF-6	All studies in healthy subjects	1245.1, 1245.3, 1245.5, 1245.6, 1245.7, 1245.8, 1245.16, 1245.17, 1245.18, 1245.27, 1245.30, 1245.40, 1245.41, 1245.43, 1245.45, 1245.50, 1245.51, 1245.58, 1245.63, 1245.79, 1275.3, 1275.5, 1276.9

SAF-1 = Safety Grouping 1; SAF-2 = Safety Grouping 2; SAF-3 = Safety Grouping 3; SAF-4 = Safety Grouping 4; SAF-5 = Safety Grouping 5; SAF-6 = Safety Grouping 6

Source: Table 5.1: 1 (Clinical Overview)

The largest pool of T2DM patients is SAF-5. This pool is the focus of the Summary of Clinical Safety, and will be the focus of this safety review. It encompasses the other safety groupings of interest (i.e. SAF-1 through SAF-4, Figure 16). To facilitate comparison with the efficacy findings, SAF-3 will also be discussed. Additional grouping or evaluation of individual studies will be performed as needed.

Figure 16 Safety Groupings



Source: Figure 5.1: 1 (Clinical Overview)

7.1.2 Categorization of Adverse Events

Adverse events were coded using version 15.0 of the Medical Dictionary for Regulatory Activities (MedDRA). Adverse event types analyzed included all AEs, nonfatal serious AEs (SAEs), AEs leading to discontinuation of study medication, other significant AEs (based on ICH E3¹), investigator-defined drug-related AEs, and AEs of special interest (AESI; i.e. decreased renal function, hepatic injury, urinary tract infection, genital infection, hypoglycemic event, bone fracture, volume depletion, and malignancy). Deaths were also analyzed. Only treatment-emergent adverse events, defined as AEs with an onset between the first intake of study drug and seven days after the last intake of study drug, are analyzed by the Applicant.

¹International Conference of Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Efficacy Guideline 3: Structure and Content of Clinical Study Reports

In the phase 3 studies, “significant adverse events” were prespecified and defined. These events were:

1. Decreased renal function (creatinine ≥ 2 x baseline and above ULRR)
2. Hepatic injury (AST and/or ALT ≥ 3 x above ULRR, combined with bilirubin ≥ 2 x above ULRR measured from the same sample) if not meeting the definition of “serious”.

“Other significant AEs” as defined in ICH E3 include marked hematological and other laboratory abnormalities (if not meeting the definition of “serious”), and any event leading to an intervention (including withdrawal of study treatment, dose reduction, or significant additional concomitant therapy).

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

For analysis of safety data, the Applicant has grouped the clinical studies (Table 49, Figure 16). The rationale for these specific groupings is as follows:

1. SAF-1 allows for assessment of the safety of empagliflozin as monotherapy.
2. SAF-2 and SAF-3 allow for direct comparison of safety and efficacy groupings as they correspond to the efficacy groupings EFF-1 and EFF-2 respectively.
3. SAF-4 allows for the safety assessment of empagliflozin in patients with T2DM without confounding comorbidities.
4. SAF-5 comprises the largest pool of data and allows for subgroup analysis and identification of rare AEs.
5. SAF-6 allows for assessment of the AEs in healthy subjects.

Studies in patients with renal impairment (1245.12), hepatic impairment (1245.13), drug-drug interaction (DDI) with diuretics (1245.42), and DDI with rifampicin and probenecid (1245.83) were not included in any of the above groups due to either: (1) no appropriate group being available (1245.12, 1245.13, 1245.42), or (2) the study was completed too late for grouping (1245.83).

Safety grouping SAF-5 will be the focus of this review as it comprises the largest group of patients with T2DM and encompasses all other safety groupings that examine patients with T2DM. To facilitate comparison with the efficacy findings, SAF-3 will also be discussed. Individual studies and additional groupings of studies will be discussed as needed.

For these subject pools, the Applicant has defined subject sets for analysis. The first of these is the treated set (TS) which encompasses all subjects who received at least one dose of randomized study medication. Randomized treatment assignment was used to determine treatment group. Assigned treatment could change in Study 1245.38 or at enrollment in the extension study, 1245.24. In the case that subjects were randomized to a different treatment during one of these studies, the treatment grouping would change. This resulted in some subjects being listed under two different treatment groupings. This was only done for the analysis of adverse events. For disposition, demographics, baseline characteristics, and safety laboratory evaluations, only the first assignment was used.

The second set was the “treated set actual” (TS actual) in which the actual study medication at the time of the adverse event was used for treatment assignment. A subject could thus appear in more than one treatment group for adverse events if there was a change in treatment (either planned or accidental).

A final group was the open-label set (OLS). In Studies 1245.20, and 1245.23 there was an option for open-label treatment with empagliflozin 25 mg for patients who were ineligible for randomization due to the HbA1c being above 10.0%. This set will not be discussed in this review.

The primary analysis for safety was based on the TS. Missing safety data were not imputed. The OLS is not included in the “total randomized” or “all randomized” groups.

7.2 Adequacy of Safety Assessments

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

As reported by the Applicant in the Summary of Clinical Safety, a total of 13,183 patients with T2DM have received treatment as part of the development program. Of these patients, 3,311 of these were treated with empagliflozin 10 mg, 4,563 of these were treated with empagliflozin 25 mg, and 4,697 of these were treated with comparators (placebo, metformin, sitagliptin, or glimepiride).

Focusing on SAF-5, the total number of patients is provided below (Table 50). These numbers are based on first treatment assignment, and do not account for patients with a change in treatment assignment as was allowed by protocol for Studies 1245.24 and 1245.38.

Table 50 Number of Patients in Safety Grouping 5 and Safety Grouping 3 by Treatment Grouping

Treatment grouping	SAF-5	SAF-3
Empa 10	3,311	830
Empa 25	4,285	822
Empa Other	601	0
All Empa	8,197	1,652
Empa 25 OL	0	257
Placebo	3,522	825
Metformin	80	0
Glimepiride	780	0
Sitagliptin	294	223
All Comp	4,676	1,048

SAF-5 = Safety Grouping 5; SAF-3 = Safety Grouping 3

Empa 10 = patients treated with empagliflozin 10 mg at first treatment assignment; Empa 25 = patients treated with empagliflozin 25 mg at first treatment assignment; Empa Other = patients treated with all doses of empagliflozin except for 10 mg and 25 mg at first treatment assignment; All Empa = all randomized empagliflozin patients; Empa 25 OL = patients treated with open-label empagliflozin (i.e. not randomized) at first treatment assignment; Placebo = patients treated with placebo at first treatment assignment; All Comp = all comparator-treated patients (placebo, glimepiride, metformin, and sitagliptin)

Source: Table 1.2.1: 2 (Summary of Clinical Safety)

Exposure to study medication is also provided by the Applicant (Table 51, Table 52). The number of patients exposed for SAF-5 is greater than the number of patients presented in Table 50 which is based on first randomized treatment assignment because the exposure numbers include those patients with a change in treatment assignment as allowed by protocol for Studies 1245.24 and 1245.38. As such, some patients may have initially been on placebo or another dose of empagliflozin, but were later rerandomized to empagliflozin 10 mg or empagliflozin 25 mg.

Table 51 Overall Exposure to Randomized Empagliflozin – Safety Grouping 5

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	N	%	N	%	N	%	N	%	N	%
Total¹	3630	100	4602	100	8400	100	3522	100	4676	100
≥ 24 weeks	2856	78.7	3738	81.2	6603	78.6	2464	70	3514	75.1
≥ 52 weeks	1720	47.4	2541	55.2	4415	52.6	1423	40.4	2333	49.9
≥ 76 weeks	601	16.6	881	19.1	1486	17.7	317	9	724	15.5
Mean exposure (days)	327.8		353.0		340.4		286.0		326.9	
Total exposure (years)	3258.2		4448.1		7827.8		2758.1		4184.4	

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator

¹The number of patients here exceeds the numbers in Table 50 reported by Applicant as the calculated exposure includes patients who were rerandomized as allowed by protocol in Studies 1245.24 and 1245.38. The number of patients reported for Table 50 is based on first treatment assignment.

Source: Table 1.2.2: 1 (Summary of Clinical Safety)

Table 52 Overall Exposure to Randomized Empagliflozin – Safety Grouping 3

	Empa 10		Empa 25		All Empa		Placebo		Sitagliptin	
	N	%	N	%	N	%	N	%	N	%
Total	830	100	822	100	1652	100	825	100	223	100
≥ 24 weeks	771	92.9	747	90.9	1518	91.9	707	85.7	204	91.5
≥ 52 weeks	434	52.3	414	50.4	848	51.3	361	43.8	93	41.7
≥ 76 weeks	82	9.9	80	9.7	162	9.8	65	7.9	24	10.8
Mean exposure (days)	344.9		338.5		341.7 ¹		309.6		326.6	
Total exposure (years)	783.8		761.7		1546.5 ²		699.2		199.4	

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin

¹estimate based on average of mean exposures for Empa 10 and Empa 25; ² estimate based on total (All Empa) x mean exposure in days (All Empa) / 365

Source: Table 1.2.2: 4 (Summary of Clinical Safety)

I calculated additional exposure estimates¹ based on the submitted clinical study reports for all studies in SAF-5 excluding Study 1245.25, and for all completed studies in SAF-5 (i.e. excluding Studies 1245.25, 1245.28, and 1245.31) (Table 53). This was done to facilitate assessment of the effect of removing the population enriched for MACE (SAF-5, excluding Study 1245.25), and the effect of removing interim study data (SAF-5, excluding Studies 1245.25, 1245.28, 1245.31). For the tables that explored these subsets of SAF-5, the treatment at the time of the onset of the adverse event was used for the grouping assignment.

¹Calculated as # of subjects x mean exposure in days / 365

Table 53 Estimated Exposures for Subgroups of Safety Grouping 5

	Empa 10	Empa 25	All Empa	Placebo	All Comp
Excluding Study 1245.25					
- Number of patients	1799	2759	4962	1741	2893
- Estimated exposure (years)	1114.3	2302.0	3536.5	1067.3	2434
Completed studies only					
- Number of patients	1798	2000	4421	1740	2112
- Estimated exposure (years)	909.1	1080.1	2108	884	1019

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators

Source: Individual study reports

7.2.2 Explorations for Dose Response

Two dosage strengths were used in the pivotal studies: 10 mg and 25 mg. Other dosages were used in other studies, but the exposures are small compared to these two groups. By comparing the incidence of AEs and laboratory abnormalities between the two dosage strengths, suggestion of dose dependence for AEs can be identified. Dose response is discussed further in 7.5.1.

7.2.3 Special Animal and/or In Vitro Testing

Refer to the Pharmacology/Toxicology review by Mukesh Summan.

7.2.4 Routine Clinical Testing

Routine testing that took place as part of the clinical studies included measurement of vital signs (including weight), and laboratory testing (including measures of glycemic control, renal function, serum electrolytes, hematologic parameters, and liver enzymes).

7.2.5 Metabolic, Clearance, and Interaction Workup

Detailed discussion of drug metabolism, transport, and excretion can be found in the Clinical Pharmacology review by Manoj Khurana.

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

From the two previously reviewed SGLT2 inhibitors, some potential adverse events were identified. From the dapagliflozin NDA, DILI, and malignancies (specifically bladder) were

concerns leading to the issuance of a Complete Response. From the canagliflozin NDA, adverse events of concern included fractures, changes in plasma lipids, volume depletion events, decreased renal function, and incidence of early cardiovascular events. Genitourinary infections were an issue identified for both dapagliflozin and canagliflozin.

7.3 Major Safety Results

7.3.1 Deaths

As reported by the Applicant, there were a total of 74 deaths in SAF-5 during the development program (Table 54). There were an additional nine fatal events during screening/run-in, fourteen fatal events in the post-treatment period¹, and five fatal events in the post-study period². Excluding the screening/run-in deaths, there are a total of 93 events occurring after initiation of randomized study drug. The majority of events (43 on treatment, fourteen after discontinuation of study drug) occurred in the ongoing CVOT.

Inclusion of the deaths that occurred in the post-treatment and post-study period does not significantly change the incidence of death for each treatment arm (Table 55). The percentage of deaths in patients from the Empa 10, Empa 25, and All Empa grouping remained lower than either the placebo group or all comparators group.

Table 54 Incidence of Death (On-Treatment) – Safety Grouping 5

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	N	%	N	%	N	%	N	%	N	%
# patients exposed ¹	3630	100	4602	100	8400	100	3522	100	4676	100
Total exposure (patient-years)	3287.3		4481.6		7893.7		2781.9		4214.4	
Deaths (on treatment)	18	0.50	23	0.50	41	0.49	29	0.82	33	0.71
Death rate per 100 patient-years ²	0.55		0.51		0.52		1.04		0.78	

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators

¹taken from total exposure (Table 51); ²calculated by N/patient-years x 100

Source: Table 2.1.2: 1 (Summary of Clinical Safety)

¹Post-treatment period defined as time between the end of the washout period (seven days after last intake of study medication) and study completion.

²Post-study period defined as after study completion

Table 55 Incidence of Death (On-Treatment, Post-Treatment, and Post-Study)

- Not adjusted for exposure

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	N	%	N	%	N	%	N	%	N	%
# patients exposed ¹	3630	100	4602	100	8400	100	3522	100	4676	100
Treatment-emergent deaths	23	0.6	31	0.7	54	0.6	35	1.0	39	0.8

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators

¹taken from Table 51

Source: Submitted AE xpt and DM xpt files, and individual study reports

To protect the integrity of the ongoing cardiovascular safety study (Study 1245.25), deaths that occurred in that study will not be discussed in this section but will be discussed in Section 7.3.5.1.1. Excluding the deaths that occurred in Study 1245.25 did not change the observation for the whole of SAF-5.

The Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOCs) with the highest incidence of fatal events were “General disorders and administration site conditions” (n=15), “Neoplasm benign, malignant and unspecified (incl cysts and polyps)” (n=12), and “Cardiac disorders” (n=13) (Table 56). The “Neoplasms benign, malignant and unspecified (incl cysts and polyps)” SOC was the only one of the three SOC in which there was a greater incidence in the empagliflozin-treated patients versus the placebo and the all comparator-treated patients (5 (0.14%) for Empa 1 vs. 7 (0.15%) for Empa 25 vs. 12 (0.14% for All Empa vs. 1 (0.03) for placebo vs. 1 (0.02%) for All Comp). No single MedDRA Preferred Term (PT) in this SOC drove the imbalance. “Sudden death” and “Pneumonia” were the only PTs occurring in more than two patients with a greater incidence in the empagliflozin-treated patients compared to placebo and comparators. Events that could be considered cardiovascular events are not included here, but will be discussed in Section 7.3.5.1.1.

For SAF-3, there were only five deaths (two (0.24%) in placebo, one (0.12%) in Empa 10, three (0.36%) in Empa 25). Based on these numbers, there does not appear to be an increased risk of death with empagliflozin for this safety grouping.

Details of study patients with their cause of death along with time from randomization follow in Table 59. Narratives for all of the fatal events in the empagliflozin-treated patients were reviewed. Based on this, no concern is raised for a specific cause of death or class of events resulting in death with empagliflozin treatment. The narratives are summarized below.

Table 56 Incidence of Fatal Events by System Organ Class and Preferred Term – Safety Grouping 5

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	3630			4602			8400			3522			4676		
Total exposure (patient-years)	3258.2			4448.1			7827.8			2758.1			4184.4		
System Organ Class - Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	0.14	0.15	7	0.15	0.16	12	0.14	0.15	1	0.03	0.04	1	0.02	0.02
- Brain neoplasm	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Colon cancer	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Hepatic cancer metastatic	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Hepatic neoplasm malignant	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Lung adenocarcinoma stage IV	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Lung neoplasm malignant	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Metastases to bone	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Metastases to liver	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Metastatic gastric cancer	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Pancreatic carcinoma metastatic	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Pancreatic neoplasm	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Rectal cancer	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Gastric cancer	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
- Malignant pleural effusion	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.02	0.02
- Pericardial effusion malignant	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.02	0.02
Infections and infestations	3	0.08	0.09	4	0.09	0.09	7	0.08	0.09	5	0.14	0.18	5	0.11	0.12
- Pneumonia	1	0.03	0.03	2	0.04	0.04	3	0.04	0.04	0	0.00	0.00	0	0.00	0.00
- Sepsis	1	0.03	0.03	2	0.04	0.04	3	0.04	0.04	1	0.03	0.04	1	0.02	0.02
- Septic shock	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	1	0.03	0.04	1	0.02	0.02
- Cellulitis	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	3630			4602			8400			3522			4676		
Total exposure (patient-years)	3258.2			4448.1			7827.8			2758.1			4184.4		
System Organ Class - Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
- Gastrointestinal infection	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
- Infected skin ulcer	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
Respiratory, thoracic and mediastinal disorders	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	3	0.09	0.11	3	0.06	0.07
- Acute respiratory failure	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Idiopathic pulmonary fibrosis	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Pulmonary embolism	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Acute respiratory distress syndrome	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
- Pulmonary edema	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
- Respiratory failure	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
Blood and lymphatic system disorders	0	0.00	0.00	2	0.04	0.04	2	0.02	0.03	0	0.00	0.00	0	0.00	0.00
- Febrile neutropenia	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Pancytopenia	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
Hepatobiliary disorders	0	0.00	0.00	2	0.04	0.04	2	0.02	0.03	0	0.00	0.00	0	0.00	0.00
- Hepatic cirrhosis	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Hepatic failure	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
Gastrointestinal disorders	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	3	0.09	0.11	3	0.06	0.07
- Esophageal rupture	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Gastric hemorrhage	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
- Gastrointestinal hemorrhage	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
- Upper gastrointestinal hemorrhage	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
Immune system disorders	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	3630			4602			8400			3522			4676		
Total exposure (patient-years)	3258.2			4448.1			7827.8			2758.1			4184.4		
System Organ Class - Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
- POEMS syndrome	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
Injury, poisoning and procedural complications	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Head injury	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
Renal and urinary disorders	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
- Renal failure acute	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
Vascular disorders	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	2	0.06	0.07	2	0.04	0.05
- Deep vein thrombosis	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
- Shock hemorrhagic	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
Investigations	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
- Hemoglobin decreased	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
Skin and subcutaneous tissue disorders	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
- Skin ulcer	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; Per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files, and individual study reports

Table 57 Incidence of Fatal Events by System Organ Class and Preferred Term – Safety Grouping 5 Excluding Study 1245.25

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1799			2759			4962			1741			2893		
Total exposure (patient-years)	1114.3			2302			3536.5			1067.3			2434		
System Organ Class - Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0.06	0.09	3	0.11	0.13	4	0.08	0.11	0	0.00	0.00	2	0.07	0.08
- Lung adenocarcinoma stage IV	0	0.00	0.00	1	0.04	0.04	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
- Metastases to bone	0	0.00	0.00	1	0.04	0.04	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
- Metastases to liver	0	0.00	0.00	1	0.04	0.04	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
- Metastatic gastric cancer	1	0.06	0.09	0	0.00	0.00	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
- Malignant pleural effusion	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04
- Pericardial effusion malignant	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04
Blood and lymphatic system disorders	0	0.00	0.00	2	0.07	0.09	2	0.04	0.06	0	0.00	0.00	0	0.00	0.00
- Febrile neutropenia	0	0.00	0.00	1	0.04	0.04	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
- Pancytopenia	0	0.00	0.00	1	0.04	0.04	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
Hepatobiliary disorders	0	0.00	0.00	2	0.07	0.09	2	0.04	0.06	0	0.00	0.00	0	0.00	0.00
- Hepatic cirrhosis	0	0.00	0.00	1	0.04	0.04	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
- Hepatic failure	0	0.00	0.00	1	0.04	0.04	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
Infections and infestations	0	0.00	0.00	2	0.07	0.09	2	0.04	0.06	0	0.00	0.00	0	0.00	0.00
- Pneumonia	0	0.00	0.00	1	0.04	0.04	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
- Sepsis	0	0.00	0.00	1	0.04	0.04	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
Gastrointestinal disorders	0	0.00	0.00	1	0.04	0.04	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
- Esophageal rupture	0	0.00	0.00	1	0.04	0.04	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
Investigations	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.09	1	0.03	0.04
- Hemoglobin decreased	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.09	1	0.03	0.04
Respiratory, thoracic and mediastinal disorders	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.09	1	0.03	0.04
- Pulmonary edema	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.09	1	0.03	0.04
Skin and subcutaneous tissue	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.09	1	0.03	0.04

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1799			2759			4962			1741			2893		
Total exposure (patient-years)	1114.3			2302			3536.5			1067.3			2434		
System Organ Class - Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
disorders															
- Skin ulcer	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.09	1	0.03	0.04

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; Per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files, and individual study reports

Table 58 Incidence of Fatal Events by System Organ Class and Preferred Term – Safety Grouping 5, Completed Studies Only

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1798			2000			4421			1740			2112		
Total exposure (patient-years)	909.1			1080.1			2108			884			1019		
System Organ Class - Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Gastrointestinal disorders	0	0.00	0.00	1	0.05	0.09	1	0.02	0.05	0	0.00	0.00	0	0.00	0.00
- Esophageal rupture	0	0.00	0.00	1	0.05	0.09	1	0.02	0.05	0	0.00	0.00	0	0.00	0.00
General disorders and administration site conditions	1	0.06	0.11	0	0.00	0.00	1	0.02	0.05	1	0.06	0.11	2	0.09	0.20
- Sudden death	1	0.06	0.11	0	0.00	0.00	1	0.02	0.05	0	0.00	0.00	0	0.00	0.00
- Death	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.05	0.10
- Sudden cardiac death	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.11	1	0.05	0.10
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	0.06	0.11	0	0.00	0.00	1	0.02	0.05	0	0.00	0.00	0	0.00	0.00
- Metastatic gastric cancer	1	0.06	0.11	0	0.00	0.00	1	0.02	0.05	0	0.00	0.00	0	0.00	0.00
Investigations	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.11	1	0.05	0.10
- Hemoglobin decreased	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.11	1	0.05	0.10
Respiratory, thoracic and mediastinal disorders	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.11	1	0.05	0.10
- Pulmonary edema	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.11	1	0.05	0.10

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1798			2000			4421			1740			2112		
Total exposure (patient-years)	909.1			1080.1			2108			884			1019		
System Organ Class - Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Skin and subcutaneous tissue disorders	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.11	1	0.05	0.10
- Skin ulcer	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.11	1	0.05	0.10

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; Per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files, and individual study reports

Table 59 Patients Treated with Empagliflozin and with Fatal Events – Safety Grouping 5, Excluding Patients from Study 1245.25

PATIENT ID	DAY	SYSTEM ORGAN CLASS	PREFERRED TERM
EMPAGLIFLOZIN 10 MG ON-TREATMENT			
1245-0023-033592	65	Cardiac disorders	Acute myocardial infarction
1245-0048-014122	90	General disorders and administration site conditions	Sudden death
EMPAGLIFLOZIN 10 MG WITHIN 7 DAYS FROM LAST DOSE OF STUDY MEDICATION			
1245-0009-008582	471	Vascular disorders	Hypertension
EMPAGLIFLOZIN 10 MG AFTER 7 DAYS FROM LAST DOSE OF STUDY MEDICATION			
1245-0033-004697	268	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastatic gastric cancer
EMPAGLIFLOZIN 25 MG ON-TREATMENT			
1245-0019-012054	NA	Gastrointestinal disorders	Esophageal rupture
1245-0028-081806	281	General disorders and administration site conditions	Multi-organ failure
1245-0028-082486	14	General disorders and administration site conditions	Sudden death
1245-0028-082883	33	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung adenocarcinoma stage IV
	33	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to bone
	33	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Metastases to liver
1245-0028-084833	NA	Hepatobiliary disorders	Hepatic cirrhosis
	270	Hepatobiliary disorders	Hepatic failure
1245-0036-003264	59	Cardiac disorders	Cardiac arrest
EMPAGLIFLOZIN 25 MG WITHIN 7 DAYS FROM LAST DOSE OF STUDY MEDICATION			
1245-0019-010813	40	Cardiac disorders	Cardiorespiratory arrest
EMPAGLIFLOZIN 25 MG AFTER 7 DAYS FROM LAST DOSE OF STUDY MEDICATION			
1245-0023-034564	290	Blood and lymphatic system disorders	Febrile neutropenia
	290	Blood and lymphatic system disorders	Pancytopenia
	290	Infections and infestations	Sepsis
1245-0028-086947	NA	Infections and infestations	Pneumonia
1245-0036-001213	95	Cardiac disorders	Cardiorespiratory arrest

DAY = days from randomization; NA = not available

Source: Table 2.1.2.2 (SCS), submitted AE xpt and DM.xpt files, and individual study reports

Summary of Narratives:

Narratives from deaths which occurred in completed studies are summarized below. Narratives from interim data from ongoing studies are included in a separate section. Narratives for patients from Study 1245.25 are summarized in Section 7.3.5.1.1.

Patient 1245-0009-008582 (empagliflozin 10 mg within seven days of last dose):

Hypertension

A 75 year old male with a past medical history of T2DM, and hypertension was randomized to empagliflozin 10 mg in Study 1245.9 and continued in the extension Study 1245.24. On day 105 since randomization in Study 1245.9, he was found dead at home. The death certificate reported hypertension as the cause of death, which was assessed by his physician based on medical history. The last reported dose of study drug was on day 104. The actual cause of death is not known.

Patient 1245-0019-010813 (empagliflozin 25 mg within seven days of last dose):

Cardiorespiratory arrest

A 40 year old male with a past medical history of T2DM, eosinophilia, bilateral joint pain, and asymptomatic hypoglycemia was randomized to empagliflozin 25 mg. On day 35 since randomization, he experienced fever, and body aches. He was hospitalized with septic shock and dengue fever on day 36. He had deterioration following hospitalization and was put on ventilator support. During his hospitalization, he was noted to have thrombocytopenia, leukocytosis, hyperbilirubinemia, hematemesis, hematuria, acute renal failure, and petechial skin rash. On day 38, he had atrial flutter/fibrillation. On day 39, he had cardiorespiratory arrest leading to death. Last dose of study medication was on day 35.

Reviewer Comment: The event of cardiorespiratory arrest appears to be secondary to septic shock and dengue fever. The other reported diagnoses could also reasonably be attributed to the dengue fever and sepsis.

Patient 1245-0019-012054 (empagliflozin 25 mg): Esophageal rupture

A 74 year old male with a past medical history of T2DM, hyperlipidemia, hypertension, glaucoma, and sleep disorder was randomized to empagliflozin 25 mg. The adverse event of esophageal rupture was entered as starting on day 65 since randomization. Following that event, he had a prolonged hospitalization, and the event resulted in death. He was hospitalized for several months with complications of the esophageal rupture including sepsis and hypotension. He died on day 207.

Reviewer Comment: There is no clear association with the study drug and the event. Only limited information is available, and alternative causes of esophageal rupture cannot be excluded.

Patient 1245-0023-033592 (empagliflozin 10 mg): Acute myocardial infarction

A 56 year old female with a past medical history of T2DM with neuropathy, hypertension, dyslipidemia, and glaucoma was randomized to receive empagliflozin 10 mg. On day 54 since randomization, she experienced precordial pain, dyspnea and an ambulance was requested. Prior to the ambulance's arrival, she died. No autopsy was performed. Death certificate reported primary cause of death as acute myocardial infarction.

Patient 1245-0023-034564 (empagliflozin 25 mg within seven days of last dose): Sepsis

A 61 year old male with a past medical history of T2DM with neuropathy, nephropathy, and retinopathy, hypercholesterolemia, coronary artery disease status post (s/p) myocardial infarction and angioplasty, chronic obstructive pulmonary disease, cerebral hemorrhage, and squamous cell lung cancer was randomized to empagliflozin 25 mg. He was hospitalized on day 371 after randomization for Study 1245.23 with recurrence of squamous cell lung cancer. He received chemotherapy. Study medication was discontinued on day 421. On day 458, neutropenic fever, pancytopenia, and sepsis were reported. He died on day 460.

Reviewer Comment: The event of sepsis is likely due to the neutropenia (probably secondary to chemotherapy). These events are unlikely to be related to study drug.

Patient 1245-0028-081806 (empagliflozin 25 mg): Multi-organ failure

A 59 year old female with a past medical history of T2DM, urinary tract infections, bladder calculi, osteoporosis, hypertension, and obesity was randomized to empagliflozin 25 mg. On day 259 since randomization, she was hospitalized with infectious diarrhea. Following hospitalization, she was found to have electrolyte imbalances. On day 266, she was found to have a pulmonary consolidation. On day 281, she developed septic shock followed by multi-organ failure. She died on day 281.

Patient 1245-0028-082486 (empagliflozin 25 mg): Sudden death

A 71 year old female with a past medical history of T2DM, depression/anxiety, dyslipidemia, fatty liver, cerebrovascular disease, and hypertension was randomized to empagliflozin 25 mg. On day 14 since randomization, she died suddenly. No further information is available.

Patient 1245-0028-082883 (empagliflozin 25 mg): Metastatic adenocarcinoma, lung

A 75 year old female with a past medical history of T2DM, hypercholesterolemia, chronic/recurrent urinary tract infections, hypertension, cerebrovascular disease, and chronic obstructive pulmonary disease was randomized to empagliflozin 25 mg. On day 33 since randomization, she was diagnosed with adenocarcinoma of the lung with bone and liver metastases. She had reported fatigue since day eleven. Study drug was discontinued on day 40.

There was no known history, no known exposure to environmental carcinogens, and no smoking history or other risk factors. She died on an unknown date.

Reviewer Comment: The exposure to study drug prior to diagnosis of metastatic lung adenocarcinoma is short, suggesting that the two are unlikely to be related.

Patient 1245-0028-084833 (empagliflozin 25 mg): Hepatic failure

A 48 year old male with a past medical history of T2DM with neuropathy, glaucoma, congenital cataract, hyperlipidemia, hypertension, hepatic steatosis, and peptic ulcer disease was randomized to empagliflozin 25 mg. On day 270 since randomization, he developed renal insufficiency and hepatic insufficiency requiring hospitalization. He reported increasing waist circumference, weight and ascites. He was icteric and developed shortness of breath. Prior to this event, he had an upper respiratory tract infection on day 260. It was also reported that there was an increase in alcohol consumption. On day 273 (during hospitalization) GI bleeding occurred. He died on day 276 with the cause of death reported as hepatorenal syndrome with cirrhosis of the liver from a toxonutritional etiology.

Reviewer Comment: The long exposure prior to this event goes against a relationship between the study drug and hepatic failure. The increased alcohol consumption may have worsened underlying liver disease leading to GI bleeding (e.g. from varices) and hepatorenal syndrome.

Patient 1245-0028-086947 (empagliflozin 25 mg after seven days from last dose):

Pneumonia

A 57 year old female with a past medical history of T2DM was randomized to empagliflozin 25 mg. Study medication was stopped on day 60 since randomization due to severe hyperglycemia. This event was deemed resolved on day 75. On an unknown date, she developed pneumonia leading to her death on day 119.

Patient 1245-0033-004697 (empagliflozin 10 mg after seven days from last dose): Gastric cancer metastatic

A 68 year old male with a past medical history of T2DM with retinopathy, coronary artery disease, heart failure, hypertension, reflux disease, hypercholesterolemia, and angina pectoris was randomized to empagliflozin 10 mg. On day 221 since randomization, he was found to have iron deficiency anemia. Study medication was discontinued on day 248. On day 264, he was admitted with a possible myocardial infarction/cerebrovascular accident (these were subsequently ruled out) and with gastrointestinal bleeding. Gastroscopy performed on day 269 showed gastric cancer, and a staging CT showed metastatic disease in the liver. He was discharged home for palliation. He died on day 446.

Reviewer Comment: The exposure prior to diagnosis seems short given the extensiveness of the disease. No imbalance in gastric cancer is noted in the development program. This event seems unlikely to be due to study drug exposure.

Patient 1245-0036-001213 (empagliflozin 25 mg after seven days from last dose):

Cardiorespiratory arrest

A 61 year old male with a past medical history of T2DM with nephropathy and retinopathy, anemia, and constipation was randomized to empagliflozin 25 mg. On day 85 since randomization, an event of septicemia was reported. This was six days after stopping study medication (last dose of study medication on day 79). On day 85, he developed chest pain at rest, and dyspnea. He was hospitalized on day 86 for chest pain, acute on chronic renal failure, and diabetic ketoacidosis. On day 92, he was hospitalized for anasarca and breathlessness. On day 93, he was placed on dopamine. On day 94, he died from cardiorespiratory arrest.

Reviewer Comment: The fatal event of cardiorespiratory arrest appears to be a complication of the earlier event of septicemia. The source of sepsis is not clear.

Patient 1245-0036-003264 (empagliflozin 25 mg): Cardiac arrest

A 54 year old male with a past medical history of T2DM with nephropathy, hypertension, dyslipidemia, and coronary artery disease was randomized to empagliflozin 25 mg. On day 59 since randomization, he experienced chest discomfort and sweating at home. He became unresponsive, a local doctor was called and he was pronounced dead the same day.

Patient 1245-0048-014122 (empagliflozin 10 mg): Sudden Death

A 58 year old female with a past medical history of T2DM, arthritis, myocardial infarction s/p percutaneous transluminal coronary angioplasty, hypercholesterolemia, and tiredness was randomized to receive empagliflozin 10 mg. On day 90 since randomization, she was found dead with evidence of vomiting prior to death. No autopsy was performed, and no further information is known.

7.3.1.1 Deaths – Four Month Safety Update

In the 4-month safety update, an additional 29 patients (0.3%) had fatal events for the period from August 31, 2012 to March 4, 2013 in the ongoing studies submitted with the NDA. The overall incidence of fatal events was less than that seen with any treatment in SAF-5 (Table 54, Table 55). Treatment assignment remains blinded for these patients.

For studies that are not included in the NDA submission, the incidence of fatal events was low. A total of five patients had fatal events (4 (0.1%) on blinded therapy, 1 (0.1%) on empagliflozin 25 mg therapy).

No significant changes to the findings from the initially submitted data result from review of the 4-month safety update. No new safety concerns are raised by this update.

7.3.2 Nonfatal Serious Adverse Events

To protect the integrity of the ongoing cardiovascular safety study (Study 1245.25), nonfatal cardiovascular serious adverse events will be discussed in Section 7.3.5.1.2. The overall incidence of nonfatal SAEs was not increased for the empagliflozin-treated patients versus the comparator-treated patients (9.58%, 10.79 events per 100 patient-years for All Empa patients vs. 12.01%, 16.54 events per 100 patient-years for placebo patients and 10.76%, 12.78 events per 100 patient-years for all comparator patients) (Table 60). The SOC of “Neoplasms benign, malignant and unspecified (incl cysts and polyps)” and “Reproductive system and breast disorders” were reported with a slightly higher incidence in the empagliflozin-treated patients than in the placebo or comparator-treated patients.

Excluding the nonfatal serious adverse events that were reported from Study 1245.25 does not significantly change the overall incidence in the empagliflozin-treated patients versus the comparator-treated patients (Table 61). The most common SOC was “Infections and infestations”. While the incidence of this SOC is not increased in the empagliflozin-treated patients compared to the comparator-treated patients, some of the PTs that map to this SOC (i.e. “Cellulitis” and “Gastroenteritis”) are slightly more common. The SOC of “Gastrointestinal disorders” was reported at a slightly greater incidence in the empagliflozin-treated patients (1.15% for All Empa) versus comparator (0.90% for All Comp). The SOC “Neoplasms benign, malignant and unspecified (incl cysts and polyps)” was reported at a slightly greater incidence in the empagliflozin-treated patients, but no single PT drove this difference.

In looking at only those studies in SAF-5 that have been completed, the SOC in which there was a greater incidence of nonfatal SAEs in the empagliflozin-treated patients compared to the comparator-treated patients were “Neoplasms benign, malignant and unspecified (incl cysts and polyps)” and “Gastrointestinal disorders” (Table 62). Among the PTs that appear with a higher frequency in the empagliflozin-treated patients were “Cellulitis”, “Lung neoplasm malignant”, and “Bladder cancer” (Table 62). All of these were reported with greater frequency in the empagliflozin-treated patients, though the incidence was < 1%.

Table 60 Incidence of Nonfatal Serious Adverse Events (by System Organ Class and Preferred Term), Occurring in > 2 Patients of the All Empagliflozin Group – Safety Grouping 5

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	3630			4602			8400			3522			4676		
Total exposure (patient-years)	3258.2			4448.1			7827.8			2758.1			4184.4		
System Organ Class - Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Total with nonfatal SAE	331	9.12	10.64	462	10.04	10.93	805	9.58	10.79	423	12.01	16.54	503	10.76	12.78
Not yet coded	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	2	0.06	0.07	2	0.04	0.05
Infections and infestations	52	1.43	1.67	74	1.61	1.66	128	1.52	1.63	74	2.10	2.69	80	1.71	1.91
- Pneumonia	6	0.17	0.19	13	0.28	0.29	20	0.24	0.25	14	0.40	0.50	16	0.34	0.38
- Cellulitis	4	0.11	0.13	9	0.20	0.20	13	0.15	0.16	5	0.14	0.18	5	0.11	0.12
- Gastroenteritis	7	0.19	0.22	4	0.09	0.09	11	0.13	0.14	3	0.09	0.11	3	0.06	0.07
- Urinary tract infection	4	0.11	0.13	5	0.11	0.11	9	0.11	0.11	6	0.17	0.22	6	0.13	0.14
- Erysipelas	3	0.08	0.10	2	0.04	0.04	5	0.06	0.06	2	0.06	0.07	2	0.04	0.05
- Gangrene	2	0.06	0.06	2	0.04	0.04	4	0.05	0.05	2	0.06	0.07	2	0.04	0.05
- Sepsis	1	0.03	0.03	3	0.07	0.07	4	0.05	0.05	2	0.06	0.07	3	0.06	0.07
- Viral infection	1	0.03	0.03	3	0.07	0.07	4	0.05	0.05	0	0.00	0.00	0	0.00	0.00
- Bronchitis	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	4	0.11	0.14	4	0.09	0.09
- Pyelonephritis acute	1	0.03	0.03	2	0.04	0.04	3	0.04	0.04	3	0.09	0.11	3	0.06	0.07
- Urosepsis	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	2	0.06	0.07	2	0.04	0.05
- Pyelonephritis	0	0.00	0.00	2	0.04	0.04	3	0.04	0.04	1	0.03	0.04	1	0.02	0.02
Gastrointestinal disorders	43	1.18	1.38	48	1.04	1.08	91	1.08	1.16	30	0.85	1.08	41	0.88	0.98
- Vomiting	1	0.03	0.03	6	0.13	0.13	7	0.08	0.09	0	0.00	0.00	0	0.00	0.00
- Gastrointestinal hemorrhage	3	0.08	0.10	3	0.07	0.07	6	0.07	0.08	2	0.06	0.07	2	0.04	0.05
- Abdominal pain	1	0.03	0.03	4	0.09	0.09	5	0.06	0.06	0	0.00	0.00	1	0.02	0.02
- Colonic polyp	3	0.08	0.10	2	0.04	0.04	5	0.06	0.06	1	0.03	0.04	3	0.06	0.07
- Gastritis	3	0.08	0.10	2	0.04	0.04	5	0.06	0.06	1	0.03	0.04	2	0.04	0.05
- Gastroesophageal reflux disease	4	0.11	0.13	1	0.02	0.02	5	0.06	0.06	1	0.03	0.04	1	0.02	0.02
- Inguinal hernia	2	0.06	0.06	2	0.04	0.04	4	0.05	0.05	1	0.03	0.04	1	0.02	0.02
- Nausea	1	0.03	0.03	3	0.07	0.07	4	0.05	0.05	0	0.00	0.00	0	0.00	0.00

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	3630			4602			8400			3522			4676		
Total exposure (patient-years)	3258.2			4448.1			7827.8			2758.1			4184.4		
System Organ Class - Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
- Abdominal hernia	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	0	0.00	0.00	1	0.02	0.02
- Abdominal pain upper	0	0.00	0.00	3	0.07	0.07	3	0.04	0.04	1	0.03	0.04	1	0.02	0.02
- Constipation	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	3	0.09	0.11	3	0.06	0.07
- Diarrhea	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	2	0.06	0.07	2	0.04	0.05
- Pancreatitis acute	1	0.03	0.03	2	0.04	0.04	3	0.04	0.04	1	0.03	0.04	2	0.04	0.05
Neoplasms benign, malignant and unspecified incl cysts and polyps	28	0.77	0.90	47	1.02	1.05	76	0.90	0.97	26	0.74	0.94	35	0.75	0.83
- Breast cancer	2	0.06	0.06	3	0.07	0.07	5	0.06	0.06	1	0.03	0.04	2	0.04	0.05
- Basal cell carcinoma	1	0.03	0.03	3	0.07	0.07	4	0.05	0.05	0	0.00	0.00	1	0.02	0.02
- Lung neoplasm malignant	2	0.06	0.06	2	0.04	0.04	4	0.05	0.05	0	0.00	0.00	0	0.00	0.00
- Pancreatic carcinoma	1	0.03	0.03	3	0.07	0.07	4	0.05	0.05	1	0.03	0.04	1	0.02	0.02
- Colon cancer	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	4	0.11	0.14	5	0.11	0.12
- Gastric cancer	0	0.00	0.00	3	0.07	0.07	3	0.04	0.04	0	0.00	0.00	0	0.00	0.00
- Malignant melanoma	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	0	0.00	0.00	0	0.00	0.00
- Prostate cancer	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	5	0.14	0.18	6	0.13	0.14
- Rectal cancer	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	0	0.00	0.00	0	0.00	0.00
- Prostatic adenoma	1	0.03	0.03	2	0.04	0.04	3	0.04	0.04	0	0.00	0.00	0	0.00	0.00
Injury, poisoning and procedural complications	26	0.72	0.84	36	0.78	0.81	63	0.75	0.80	28	0.80	1.01	38	0.81	0.91
- Fall	5	0.14	0.16	10	0.22	0.22	15	0.18	0.19	6	0.17	0.22	6	0.13	0.14
- Traumatic fracture	6	0.17	0.19	3	0.07	0.07	9	0.11	0.11	6	0.17	0.22	7	0.15	0.17
- Road traffic accident	2	0.06	0.06	3	0.07	0.07	5	0.06	0.06	3	0.09	0.11	5	0.11	0.12
- Contusion	1	0.03	0.03	2	0.04	0.04	3	0.04	0.04	2	0.06	0.07	2	0.04	0.05
- Ankle fracture	1	0.03	0.03	2	0.04	0.04	3	0.04	0.04	0	0.00	0.00	0	0.00	0.00
- Concussion	1	0.03	0.03	2	0.04	0.04	3	0.04	0.04	0	0.00	0.00	0	0.00	0.00
- Ligament rupture	1	0.03	0.03	2	0.04	0.04	3	0.04	0.04	1	0.03	0.04	2	0.04	0.05
Vascular disorders	21	0.58	0.67	36	0.78	0.81	57	0.68	0.72	38	1.08	1.37	40	0.86	0.95
- Deep vein thrombosis	0	0.00	0.00	3	0.07	0.07	3	0.04	0.04	0	0.00	0.00	0	0.00	0.00

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	3630			4602			8400			3522			4676		
Total exposure (patient-years)	3258.2			4448.1			7827.8			2758.1			4184.4		
System Organ Class - Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
- Hematoma	0	0.00	0.00	3	0.07	0.07	3	0.04	0.04	0	0.00	0.00	0	0.00	0.00
- Thrombosis	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	1	0.03	0.04	1	0.02	0.02
- Thrombophlebitis	1	0.03	0.03	1	0.02	0.02	2	0.02	0.03	0	0.00	0.00	1	0.02	0.02
Musculoskeletal and connective tissue disorders	29	0.80	0.93	24	0.52	0.54	53	0.63	0.67	26	0.74	0.94	35	0.75	0.83
- Osteoarthritis	8	0.22	0.26	7	0.15	0.16	15	0.18	0.19	5	0.14	0.18	7	0.15	0.17
- Back pain	2	0.06	0.06	2	0.04	0.04	4	0.05	0.05	3	0.09	0.11	4	0.09	0.09
- Rotator cuff syndrome	3	0.08	0.10	1	0.02	0.02	4	0.05	0.05	2	0.06	0.07	2	0.04	0.05
- Pain in extremity	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	2	0.06	0.07	2	0.04	0.05
General disorders and administration site conditions	16	0.44	0.51	33	0.72	0.74	50	0.60	0.64	24	0.68	0.87	30	0.64	0.71
- Non-cardiac chest pain	1	0.03	0.03	7	0.15	0.16	8	0.10	0.10	1	0.03	0.04	2	0.04	0.05
- Pyrexia	4	0.11	0.13	4	0.09	0.09	8	0.10	0.10	1	0.03	0.04	2	0.04	0.05
Renal and urinary disorders	10	0.28	0.32	21	0.46	0.47	31	0.37	0.39	30	0.85	1.08	31	0.66	0.74
- Renal failure acute	4	0.11	0.13	9	0.20	0.20	13	0.15	0.16	8	0.23	0.29	9	0.19	0.21
- Renal failure	2	0.06	0.06	2	0.04	0.04	4	0.05	0.05	2	0.06	0.07	2	0.04	0.05
- Renal failure chronic	0	0.00	0.00	3	0.07	0.07	3	0.04	0.04	0	0.00	0.00	0	0.00	0.00
Respiratory, thoracic and mediastinal disorders	11	0.30	0.35	16	0.35	0.36	27	0.32	0.34	24	0.68	0.87	27	0.58	0.64
- Dyspnea	2	0.06	0.06	4	0.09	0.09	6	0.07	0.08	7	0.20	0.25	8	0.17	0.19
- Pleural effusion	0	0.00	0.00	3	0.07	0.07	3	0.04	0.04	2	0.06	0.07	2	0.04	0.05
Metabolism and nutrition disorders	9	0.25	0.29	17	0.37	0.38	26	0.31	0.33	23	0.65	0.83	29	0.62	0.69
- Hypoglycemia	5	0.14	0.16	6	0.13	0.13	11	0.13	0.14	3	0.09	0.11	3	0.06	0.07
- Dehydration	2	0.06	0.06	3	0.07	0.07	5	0.06	0.06	1	0.03	0.04	2	0.04	0.05
- Hyperglycemia	1	0.03	0.03	2	0.04	0.04	3	0.04	0.04	4	0.11	0.14	6	0.13	0.14
Hepatobiliary disorders	9	0.25	0.29	16	0.35	0.36	25	0.30	0.32	9	0.26	0.32	14	0.30	0.33
- Cholecystitis acute	3	0.08	0.10	5	0.11	0.11	8	0.10	0.10	3	0.09	0.11	6	0.13	0.14

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	3630			4602			8400			3522			4676		
Total exposure (patient-years)	3258.2			4448.1			7827.8			2758.1			4184.4		
System Organ Class - Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
- Cholelithiasis	5	0.14	0.16	2	0.04	0.04	7	0.08	0.09	2	0.06	0.07	3	0.06	0.07
- Cholecystitis	2	0.06	0.06	2	0.04	0.04	4	0.05	0.05	2	0.06	0.07	3	0.06	0.07
Surgical and medical procedures	9	0.25	0.29	9	0.20	0.20	18	0.21	0.23	15	0.43	0.54	16	0.34	0.38
- Coronary artery bypass	2	0.06	0.06	2	0.04	0.04	4	0.05	0.05	1	0.03	0.04	1	0.02	0.02
- Percutaneous coronary intervention	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	0	0.00	0.00	0	0.00	0.00
Reproductive system and breast disorders	7	0.19	0.22	8	0.17	0.18	15	0.18	0.19	4	0.11	0.14	7	0.15	0.17
- Benign prostatic hyperplasia	5	0.14	0.16	3	0.07	0.07	8	0.10	0.10	1	0.03	0.04	3	0.06	0.07
Eye disorders	10	0.28	0.32	5	0.11	0.11	15	0.18	0.19	5	0.14	0.18	8	0.17	0.19
- Glaucoma	2	0.06	0.06	2	0.04	0.04	4	0.05	0.05	1	0.03	0.04	1	0.02	0.02
- Retinal detachment	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	0	0.00	0.00	1	0.02	0.02
- Cataract	1	0.03	0.03	2	0.04	0.04	3	0.04	0.04	1	0.03	0.04	2	0.04	0.05
Skin and subcutaneous tissue disorders	4	0.11	0.13	10	0.22	0.22	15	0.18	0.19	14	0.40	0.50	14	0.30	0.33
- Skin ulcer	1	0.03	0.03	5	0.11	0.11	6	0.07	0.08	5	0.14	0.18	5	0.11	0.12
- Diabetic foot	1	0.03	0.03	3	0.07	0.07	4	0.05	0.05	6	0.17	0.22	6	0.13	0.14
Investigations	7	0.19	0.22	7	0.15	0.16	14	0.17	0.18	9	0.26	0.32	9	0.19	0.21
Blood and lymphatic system disorders	5	0.14	0.16	4	0.09	0.09	9	0.11	0.11	4	0.11	0.14	6	0.13	0.14
Psychiatric disorders	6	0.17	0.19	1	0.02	0.02	7	0.08	0.09	12	0.34	0.43	13	0.28	0.31
Ear and labyrinth disorders	0	0.00	0.00	7	0.15	0.16	7	0.08	0.09	5	0.14	0.18	5	0.11	0.12
- Vertigo	0	0.00	0.00	4	0.09	0.09	4	0.05	0.05	2	0.06	0.07	2	0.04	0.05
Endocrine disorders	1	0.03	0.03	3	0.07	0.07	5	0.06	0.06	3	0.09	0.11	4	0.09	0.09
- Goitre	1	0.03	0.03	2	0.04	0.04	3	0.04	0.04	1	0.03	0.04	2	0.04	0.05
Congenital, familial and genetic disorders	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	3	0.09	0.11	3	0.06	0.07

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	3630			4602			8400			3522			4676		
Total exposure (patient-years)	3258.2			4448.1			7827.8			2758.1			4184.4		
System Organ Class - Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100

Empa 10 = empagliflozin 10 mg; Empa 25 = Empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; Per 100 = events per 100 patient-years

Source: Table 5.7.5.1 (Integrated Summary of Safety)

Table 61 Incidence of Nonfatal Serious Adverse Events (by System Organ Class and Preferred Term), Occurring in > 2 Patients of the All Empagliflozin Group – Safety Grouping 5 Excluding Study 1245.25

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1799			2759			4962			1741			2893		
Total exposure (patient-years)	1114.3			2302			3536.5			1067.3			2434		
System Organ Class - Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Infections and infestations	16	0.89	1.44	48	1.74	2.09	66	1.33	1.87	27	1.55	2.53	35	1.21	1.44
- Cellulitis	2	0.11	0.18	6	0.22	0.26	8	0.16	0.23	1	0.06	0.09	1	0.03	0.04
- Pneumonia	1	0.06	0.09	3	0.11	0.13	5	0.10	0.14	4	0.23	0.37	6	0.21	0.25
- Gastroenteritis	1	0.06	0.09	3	0.11	0.13	4	0.08	0.11	0	0.00	0.00	0	0.00	0.00
- Urinary tract infection	1	0.06	0.09	3	0.11	0.13	4	0.08	0.11	4	0.23	0.37	4	0.14	0.16
- Viral infection	1	0.06	0.09	3	0.11	0.13	4	0.08	0.11	0	0.00	0.00	0	0.00	0.00
- Pyelonephritis	0	0.00	0.00	2	0.07	0.09	3	0.06	0.08	0	0.00	0.00	0	0.00	0.00
Injury, poisoning and procedural complications	22	1.22	1.97	37	1.34	1.61	60	1.21	1.70	19	1.09	1.78	33	1.14	1.36
- Fall	3	0.17	0.27	6	0.22	0.26	9	0.18	0.25	3	0.17	0.28	3	0.10	0.12
- Ligament rupture	1	0.06	0.09	2	0.07	0.09	3	0.06	0.08	0	0.00	0.00	1	0.03	0.04
Gastrointestinal disorders	20	1.11	1.79	37	1.34	1.61	57	1.15	1.61	12	0.69	1.12	26	0.90	1.07
- Abdominal hernia	2	0.11	0.18	1	0.04	0.04	3	0.06	0.08	0	0.00	0.00	1	0.03	0.04
- Abdominal pain	0	0.00	0.00	3	0.11	0.13	3	0.06	0.08	0	0.00	0.00	1	0.03	0.04
- Colonic polyp	1	0.06	0.09	2	0.07	0.09	3	0.06	0.08	1	0.06	0.09	3	0.10	0.12

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1799			2759			4962			1741			2893		
Total exposure (patient-years)	1114.3			2302			3536.5			1067.3			2434		
System Organ Class - Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
- Duodenal ulcer	1	0.06	0.09	2	0.07	0.09	3	0.06	0.08	0	0.00	0.00	0	0.00	0.00
- Gastrointestinal hemorrhage	0	0.00	0.00	3	0.11	0.13	3	0.06	0.08	0	0.00	0.00	0	0.00	0.00
- Inguinal hernia	2	0.11	0.18	1	0.04	0.04	3	0.06	0.08	0	0.00	0.00	0	0.00	0.00
- Vomiting	0	0.00	0.00	3	0.11	0.13	3	0.06	0.08	0	0.00	0.00	0	0.00	0.00
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	15	0.83	1.35	35	1.27	1.52	51	1.03	1.44	13	0.75	1.22	24	0.83	0.99
- Breast cancer	1	0.06	0.09	3	0.11	0.13	4	0.08	0.11	1	0.06	0.09	2	0.07	0.08
- Lung neoplasm malignant	2	0.11	0.18	2	0.07	0.09	4	0.08	0.11	0	0.00	0.00	0	0.00	0.00
- Bladder cancer	2	0.11	0.18	1	0.04	0.04	3	0.06	0.08	0	0.00	0.00	0	0.00	0.00
- Colon cancer	2	0.11	0.18	1	0.04	0.04	3	0.06	0.08	3	0.17	0.28	4	0.14	0.16
- Gastric cancer	0	0.00	0.00	3	0.11	0.13	3	0.06	0.08	0	0.00	0.00	0	0.00	0.00
- Prostate cancer	2	0.11	0.18	1	0.04	0.04	3	0.06	0.08	3	0.17	0.28	4	0.14	0.16
Musculoskeletal and connective tissue disorders	14	0.78	1.26	14	0.51	0.61	28	0.56	0.79	13	0.75	1.22	24	0.83	0.99
- Osteoarthritis	5	0.28	0.45	6	0.22	0.26	11	0.22	0.31	2	0.11	0.19	4	0.14	0.16
General disorders and administration site conditions	3	0.17	0.27	18	0.65	0.78	22	0.44	0.62	7	0.40	0.66	13	0.45	0.53
- Noncardiac chest pain	0	0.00	0.00	4	0.14	0.17	4	0.08	0.11	1	0.06	0.09	2	0.07	0.08
- Pyrexia	0	0.00	0.00	4	0.14	0.17	4	0.08	0.11	0	0.00	0.00	1	0.03	0.04
Hepatobiliary disorders	8	0.44	0.72	11	0.40	0.48	19	0.38	0.54	7	0.40	0.66	14	0.48	0.58
- Cholecystitis acute	1	0.06	0.09	3	0.11	0.13	4	0.08	0.11	3	0.17	0.28	6	0.21	0.25
- Cholelithiasis	2	0.11	0.18	2	0.07	0.09	4	0.08	0.11	1	0.06	0.09	2	0.07	0.08
- Cholecystitis	2	0.11	0.18	1	0.04	0.04	3	0.06	0.08	2	0.11	0.19	3	0.10	0.12
Renal and urinary disorders	3	0.17	0.27	12	0.43	0.52	15	0.30	0.42	18	1.03	1.69	19	0.66	0.78
- Renal failure acute	1	0.06	0.09	5	0.18	0.22	6	0.12	0.17	4	0.23	0.37	5	0.17	0.21
- Renal failure	2	0.11	0.18	2	0.07	0.09	4	0.08	0.11	1	0.06	0.09	1	0.03	0.04
Metabolism and nutrition disorders	2	0.11	0.18	11	0.40	0.48	13	0.26	0.37	10	0.57	0.94	17	0.59	0.70
- Hypoglycemia	0	0.00	0.00	5	0.18	0.22	5	0.10	0.14	0	0.00	0.00	0	0.00	0.00
Reproductive system and breast	4	0.22	0.36	7	0.25	0.30	11	0.22	0.31	1	0.06	0.09	4	0.14	0.16

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1799			2759			4962			1741			2893		
Total exposure (patient-years)	1114.3			2302			3536.5			1067.3			2434		
System Organ Class - Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
disorders															
- Benign prostatic hyperplasia	3	0.17	0.27	2	0.07	0.09	5	0.10	0.14	0	0.00	0.00	2	0.07	0.08
Respiratory, thoracic and mediastinal disorders	2	0.11	0.18	9	0.33	0.39	11	0.22	0.31	10	0.57	0.94	14	0.48	0.58
Eye disorders	6	0.33	0.54	3	0.11	0.13	9	0.18	0.25	4	0.23	0.37	8	0.28	0.33
Skin and subcutaneous tissue disorders	0	0.00	0.00	7	0.25	0.30	8	0.16	0.23	2	0.11	0.19	2	0.07	0.08
- Diabetic foot	0	0.00	0.00	3	0.11	0.13	3	0.06	0.08	0	0.00	0.00	0	0.00	0.00
Ear and labyrinth disorders	1	0.06	0.09	6	0.22	0.26	7	0.14	0.20	2	0.11	0.19	2	0.07	0.08
Investigations	2	0.11	0.18	5	0.18	0.22	7	0.14	0.20	3	0.17	0.28	3	0.10	0.12
Endocrine disorders	1	0.06	0.09	4	0.14	0.17	6	0.12	0.17	2	0.11	0.19	3	0.10	0.12
- Goitre	1	0.06	0.09	2	0.07	0.09	3	0.06	0.08	1	0.06	0.09	2	0.07	0.08
Surgical and medical procedures	3	0.17	0.27	3	0.11	0.13	6	0.12	0.17	2	0.11	0.19	3	0.10	0.12
Blood and lymphatic system disorders	0	0.00	0.00	3	0.11	0.13	3	0.06	0.08	2	0.11	0.19	4	0.14	0.16
Congenital, familial and genetic disorders	2	0.11	0.18	1	0.04	0.04	3	0.06	0.08	2	0.11	0.19	2	0.07	0.08

Empa 10 = empagliflozin 10 mg; Empa 25 = Empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; Per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files, and individual study reports

Table 62 Incidence of Nonfatal Serious Adverse Events (by System Organ Class and Preferred Term), Occurring in > 2 Patients of the All Empagliflozin Group – Safety Grouping 5, Completed Studies Only

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1798			2000			4421			1740			2112		
Total exposure (patient-years)	909.1			1080.1			2108			884			1019		
System Organ Class - Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Injury, poisoning and procedural complications	20	1.11	2.20	19	0.95	1.76	42	0.95	1.99	16	0.92	1.81	22	1.04	2.16
- Fall	3	0.17	0.33	2	0.10	0.19	5	0.11	0.24	2	0.11	0.23	2	0.09	0.20
Infections and infestations	10	0.56	1.10	24	1.20	2.22	36	0.81	1.71	23	1.32	2.60	23	1.09	2.26
- Cellulitis	1	0.06	0.11	4	0.20	0.37	5	0.11	0.24	1	0.06	0.11	1	0.05	0.10
- Pneumonia	0	0.00	0.00	3	0.15	0.28	4	0.09	0.19	3	0.17	0.34	3	0.14	0.29
- Urinary tract infection	1	0.06	0.11	3	0.15	0.28	4	0.09	0.19	2	0.11	0.23	2	0.09	0.20
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7	0.39	0.77	23	1.15	2.13	36	0.81	1.71	12	0.69	1.36	13	0.62	1.28
- Lung neoplasm malignant	2	0.11	0.22	2	0.10	0.19	4	0.09	0.19	0	0.00	0.00	0	0.00	0.00
- Bladder cancer	1	0.06	0.11	1	0.05	0.09	3	0.07	0.14	0	0.00	0.00	0	0.00	0.00
- Breast cancer	1	0.06	0.11	2	0.10	0.19	3	0.07	0.14	1	0.06	0.11	2	0.09	0.20
Gastrointestinal disorders	16	0.89	1.76	14	0.70	1.3	32	0.72	1.52	11	0.63	1.24	11	0.52	1.08
- Duodenal ulcer	1	0.06	0.11	1	0.05	0.09	3	0.07	0.14	0	0.00	0.00	0	0.00	0.00
Hepatobiliary disorders	7	0.39	0.77	6	0.30	0.56	14	0.32	0.66	7	0.40	0.79	7	0.33	0.69
- Cholecystitis	2	0.11	0.22	1	0.05	0.09	3	0.07	0.14	2	0.11	0.23	2	0.09	0.20
- Cholecystitis acute	1	0.06	0.11	2	0.10	0.19	3	0.07	0.14	3	0.17	0.34	3	0.14	0.29
- Cholelithiasis	2	0.11	0.22	1	0.05	0.09	3	0.07	0.14	1	0.06	0.11	1	0.05	0.10
Renal and urinary disorders	2	0.11	0.22	7	0.35	0.65	9	0.20	0.43	13	0.75	1.47	13	0.62	1.28
- Renal failure acute	1	0.06	0.11	3	0.15	0.28	4	0.09	0.19	4	0.23	0.45	4	0.19	0.39
Metabolism and nutrition disorders	1	0.06	0.11	6	0.30	0.56	8	0.18	0.38	9	0.52	1.02	9	0.43	0.88
- Hypoglycemia	0	0.00	0	4	0.20	0.37	4	0.09	0.19	0	0.00	0.00	0	0.00	0.00
Musculoskeletal and connective tissue disorders	9	0.50	0.99	6	0.30	0.56	15	0.34	0.71	9	0.52	1.02	9	0.43	0.88
- Osteoarthritis	4	0.22	0.44	3	0.15	0.28	7	0.16	0.33	1	0.06	0.11	1	0.05	0.10

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1798			2000			4421			1740			2112		
Total exposure (patient-years)	909.1			1080.1			2108			884			1019		
System Organ Class - Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Investigations	1	0.06	0.11	4	0.20	0.37	6	0.14	0.28	1	0.06	0.11	1	0.05	0.10
Reproductive system and breast disorders	3	0.17	0.33	2	0.10	0.19	5	0.11	0.24	0	0.00	0.00	0	0.00	0.00
- Benign prostatic hyperplasia	3	0.17	0.33	1	0.05	0.09	4	0.09	0.19	0	0.00	0.00	0	0.00	0.00
Endocrine disorders	0	0.00	0.00	3	0.15	0.28	4	0.09	0.19	1	0.06	0.11	1	0.05	0.10
Ear and labyrinth disorders	0	0.00	0.00	2	0.10	0.19	3	0.07	0.14	1	0.06	0.11	1	0.05	0.10

Empa 10 = empagliflozin 10 mg; Empa 25 = Empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; Per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files, and individual study reports

Narratives of the nonfatal serious adverse events were reviewed. Review of the narratives did not raise significant concern for a specific SAE or SAE type occurring as a result of empagliflozin treatment. Selected narratives with additional comments are summarized below. Narratives for patients from Study 1245.25 and for potential nonfatal cardiovascular events are discussed in Section 7.3.5.1.2.

Patient 1245-0010-003215 (empagliflozin 50 mg): Pyelonephritis

A 56 year old female with past medical history of thyroiditis, migraine, and arthralgia experienced an event of pyelonephritis requiring hospitalization on day 29 of study treatment. She was started on antibiotic therapy, and study drug was discontinued on day 30. Her baseline metformin was held until day 34. She recovered from the event on day 35.

Reviewer Comment: This early case of pyelonephritis was assessed as not related to study drug therapy by the investigator and the Applicant. This may be too casual of an assessment, as glucosuria could potentially increase the risk of UTIs and pyelonephritis. However, no imbalance in pyelonephritis was seen in the development program.

Patient 1245-0013-40001 (empagliflozin 50 mg single dose): Hospitalization for hepatic cirrhosis

A 37 year old male with baseline moderate liver impairment (Child-Pugh class B) was given a single dose of empagliflozin 50 mg. Eight days after study drug administration, he was hospitalized with deterioration of hepatic cirrhosis. He has hepatitis C cirrhosis and alcohol abuse at baseline, and had not been following treatment recommendations. He recovered and was started on anti-viral therapy and recommendations to cease alcohol consumption.

Reviewer Comment: Though the time course is suggestive of a relationship with the study drug and the event, the concomitant noncompliance with therapy and lifestyle recommendations makes the assessment complicated.

Patient 1245-0020-022271 (empagliflozin 25 mg): Tibia fracture

A 52 year old male with a past medical history of hypertension, dyslipidemia, and coronary artery disease (CAD) experienced a tibia plate fracture on day 124 of study treatment. He reported a fall leading to the fracture which required surgical intervention.

Reviewer Comment: No details of the fall event are available. It is not clear if hypoglycemia, symptoms concerning for a cerebrovascular or CV event, or symptoms concerning for hypotension preceded the fall.

Patient 1245-0020-023731 (empagliflozin 10 mg): Liver disorder

A 66 year old male was found to have a liver mass on day 93 of study treatment. He reported after this finding that there had been a prior diagnosis of liver cancer with a resection operation performed two years before enrollment. He was hospitalized for an unknown treatment and eventually discharged home on day 113. Study medication was discontinued on day 99.

Reviewer Comment: This event would be more appropriately coded as “hepatic neoplasm”.

Patient 1245-0024-004808 (empagliflozin 25 mg): Concussion and fall

A 67 year old male with past medical history of hypothyroidism and coronary artery disease status post bypass experienced a fall from a ladder and a concussion on day 370. He recovered on day 371.

Reviewer Comment: No information with regards to symptoms (e.g. dizziness) or hypoglycemia preceding the fall is provided.

Patient 1245-0024-008567 (empagliflozin 10 mg): Wrist fracture, ligament rupture

A 63 year old male with past medical history of hypertension, reflux, and benign prostatic hypertrophy (BPH) experienced a wrist fracture and ligament rupture on day 388. On day 351 he reported that he had a fall and symptoms started at that time.

Reviewer Comment: There is no information regarding the presence or absence of symptoms surrounding the fall (e.g. dizziness, hypoglycemic symptoms).

Patient 1245-0033-006222 (empagliflozin 25 mg): Volume depletion, acute renal failure

A 76 year old female with past medical history of hypertension, peripheral vascular disease, sleep apnea, and dyslipidemia experienced volume depletion and acute renal failure leading to hospitalization on the same day as the first dose of study medication. These events were confounded by the concomitant use of furosemide and angiotensin converting enzyme (ACE)-inhibitor. Study medication was stopped on day 16.

Reviewer Comment: The acuity of onset and mechanism of action of empagliflozin raises suspicion that this is directly related to study drug use. Causality is confounded by other concomitant medication. It is not clear if labs from the day of first dose of medication were from before starting study medication or after starting study medication.

7.3.2.1 Nonfatal Serious Adverse Events – Four Month Safety Update

In the 4-month safety update, an additional 653 patients (5.8%) had SAEs for the period from August 31, 2012 to March 4, 2013 in the ongoing studies submitted with the NDA. Nine of these patients had fatal events. The overall incidence of SAEs was less than that seen with any treatment group in SAF-5 (Table 60). The only PT which was reported in > 0.2% of patients was “Angina unstable”. Treatment assignment remains blinded for these patients.

For studies that are not included in this NDA submission, patients treated with empagliflozin 10 mg had the highest incidence of SAEs (7.1% - Empa 10 vs. 5.6% - Empa 25 vs. 4.8% - metformin vs. 4.6% - blinded)). This was less than that seen in any treatment group in SAF-5. Malignancy events were more common in the comparator-treated (i.e. metformin-treated) patients (one (1.6%) - Gastric cancer; one (1.6%) - Adenocarcinoma of colon; one (1.6%) - Lung neoplasm malignant) with the exception of prostate cancer which was more common in the empagliflozin 25 mg-treated patients (four (0.6%)). The overall incidence of malignancy events remained low. In the empagliflozin 10 mg-treated patients, the PTs “Acute myocardial infarction”, “Angina pectoris”, “Lumbar spinal stenosis”, and “Femur fracture” were reported in > 0.2% of patients (i.e. two patients). Subjects who remained on blinded treatment had no PTs reported in > 0.2% of patients.

No significant changes to the findings from the initially submitted data result from review of the 4-month safety update. No new safety concerns are raised by this update.

7.3.3 Dropouts and/or Discontinuations

The overall premature discontinuation/dropout rate for SAF-5 was 16.97%. In comparing treatment groups, there was a lower premature discontinuation rate in the empagliflozin-treated patients than in the comparators (Table 63). Excluding those patients who discontinued prematurely due to failure to continue in an extension study, the most common reason for premature discontinuation was an adverse event.

The percentage of patients who discontinued due to an adverse event in the empagliflozin-treated patients was slightly higher with Empa 25 vs. Empa 10, but both were lower than placebo. A

slightly greater percentage of patients discontinued for worsening of disease under study or other pre-existing disease in the placebo and comparator group than in either empagliflozin-treated group.

The most common SOC for adverse events resulting in discontinuation was “Infections and infestations” (Table 64). The most common adverse events leading to discontinuation were from the customized MedDRA query (CMQ) for urinary tract infections. Potential cardiovascular events leading to discontinuation are discussed in Section 7.3.5.1.3. The PT “Weight decreased” was also a more frequent cause for discontinuation in the empagliflozin-treated patients (particularly in the Empa 25 group) vs. comparator-treated patients. The PT “Hypoglycemia” was reported more frequently in the comparator-treated patients than in the empagliflozin-treated groups as a reason for discontinuation. Discontinuations due to cardiovascular events are discussed in Section 7.3.5.1.3.

Table 63 Incidence of Premature Discontinuations by Treatment Group – Safety Grouping
5

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	N	%	N	%	N	%	N	%	N	%
Treated	3311	100	4285	100	8197	100	3522	100	4676	100
Prematurely discontinued from study medication	518	15.64	630	14.70	1261	15.38	700	19.88	923	19.74
– Adverse event	123	3.71	174	4.06	321	3.92	152	4.32	187	4.00
– Worsening of disease under study	10	0.30	9	0.21	19	0.23	13	0.37	16	0.34
– Worsening of other pre-existing disease	13	0.39	21	0.49	37	0.45	19	0.54	24	0.51
– Other adverse event	100	3.02	144	3.36	265	3.23	120	3.41	147	3.14
– Lack of efficacy	2	0.06	4	0.09	11	0.13	17	0.48	22	0.47
– Noncompliant with protocol	14	0.42	25	0.58	42	0.51	24	0.68	36	0.77
– Lost to follow-up	24	0.72	37	0.86	64	0.78	44	1.25	62	1.33
– Patient refusal to continue, not due to AE	79	2.39	79	1.84	175	2.13	104	2.95	130	2.78
– Did not continue in extension study	204	6.16	210	4.90	470	5.73	248	7.04	331	7.08
– Other	64	1.93	93	2.17	162	1.98	97	2.75	141	3.02
– Study drug stopped, reason missing	8	0.24	8	0.19	16	0.20	14	0.40	14	0.30

Empa 10 = empagliflozin 10 mg; Empa 25 = Empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; AE = adverse event

Source: Table 2.5.1 (Integrated Summary of Safety)

Table 64 Incidence of Adverse Events Leading to Discontinuation – Safety Grouping 5, Treated Set

– For events occurring in $\geq 0.2\%$ of patients in any group

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
System Organ Class – Preferred Term	N	%	N	%	N	%	N	%	N	%
Treated	3630	100	4602	100	8400	100	3522	100	4676	100
Subjects with adverse events leading to discontinuation	174	4.79	226	4.91	412	4.9	188	5.34	222	4.75
Infections and infestations	31	0.85	34	0.74	67	0.80	22	0.62	23	0.49
– Urinary tract infection CMQ	11	0.30	10	0.22	21	0.25	3	0.09	3	0.06
Investigations	16	0.44	22	0.48	38	0.45	17	0.48	20	0.43
– Weight decreased	2	0.06	7	0.15	9	0.11	0	0.00	0	0.00
Metabolism and nutrition disorders	7	0.19	12	0.26	20	0.24	12	0.34	18	0.38
– Hypoglycemia	3	0.08	4	0.09	7	0.08	4	0.11	8	0.17

Empa 10 = empagliflozin 10 mg; Empa 25 = Empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; CMQ = customized MedDRA query

Source: Table 2.1.1.2: 1 (Summary of Clinical Safety)

For the safety grouping SAF-3, premature discontinuation for reasons other than not continuing in the extension trial occurred with a lower incidence in the empagliflozin-treated patients (10.8% for 10 mg dose, 12.8% for 25 mg dose) and in the sitagliptin-treated patients (12.2%) than in the placebo-treated patients (17.1%), (Table 65). No reason for discontinuation occurred more frequently in any of the treatment arms compared to placebo. Review of the adverse events that results in discontinuation of study medication did not reveal a clear imbalance for any individual PT (Table 66).

Table 65 Incidence of Premature Discontinuation by Treatment Group – Safety Grouping 3

	Empa 10		Empa 25		Placebo		Sitagliptin	
	N	%	N	%	N	%	N	%
Treated	830	100	822	100	825	100	223	100
Prematurely discontinued from study medication	260	31.33	278	33.82	350	42.42	78	34.98
– Adverse event	24	2.89	34	4.14	35	4.24	6	2.69
– Worsening of disease under study	3	0.36	1	0.12	2	0.24	0	0.00
– Worsening of other pre-existing disease	3	0.36	5	0.61	0	0.00	0	0.00
– Other adverse event	18	2.17	28	3.41	33	4	6	2.69
– Lack of efficacy	0	0.00	1	0.12	4	0.48	0	0.00
– Noncompliant with protocol	5	0.60	7	0.85	11	1.33	0	0.00
– Lost to follow-up	14	1.69	17	2.07	24	2.91	4	1.79
– Patient refusal to continue, not due to AE	27	3.25	28	3.41	41	4.97	8	3.59
– Did not continue in extension study	170	20.48	173	21.05	209	25.33	51	22.87
– Other	19	2.29	18	2.19	25	3.03	9	4.04
– Study drug stopped, reason missing	1	0.12	0	0.00	1	0.12	0	0

Empa 10 = empagliflozin 10 mg; Empa 25 = Empagliflozin 25 mg; All Empa = all randomized empagliflozin; AE = adverse event

Source: Table 1.2.1: 5 (Summary of Clinical Safety)

Table 66 Incidence of Adverse Events Leading to Discontinuation – Safety Grouping 3, Treated Set

- For events occurring in > 0.2% of patients in any group

System Organ Class – Preferred Term	Empa 10		Empa 25		Placebo		Sitagliptin	
	N	%	N	%	N	%	N	%
Treated	830	100	822	100	825	100	223	100
Subjects with adverse events leading to discontinuation	25	3.01	34	4.14	35	4.24	5	2.24
Infections and infestations	6	0.72	6	0.73	2	0.24	0	0.00
– Urinary tract infection	2	0.24	1	0.12	1	0.12	0	0.00
Cardiac disorders	3	0.36	2	0.24	5	0.61	1	0.45
– Myocardial infarction	0	0.00	0	0.00	3	0.36	0	0.00
Gastrointestinal disorders	3	0.36	5	0.61	6	0.73	0	0.00
– Nausea	0	0.00	1	0.12	1	0.12	0	0.00
– Diarrhea	0	0.00	0	0.00	2	0.24	0	0.00
– Constipation	0	0.00	0	0.00	2	0.24	0	0.00

	Empa 10		Empa 25		Placebo		Sitagliptin	
System Organ Class – Preferred Term	N	%	N	%	N	%	N	%
Treated	830	100	822	100	825	100	223	100
Musculoskeletal and connective tissue disorders	0	0.00	1	0.12	3	0.36	0	0.00
– Myalgia	0	0.00	1	0.12	2	0.24	0	0.00
– Muscular weakness	0	0.00	0	0.00	0	0.00	2	0.24
Investigations	2	0.24	8	0.97	0	0.00	4	0.48
– Blood creatinine increased	1	0.12	1	0.12	0	0.00	2	0.24
– Weight decreased	0	0.00	3	0.36	0	0.00	0	0.00
– Beta-N-acetyl-D-glucosaminidase increased ¹	0	0.00	2	0.24	0	0.00	0	0.00
Renal and urinary disorders	5	0.60	1	0.12	0	0.00	1	0.12
– Renal failure	2	0.24	0	0.00	0	0.00	1	0.12

Empa 10 = empagliflozin 10 mg; Empa 25 = Empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator

¹Measured in Chinese patients as requested by local authorities

Source: Table 2.1.1.2: 2 (Summary of Clinical Safety)

7.3.4 Significant Adverse Events

Prespecified significant adverse events in the phase 3 studies were (1) decreased renal function (serum creatinine $\geq 2x$ above baseline and above ULRR), and (2) hepatic injury (AST and/or ALT above $3x$ ULRR, bilirubin $\geq 2x$ ULRR). These events are discussed further in Sections 7.3.5.6 and 7.3.5.2.

Other significant adverse events were defined by the Applicant based on ICH E3. These events were marked hematological and other laboratory abnormalities, and events leading to an intervention that were not reported as an SAE. Interventions could include withdrawal of study medication, reduction in dose, or significant additional therapy.

For SAF-5, the overall incidence of other significant adverse events was not increased with empagliflozin treatment (Table 67). The most common other significant adverse events were in the “Infections and infestations” SOC. These were reported with a higher frequency in the empagliflozin-treated patients than in the comparator-treated patients. Within this SOC, the PT “Urinary tract infections” was the most frequent event and was reported with higher frequency in the empagliflozin-treated patients. This is discussed further in Section 7.3.5.5. The PTs “Dizziness” and “Weight decreased” were more common in the empagliflozin-treated patients (particularly with the 25 mg dose), as were the SOCs “Renal and urinary disorder” and “Reproductive system and breast disorders”. For these SOCs, no individual PT was reported in $\geq 0.2\%$ of any group.

Similar to the findings seen with SAF-5, the SAF-3 grouping did not demonstrate an increased incidence of other significant adverse events with empagliflozin compared to placebo (Table 68). An increased incidence in the “Infections and infestations” SOC, “Metabolism and nutrition disorders” SOC, “Renal and urinary disorders” SOC, “Reproductive system and breast disorders” SOC, and “Investigations” SOC was seen with empagliflozin treatment compared to placebo. Individual PTs that demonstrated an increased incidence with empagliflozin treatment compared to placebo were “Urinary tract infection”, “Hypoglycemia”, “Weight decreased”, and “Beta-N-acetyl-D-glucosaminidase increased”.

Table 67 Other Significant Adverse Events (by System Organ Class and Preferred Term), Occurring in $\geq 0.2\%$ of Patients in Any Group - Safety Grouping 5

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
System Organ Class – Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Number of patients	3630			4602			8400			3522			4676		
Number with other significant adverse events, N (%)	106 (2.9)			128 (2.8)			242 (2.9)			91 (2.6)			136 (2.9)		
Incidence per 100 patient-years	3.25			2.87			3.08			3.29			3.25		
Infections and infestations	25	0.69	0.76	24	0.52	0.54	49	0.58	0.62	9	0.26	0.32	10	0.21	0.24
– Urinary tract infection	11	0.30	0.33	8	0.17	0.18	19	0.23	0.24	2	0.06	0.07	2	0.04	0.05
Investigations	12	0.33	0.37	20	0.43	0.45	32	0.38	0.41	15	0.43	0.54	18	0.38	0.43
– Weight decreased	2	0.06	0.06	7	0.15	0.16	9	0.11	0.11	0	0.00	0.00	0	0.00	0.00
Renal and urinary disorders	14	0.39	0.43	18	0.39	0.40	32	0.38	0.41	4	0.11	0.14	4	0.09	0.09
Gastrointestinal disorders	13	0.36	0.40	18	0.39	0.40	31	0.37	0.39	15	0.43	0.54	19	0.41	0.45
Skin and subcutaneous tissue disorders	11	0.30	0.33	15	0.33	0.33	29	0.35	0.37	6	0.17	0.22	9	0.19	0.21
Reproductive system and breast disorders	12	0.33	0.37	14	0.30	0.31	27	0.32	0.34	3	0.09	0.11	4	0.09	0.09
Nervous system disorders	8	0.22	0.24	16	0.35	0.36	24	0.29	0.30	9	0.26	0.32	18	0.38	0.43
– Dizziness	3	0.08	0.09	7	0.15	0.16	10	0.12	0.13	2	0.06	0.07	6	0.13	0.14
Metabolism and nutrition disorders	10	0.28	0.30	10	0.22	0.22	21	0.25	0.27	10	0.28	0.36	30	0.64	0.71
– Hypoglycemia	6	0.17	0.18	3	0.07	0.07	9	0.11	0.11	3	0.09	0.11	21	0.45	0.50
General disorders and administration site conditions	10	0.28	0.30	7	0.15	0.16	17	0.20	0.22	7	0.20	0.25	9	0.19	0.21
Musculoskeletal and connective tissue disorders	2	0.06	0.06	9	0.20	0.20	12	0.14	0.15	3	0.09	0.11	3	0.06	0.07

Empa 10 = empagliflozin 10 mg; Empa 25 = Empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; Per 100 = events per 100 patient-years

Source: Table 2.1.4: 1 (Summary of Clinical Safety) and Table 5.9.5.1 (Integrated Summary of Safety)

Table 68 Other Significant Adverse Events (by System Organ Class and Preferred Term), Occurring in $\geq 0.2\%$ of Patients in Any Group – Safety Grouping 3

	Empa 10			Empa 25			All Empa			Placebo			Sitagliptin			All Comp		
System Organ Class – Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Number of patients	830			822			1652			825			223			1048		
Number with other significant adverse events, N (%)	17 (2.0)			24 (2.9)			41 (2.5)			22 (2.7)			4 (1.8)			26 (2.5)		
Incidence per 100 patient-years	2.16			3.14			2.65			3.12			1.99			2.87		
Infections and infestations	5	0.60	0.63	4	0.49	0.52	9	0.54	0.58	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00
– Urinary tract infection	2	0.24	0.25	1	0.12	0.13	3	0.18	0.19	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00
Metabolism and nutrition disorders	3	0.36	0.38	0	0.00	0.00	3	0.18	0.19	2	0.20	0.28	0	0.00	0.00	2	0.19	0.22
– Hypoglycemia	3	0.36	0.38	0	0.00	0.00	3	0.18	0.19	1	0.10	0.14	0	0.00	0.00	1	0.10	0.11
Nervous system disorders	1	0.12	0.13	4	0.49	0.52	5	0.30	0.32	3	0.40	0.43	2	0.86	1.00	5	0.48	0.55
Psychiatric disorders	1	0.12	0.13	0	0.00	0.00	1	0.06	0.06	0	0.00	0.00	1	0.43	0.50	1	0.10	0.11
– Depression	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.43	0.50	1	0.10	0.11
Gastrointestinal disorders	1	0.12	0.13	4	0.49	0.52	5	0.30	0.32	6	0.70	0.85	0	0.00	0.00	6	0.57	0.66
– Diarrhea	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	2	0.20	0.28	0	0.00	0.00	2	0.19	0.22
– Constipation	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	2	0.20	0.28	0	0.00	0.00	2	0.19	0.22
Skin and subcutaneous disorders	1	0.12	0.13	2	0.24	0.26	3	0.18	0.19	2	0.20	0.28	0	0.00	0.00	2	0.19	0.22
Musculoskeletal and connective tissue disorders	0	0.00	0.00	1	0.12	0.13	1	0.06	0.06	3	0.40	0.43	0	0.00	0.00	3	0.29	0.33
– Muscular weakness	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	2	0.20	0.28	0	0.00	0.00	2	0.19	0.22
– Myalgia	0	0.00	0.00	1	0.12	0.13	1	0.06	0.06	2	0.20	0.28	0	0.00	0.00	2	0.19	0.22
Renal and urinary disorders	3	0.36	0.38	0	0.00	0.00	3	0.18	0.19	1	0.10	0.14	0	0.00	0.00	1	0.10	0.11
Reproductive system and breast disorders	2	0.24	0.25	2	0.24	0.26	4	0.24	0.26	1	0.10	0.14	0	0.00	0.00	1	0.10	0.11
Cardiac disorders	1	0.12	0.13	1	0.12	0.13	2	0.12	0.13	1	0.10	0.14	1	0.43	0.50	2	0.19	0.22
– Palpitations	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.10	0.14	1	0.43	0.50	2	0.19	0.22

	Empa 10			Empa 25			All Empa			Placebo			Sitagliptin			All Comp		
System Organ Class – Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Number of patients	830			822			1652			825			223			1048		
General disorders and administration site conditions	0	0.00	0.00	1	0.12	0.13	1	0.06	0.06	2	0.20	0.28	0	0.00	0.00	2	0.19	0.22
Investigations	2	0.24	0.25	8	0.97	1.04	10	0.61	0.64	3	0.40	0.43	0	0.00	0.00	3	0.29	0.33
– Weight decreased	0	0.00	0.00	3	0.36	0.30	3	0.18	0.19	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00
– Beta-n-acetyl-D-glucosaminidase increased ¹	0	0.00	0.00	2	0.24	0.26	2	0.12	0.13	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00

Empa 10 = empagliflozin 10 mg; Empa 25 = Empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; Per 100 = events per 100 patient-years

¹Measured in Chinese patients as requested by local authority

Source: Table 5.9.3.1 (Integrated Summary of Safety)

7.3.5 Submission Specific Safety Concerns

7.3.5.1 Cardiovascular Safety

With all antidiabetic therapies, cardiovascular safety is a concern. No signal of increased cardiovascular risk with empagliflozin was seen in the development program. From the cardiovascular (CV) meta-analysis, there is no apparent increased cardiovascular risk with empagliflozin treatment compared to placebo, (b) (4)

(b) (4). However, it is reassuring that the hazard ratio from the CV meta-analysis compared to placebo for the primary endpoint of 4-point MACE¹ (b) (4) and the upper bound of the 95% confidence interval did not exceed 1.8, which is the prespecified upper bound discussed in the FDA's "Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes". Interim analysis of the ongoing CV outcomes trial (CVOT) is consistent with this finding from the CV meta-analysis. In the overall CV meta-analysis, an estimated hazard ratio (b) (4) was seen for the individual endpoint of (b) (4)

In preceding sections, information from the ongoing cardiovascular safety study (Study 1245.25) and potential cardiovascular events was removed. The removed data for those sections will be discussed here, followed by discussion of the analysis of cardiovascular safety.

Based on the currently available data, there does not appear to be an increased risk of CV events with empagliflozin. (b) (4)

For detailed review of the submitted cardiovascular safety meta-analysis, see the review by Janelle Charles.

¹4-point MACE = MACE+; events include CV death, non-fatal MI, non-fatal stroke, and hospitalization for unstable angina

7.3.5.1.1 Deaths

For the overall grouping SAF-5, no increased incidence of death was seen in the empagliflozin treated patients compared to placebo or other comparators. The majority of deaths came from Study 1245.25. Excluding those subjects did not change this observation. A summary of empagliflozin treated patient deaths from Study 1245.25 (Table 70) along with a summary of the provided narratives follows below. In examining only those events that could be considered fatal cardiovascular events, only the PT “Sudden death” demonstrated an increased incidence in the empagliflozin treated patients compared to placebo or other comparators in SAF-5, the pool of patients from SAF-5 that excluded Study 1245.25, or the pool of patients from completed studies in SAF-5 (Table 71, Table 72, and Table 73). Though the incidence was greater in the empagliflozin treated patients, it was not markedly increased over placebo or comparators, and occurred in < 1% of empagliflozin treated patients.

Table 69 Incidence of Death – Safety Grouping 5, Excluding Study 1245.25 and for Completed Studies

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	N	%	N	%	N	%	N	%	N	%
Excluding Study 1245.25:										
# patients	1799	100	2759	100	4962	100	1741	100	2893	100
Total exposure (patient-years)	1114.3		2302.0		3536.5		1067.3		2434.0	
Deaths	4	0.22	10	0.36	14	0.28	9	0.52	13	0.45
Per 100 patient-years	0.36		0.43		0.40		0.84		0.53	
Completed studies only:										
# patients	1798	100	2000	100	4421	100	1740	100	2112	100
Total exposure (patient-years)	909.1		1080.1		2108.0		884.0		1019.0	
Deaths	4	0.22	4	0.20	8	0.18	9	0.52	10	0.47
Per 100 patient-years	0.44		0.37		0.38		1.02		0.98	

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators

Source: Submitted AE xpt and DM xpt files, and individual study reports

Table 70 Summary of Deaths in Empagliflozin Treated Patients from Study 1245.25

PATIENT ID	DAY	SYSTEM ORGAN CLASS	PREFERRED TERM
Empagliflozin 10 mg on-treatment			
1245-0025	(b) (4) 435	General disorders and administration site conditions	Death
1245-0025	429	General disorders and administration site conditions	Death
1245-0025	338	Nervous system disorders	Cerebrovascular accident
1245-0025	241	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lung neoplasm malignant
1245-0025	286	General disorders and administration site conditions	Sudden cardiac death
1245-0025	426	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Brain neoplasm
1245-0025	265	General disorders and administration site conditions	Sudden death
1245-0025	98	General disorders and administration site conditions	Sudden death
1245-0025	99	Infections and infestations	Sepsis
1245-0025	371	Cardiac disorders	Cardiac failure
1245-0025	10	Cardiac disorders	Acute myocardial infarction
1245-0025	38	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hepatic cancer metastatic
	38	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Pancreatic carcinoma metastatic
Empagliflozin 10 mg w/in 7 days from last dose of study medication			
1245-0025	358	General disorders and administration site conditions	Sudden death
1245-0025	264	General disorders and administration site conditions	Sudden death
1245-0025	30	Respiratory, thoracic and mediastinal disorders	Acute respiratory failure
	30	Infections and infestations	Pneumonia
	30	Renal and urinary disorders	Renal failure acute
	30	Infections and infestations	Septic shock
Empagliflozin 10 mg after 7 days from last dose of study medication			
1245-0025	384	Immune system disorders	POEMS syndrome
1245-0025	212	Cardiac disorders	Left ventricular failure
1245-0025	298	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism
1245-0025	198	Nervous system disorders	Cerebrovascular accident
Empagliflozin 25 mg on-treatment			
1245-0025	5	General disorders and administration site conditions	Sudden death
1245-0025	201	Cardiac disorders	Ventricular fibrillation
1245-0025	279	Infections and infestations	Pneumonia
1245-0025	296	Nervous system disorders	Cerebrovascular accident
1245-0025	183	General disorders and administration site conditions	Death
1245-0025	40	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Colon cancer
1245-0025	101	Cardiac disorders	Cardiogenic shock
1245-0025	159	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Rectal cancer
1245-0025	41	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Pancreatic neoplasm
1245-0025	43	General disorders and administration site conditions	Sudden death
1245-0025	154	Cardiac disorders	Acute myocardial infarction
1245-0025	123	General disorders and administration site conditions	Death
1245-0025	44	Nervous system disorders	Cerebrovascular accident
Empagliflozin 25 mg w/in 7 days from last dose of study medication			
1245-0025	2	Injury, poisoning and procedural complications	Head injury
1245-0025	219	Cardiac disorders	Acute myocardial infarction

PATIENT ID	DAY	SYSTEM ORGAN CLASS	PREFERRED TERM
Empagliflozin 25 mg after 7 days from last dose of study medication			
1245-0025- (b) (4)	260	Cardiac disorders	Myocardial infarction
1245-0025- (b) (4)	445	Respiratory, thoracic and mediastinal disorders	Idiopathic pulmonary fibrosis
1245-0025- (b) (4)	120	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Hepatic neoplasm malignant
1245-0025- (b) (4)	299	General disorders and administration site conditions	Cardiac death
1245-0025- (b) (4)	95	Infections and infestations	Sepsis
1245-0025- (b) (4)	244	Cardiac disorders	Cardiorespiratory arrest

Summarized Narratives for Deaths in Empagliflozin Treated Patient from Study 1245.25:

Patient 1245-0025- (b) (4) (empagliflozin 10 mg within seven days of last dose): POEMS

A 62 year old male with a past medical history of T2DM with neuropathy, hypertension, hypercholesterolemia, coronary artery disease s/p bypass, and depression was randomized to empagliflozin 10 mg. On day 190 since randomization, he was diagnosed with worsening neuropathy and POEMS which resulted in hospitalization. Study medication was discontinued on day 190. He presented with worsening neuropathy pain and difficulty walking. This event of worsening neuropathy was considered recovered with sequelae on day 194. On day 384, he had worsening of POEMS and was hospitalized. He died on day 397.

Reviewer Comment: POEMS syndrome is characterized by the constellation of polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes. Aside from the reported worsening neuropathy, there is no other information provided which would suggest the diagnosis of POEMS. In particular, there is no information with regard to monoclonal proteins or a monoclonal plasma cell proliferative disorder, which is central to the diagnosis. Additionally, the long duration from discontinuation of study drug to death does not support a relationship with the study drug. More detailed information regarding the hospitalization prior to his death is not provided. The diagnosis of POEMS is unclear.

Patient 1245-0025- (b) (4) (empagliflozin 25 mg within seven days of last dose): Myocardial infarction

A 43 year old male with a past medical history of T2DM with nephropathy and neuropathy, hypertension, hypercholesterolemia, congestive heart failure, coronary artery disease, peripheral vascular disease, and cerebrovascular disease was randomized to empagliflozin 25 mg. Study medication was stopped on day 195 since randomization due to worsening of pre-existing disease. On day 259, he had a myocardial infarction. He died on day 264.

Reviewer Comment: Due to the time from discontinuation of study drug to the event, it seems unlikely that the two are related.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg within 7 days of last dose): Sudden death

A 63 year old male was randomized to empagliflozin 10 mg. No narrative is provided. From review of the submitted datasets, he reported an AE of hypotension on day 288, and erectile dysfunction on day 327. Study medication was apparently discontinued on day 357. On day 358, an event of sudden death was reported.

Patient 1245-0025- (b) (4) (empagliflozin 25 mg): Sudden death

A 76 year old male with a past medical history of T2DM with nephropathy and neuropathy, hypercholesterolemia, coronary artery disease s/p stent, history of myocardial infarction, vitamin B deficiency, Dupuytren's contracture, and erectile dysfunction was randomized to empagliflozin 25 mg. On day five since randomization, the patient died. No further information is known.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg within seven days of last dose): Sudden death

A 74 year old male with a past medical history of T2DM, chronic obstructive pulmonary disease, coronary artery disease, heart failure, claudication, hypercholesterolemia, and ischemic left bundle branch block was randomized to empagliflozin 10 mg. On day 107, he was diagnosed with an ulcer of the ascending large intestine leading to hospitalization. He developed a moderate hypoglycemic event on day 113, with a severe hypoglycemic event occurring on day 114. He received antibiotics and intravenous fluids and was discharged from the hospital on day 121 following a colonoscopy. The ulcer was resolved on day 145. Study medication had been discontinued on day 114, and was restarted on day 138.

On day 263, the event of sudden death was reported. No additional information is known.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg): Death

A 53 year old male with a past medical history of T2DM, atrial fibrillation, cardiac aneurysm, heart failure, hypercholesterolemia, ankle osteoarthritis, and adiposity was randomized to receive empagliflozin 10 mg. On day 435 since randomization, he was found dead at home. No autopsy was performed, and the cause of death is unknown.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg): Death

A 79 year old female with a past medical history of T2DM with nephropathy, hypertension, obesity, exertional dyspnea, chronic renal insufficiency, coronary artery disease, ischemic cardiomyopathy, hypercholesterolemia, hypersomnia, epigastric hernia, anxiety, and polyarthrititis was randomized to receive empagliflozin 10 mg. On day 429 since randomization, she was

found dead at home. Cause of death is unknown.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg): Cerebrovascular accident

A 76 year old male with a past medical history of T2DM, hypertension, hypercholesterolemia, hyperuricemia, coronary artery disease, peripheral vascular disease, aortic aneurysm, chronic obstructive pulmonary disease, and previous myocardial infarction s/p bypass graft was randomized to empagliflozin 10 mg. On day 107 since randomization, he had a transient ischemic attack requiring hospitalization. At that time atorvastatin and clopidogrel were started. On day 337 he had a stroke that required hospitalization and resulted in his death. Details of his course after the stroke are not available other than that he died on day 430.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg): Lung neoplasm malignant

A 72 year old male with a past medical history of T2DM, peripheral vascular disease, hypertension, chronic/recurrent urinary tract infections, previous smoking history, and irritable bowel syndrome was randomized to empagliflozin 10 mg. On day 241 since randomization, he presented to the emergency room with complaints of chest pain and was admitted for further work-up. Work-up included a CT scan of the chest which revealed a left lung carcinoma with chest wall infiltration. Biopsy performed on day 249 was consistent with squamous cell carcinoma. Chemotherapy was started. Study drug was stopped on day 308. He died on day 351. No additional information about his death is provided.

Reviewer comment: An imbalance in lung cancer events was noted in the development program and is discussed further below. The patient had a history of smoking which is a known risk factor for lung cancer. This seems unlikely to be due to treatment with empagliflozin.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg): Sudden cardiac death

A 58 year old male with a past medical history of T2DM with nephropathy, hypertension, hyperlipidemia, ischemic heart disease, myocardial infarction/coronary artery disease s/p bypass graft and drug-eluting stent, and reflux disease was randomized to empagliflozin 10 mg. On day 286 since randomization, he reported sudden epigastric pain, nausea, and vomiting. Emergency medical services were called; he was unconscious and unresponsive at their arrival. Cause of death on the death certificate was cardiac arrest.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg): Brain neoplasm

A 76 year old male with a past medical history of T2DM with retinopathy and neuropathy, hypertension, peripheral vascular disease, moderate renal impairment, and 1st degree atrioventricular block was randomized to empagliflozin 10 mg. He had a history of smoking,

had no personal or family history of cancer, had no personal history of occupational chemical exposure, and denied alcohol intake. On day 426 since randomization, he was hospitalized with hemiparesis and cognitive impairment and found to have a brain tumor. He was treated with dexamethasone, phenytoin, and ranitidine. No further evaluation or treatment was pursued. He was discharged on day 432. Study drug was stopped on day 447. He was subsequently hospitalized and died on day 460.

Patient 1245-0025- (b) (4) (empagliflozin 25 mg after seven days from last dose): Idiopathic pulmonary fibrosis

A 68 year old male with a past medical history of T2DM, coronary artery disease, hypertension, and mixed dyslipidemia was randomized to empagliflozin 25 mg. On day 239 since randomization, he was diagnosed with pulmonary fibrosis. Study medication was stopped on day 252. Prior to the diagnosis of pulmonary fibrosis, he had been treated with amiodarone for atrial fibrillation/flutter starting on day 37 since randomization. On day 344, he had a severe exacerbation of pulmonary fibrosis. He required mechanical ventilation on day 350, and died on day 364. Additional events during the hospitalization included atrial fibrillation, respiratory infection, and upper gastrointestinal (GI) bleeding.

Reviewer Comment: The event of pulmonary fibrosis could be related to treatment with amiodarone rather than to treatment with study drug. Pulmonary fibrosis is a known adverse event with amiodarone use.

Patient 1245-0025- (b) (4) empagliflozin 25 mg within seven days of last dose): Head injury

A 59 year old female with a past medical history of T2DM with neuropathy, retinopathy, and nephropathy, hypertension, blindness, peripheral vascular disease, heart failure, dyslipidemia, and recurrent urinary tract infections was randomized to empagliflozin 25 mg. On day two since randomization, she suffered head trauma. She fell from a ladder or stairs with direct head trauma. Her baseline blindness was thought to contribute to the event. Study drug was stopped that day, and she only received the study drug on day one. She died on day five as a result of the head trauma.

Reviewer Comment: It is possible to speculate that the study drug induced hypotension/volume depletion leading to syncope which caused the fall, but the provided explanation of fall due to blindness is also plausible. There is not enough information to make a reasonable assessment of causality.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg): Sudden death

A 59 year old male with a past medical history of T2DM, hypertension, previous myocardial infarction, coronary artery disease, and unstable angina was randomized to empagliflozin 10 mg. On day 265 since randomization, he died. No information is reported regarding cause of death, but it was considered to be an outcome event of cardiovascular death.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg): Sudden death

A 59 year old male with a past medical history of T2DM, hypertension, and peripheral vascular disease was randomized to empagliflozin 10 mg. On day 98 since randomization, he died of an apparent cardiovascular event. No additional information is known.

Patient 1245-0025- (b) (4) (empagliflozin 25 mg): Ventricular fibrillation

A 63 year old male with a past medical history of T2DM, hyperlipidemia, hypertension, and coronary artery disease was randomized to empagliflozin 25 mg. On day 201 since randomization, he had a sudden collapse that was attributed to ventricular fibrillation. The patient was resuscitated and hospitalized, and died on day 209.

Patient 1245-0025- (b) (4) (empagliflozin 25 mg): Pneumonia

A 73 year old male was randomized to empagliflozin 25 mg. No narrative is provided for this case. On day 279, he developed pneumonia. Study medication had been stopped at an unknown time during the preceding 25 days. He died on day 284.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg): Sepsis

A 79 year old female with a past medical history of T2DM with neuropathy, hypertension, coronary artery disease, atrial fibrillation, heart failure from dilated cardiomyopathy, mitral regurgitation, peripheral vascular disease, emphysema, anxiety, vertebrobasilar insufficiency, and extrapyramidal syndrome was randomized to receive empagliflozin 10 mg. On day 24 since randomization, she presented with pain and pallor with functional deficiency in the left lower limb. She was hospitalized with severe peripheral ischemia. On day 29, she had amputation of the left lower limb. She was subsequently discharged on day 55. On day 91, she was suspected to have a urinary tract infection. On day 99, she was diagnosed with sepsis and started on treatment with antibiotics. She refused hospitalization. Study drug was stopped on day 106. On day 114, she was reported to be refusing medication, oral intake, and hospitalization. She died on day 122 due to sepsis.

Reviewer Comment: This case could arguably be attributed to empagliflozin. The increased glucose in the urine may predispose to urinary tract infections. If left untreated, this could lead to sepsis and eventually death.

Patient 1245-0025- (b) (4) (empagliflozin 25 mg): Cerebrovascular accident

A 60 year old male with a past medical history of T2DM, cerebrovascular disease/accident, hypertension, dyslipidemia, and hypothyroidism was randomized to empagliflozin 25 mg. On day 176, he had a syncopal event resulting in fall and fracture of facial bones resulting in hospitalization and discontinuation of study medication. No hypoglycemia was reported. He was noted to have recovered from these events on day 180 and was discharged from the hospital. On day 209, he was restarted on study medication. On day 296, he had a cerebrovascular accident requiring hospitalization. He died on day 305 due to the event.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg after seven days from last dose): Left ventricular failure

A 52 year old male with a past medical history of T2DM, hypertension, coronary artery disease, and mild renal impairment was randomized to empagliflozin 10 mg. On day 212 since randomization, he was hospitalized for severe left ventricular failure. The last reported dose of study medication was on day 200. Prior to hospitalization, he had recovered from an upper respiratory tract infection on day 197. He died on day 213.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg): Cardiac failure

A 63 year old male with a past medical history of T2DM, coronary artery disease, hypertension, and cardiomyopathy was randomized to empagliflozin 10 mg. On day 160 since randomization, he was diagnosed with sepsis leading to hospitalization. He was admitted to the intensive care unit with shortness of breath, cough, and restlessness. Elevated white blood count, positive urine culture, and renal and hepatic impairment were noted. He was reported to have recovered from sepsis and urinary tract infection on day 167, and was discharged. Hepatic and renal impairment improved as well. On day 317 since randomization, he was hospitalized with severe congestive heart failure. This event was deemed resolved on day 321. On day 365, he developed a severe decrease in renal function. Study drug was discontinued on day 365 as a result. On day 367, he was diagnosed with a urinary tract infection which was treated with antibiotics. On day 371, he developed severe cardiac failure and died on day 368 despite treatment with furosemide and lactulose.

Reviewer Comment: The first event of sepsis could have contributed to the renal and hepatic impairment. It is unlikely that these are related to study drug treatment as they improved following recovery from sepsis and without reported discontinuation of the study drug. Whether the later events of decreased renal function and heart failure leading to death are related to study drug is less clear. The development of heart failure speaks against excess diuretic effect, and the timeframe of exposure seems to be too long for this to be from a direct nephrotoxic effect of the drug.

**Patient 1245-0025 (b) (4) (empagliflozin 25 mg after seven days from last dose):
Hepatocellular cancer**

A 66 year old male with a past medical history of T2DM, hypertension, dyslipidemia, dyspepsia, peripheral vascular disease, and coronary artery disease s/p bypass and MI was randomized to empagliflozin 25 mg. On day 86 since randomization, he was noted to have elevated liver enzymes. Hepatomegaly with tenderness was noted on day 115, and study medication was stopped. He was diagnosed on day 120 with hepatocellular cancer, which resulted in death on day 146.

Reviewer Comment: The exposure to study drug prior to diagnosis of hepatocellular cancer is short, suggesting that the two are unlikely to be related.

Patient 1245-0025 (b) (4) (empagliflozin 25 mg): Death

A 68 year old male with a past medical history of T2DM, hypertension, mixed hyperlipidemia, coronary artery disease s/p bypass, cataracts, prostatic hypertrophy, and prostatitis was randomized to empagliflozin 25 mg. On day 103 since randomization, he was diagnosed with pneumonia. He had a pleural effusion and weight loss which led to hospitalization and evaluation for possible tuberculosis. Testing of the pleural fluids was negative for tuberculosis. On day 158, he was hospitalized for a lung biopsy and thoracotomy for unclear indications. On day 187, he died. Precise cause of death is not known.

Patient 1245-0025 (b) (4) (empagliflozin 25 mg): Colon cancer

A 69 year old female with a past medical history of T2DM, hypertension, hyperlipidemia, and coronary artery disease s/p bypass was randomized to empagliflozin 25 mg. On day 40 since randomization, she was hospitalized with epigastric pain and anemia. She was given a diagnosis of chronic gastritis. On day 75, she reported constipation, and was again admitted to the hospital. On day 77, she was started on iron supplements but her anemia worsened and she was admitted to the hospital on day 114. Colonoscopy was performed on day 141 but the scope could not be passed. During the procedure she had a non-ST elevation MI. Repeat colonoscopy was attempted on day 142. A lesion in the transverse and sigmoid colon was seen with barium

enema leading to the diagnosis of colon cancer. She was discharged from the hospital on day 148 with palliative measures. She died on day 205. Prior to her death she had poor oral intake and was noted to have electrolyte abnormalities and episodes of hypoglycemia.

Reviewer Comment: It is unlikely that this event is due to study drug use. The initial finding of anemia (which can precede actual diagnosis of colon cancer) was made soon after initiation of study drug. The MI that occurred during the colonoscopy is more likely to be due to the procedure in a patient already at risk for an MI rather than to the use of study drug.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg): Acute myocardial infarction

A 56 year old male with a past medical history of T2DM with nephropathy, hypertension, obesity, and coronary artery disease was randomized to empagliflozin 10 mg. On day ten since randomization, he experienced a severe acute myocardial infarction resulting in death.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg): Hepatic cancer metastatic; Pancreatic cancer metastatic

A 63 year old male with a past medical history of T2DM with retinopathy, nephropathy, and neuropathy, coronary artery disease with history of myocardial infarction, hypertension, hypercholesterolemia, and goiter was randomized to empagliflozin 10 mg. On day 37, he was diagnosed with metastatic adenocarcinoma of the liver and pancreas. On day -30, he had complained of right upper quadrant pain. On day 37, the pain progressed and ultrasound showed multiple hepatic masses. He was not felt to be a candidate for treatment, but was felt to be a candidate for palliative chemotherapy. As part of his evaluation, he underwent a liver biopsy which was followed by a nonfatal stroke on day 52. He died on day 100.

Reviewer Comment: This is unlikely to be due to treatment with empagliflozin. Initial symptoms appeared before initiation of study drug, and the short exposure is not consistent with the typical timeframe for development of metastatic cancer.

Patient 1245-0025- (b) (4) (empagliflozin 25 mg): Cardiogenic shock

A 63 year old male with a past medical history of T2DM, coronary artery disease s/p bypass, hypertension, mixed hyperlipidemia, and supraventricular tachycardia was randomized to empagliflozin 25 mg. On day seven since randomization, he had nausea and vomiting. This resolved on day 17. On day 101, he developed cardiogenic shock leading to hospitalization. Details of presenting complaints are not known. He died on day 103.

Patient 1245-0025- (b) (4) (empagliflozin 25 mg after seven days from last dose): Cardiac death

A 73 year old male with a past medical history of T2DM with neuropathy, hypertension, hyperlipidemia, coronary artery disease s/p stent, and ventricular tachycardia was randomized to empagliflozin 25 mg. Last day of study medication was on day 268 since randomization. On day 278, he had hypoglycemia. He was also hospitalized for cellulitis that same day. He received antibiotics and was discharged to a rehabilitation facility. On day 299, he died from “cardiac death” (i.e. myocardial infarction)

Reviewer Comment: This is unlikely to be related to study drug as it was discontinued well before all of these events.

Patient 1245-0025- (b) (4) (empagliflozin 25 mg after seven days from last dose): Sepsis

A 70 year old male was randomized to empagliflozin 25 mg. No narrative is provided for this case. On day 95, he experienced sepsis. Study medication was discontinued on day 29 for unclear reasons. He died on day 113.

Reviewer Comment: Sepsis occurred 66 days after the last dose of study drug, and death occurred 82 days after the last dose of study drug. Based on the length of time from discontinuation of study drug and the events, it is unlikely that this event is related to study drug use.

Patient 1245-0025- (b) (4) (empagliflozin 25 mg within seven days after last dose): Acute myocardial infarction

A 58 year old male with a past medical history of T2DM with nephropathy and retinopathy, hyperlipidemia, hypertension, coronary artery disease, peripheral vascular disease, and chronic peptic ulcer disease was randomized to empagliflozin 25 mg. On day 219 since randomization, he experienced an ST elevation myocardial infarction leading to hospitalization. Last dose of study medication was on day 218. He died on day 235.

Patient 1245-0025- (b) (4) (empagliflozin 25 mg): Rectal cancer

A 53 year old male with a past medical history of T2DM, coronary artery disease s/p angioplasty, hypertension, hyperlipidemia, and obesity was randomized to empagliflozin 25 mg. On day 159 since randomization, he was diagnosed with rectal adenocarcinoma. Study medication was discontinued on day 215. He had an ileostomy and was started on chemotherapy on day 218. Acute renal failure, dehydration and a wound infection were diagnosed on day 243 leading to hospitalization. He recovered from these events on day 264. He was hospitalized for abdominal pain and icterus on day 312. No information regarding liver laboratory tests or

hospital course is provided. He was treated in the emergency department on day 328 for dyspnea. Right eye swelling was noted on day 336. He died on day 337.

Reviewer Comment: The exposure to study drug prior to diagnosis of rectal cancer is short, suggesting that the two are unlikely to be related. Detailed information regarding the events more immediate to his death is not provided.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg after seven days from last dose):

Pulmonary embolism

A 68 year old male with a past medical history of T2DM with neuropathy, coronary artery disease s/p bypass, hypertension, venous stasis with varicose veins, reflux disease, and B12 deficiency was randomized to empagliflozin 10 mg. On day 257 since randomization, he was diagnosed with lymphoma leading to hospitalization and discontinuation of study medication. On day 296 (40 days after discontinuing study medication), he was hospitalized with severe dehydration and increased creatinine. On day 298, he experienced a severe pulmonary embolism leading to death.

Reviewer Comment: These events are unlikely to be related to study drug. While dehydration is theoretically possible from treatment with empagliflozin, this event occurred 40 days after stopping study drug. Given the diagnosis of lymphoma, he could be considered to have a hypercoagulable state predisposing him to thromboembolic disease.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg after seven days from last dose):

Cerebrovascular accident

An 87 year old female was randomized to empagliflozin 10 mg. No narrative is provided. From review of the submitted datasets, she reported an AE of dizziness and vomiting on day 79. Study medication was apparently discontinued on day 83. On day 198 an event of cerebrovascular accident was reported as resulting in death.

Reviewer Comment: The cerebrovascular accident and death occurred 115 days after discontinuation of study drug. Based on the duration of time between discontinuation of study drug and the event, this is unlikely to be due to study drug.

Patient 1245-0025- (b) (4) (empagliflozin 25 mg): Pancreatic neoplasm

A 64 year old male with a past medical history of T2DM, cerebrovascular disease, cerebrovascular accident, hypertension, lipid disorder, diverticulosis, and erectile dysfunction was randomized to empagliflozin 25 mg. On day 41 since randomization, he was diagnosed with a pancreatic tumor. Study medication was stopped on day 54. He was hospitalized on day 55

with jaundice, epigastric pain, anorexia, and weight loss. Liver metastases were diagnosed. Further imaging showed dilation of the biliary tract. Deep vein thrombosis (DVT) was diagnosed during the hospitalization on day 56. A percutaneous biliary drain was placed on day 60. He was discharged on day 64. He died on day 98.

Reviewer Comment: The exposure to study drug prior to diagnosis of pancreatic tumor is quite short, suggesting that the two are unlikely to be related. The DVT is more likely related to a hypercoagulable state as a result of the malignancy.

Patient 1245-0025- (b) (4) (empagliflozin 25 mg after seven days from last dose): Pancreatic cancer

A 69 year old female with a past medical history of T2DM with neuropathy, coronary artery disease, cerebrovascular disease, dyslipidemia, hypertension, hyperthyroidism, and recurrent urinary tract infections was randomized to empagliflozin 25 mg. On day 47 since randomization, she developed pneumonia requiring hospitalization. She was treated with antibiotics and discharged on day 61. She was reported to have recovered from the pneumonia on day 67. On day 164, she developed jaundice. On day 173 she developed chills, back pain, malaise, and abdominal pain. She was eventually diagnosed with pancreatic carcinoma with severe bile duct obstruction. Study medication was discontinued on day 192. On day 244, she had cardiorespiratory arrest and died.

Reviewer Comment: The exposure to study drug prior to diagnosis of pancreatic cancer is short, suggesting that the two are unlikely to be related. The fatal event of cardiorespiratory arrest took place at home, and is likely a complication of her poor state of health due to her pancreatic cancer.

Patient 1245-0025- (b) (4) (empagliflozin 10 mg within seven days of last dose): Pneumonia, Septic shock

A 68 year old female with a past medical history of T2DM, hypercholesterolemia, coronary artery disease s/p stent placement, chronic obstructive pulmonary disease, reflux disease, hypertension, asthma, arthritis, and anxiety was randomized to empagliflozin 10 mg. On day 30 since randomization, she presented with hypotension and hypoxia leading to hospitalization with a severe community-acquired pneumonia, septic shock, acute respiratory failure, and acute renal failure. She was treated with antibiotics, and mechanical ventilation. Her condition worsened, and she died on day 31.

Reviewer Comment: This is unlikely to be related to study drug use. Chronic obstructive pulmonary disease (COPD) is a risk for pneumonia, and respiratory failure. Sepsis can cause acute renal failure.

Patient 1245-0025- (b) (4) (empagliflozin 25 mg): Sudden death

A 61 year old female with a past medical history of T2DM, coronary artery disease, hypertension, hypercholesterolemia, and myocardial infarction was randomized to empagliflozin 25 mg. On day 21 since randomization, she had a myocardial infarction. This event was assessed as resolved on day 26. On day 43, she died suddenly. No further information is available.

Patient 1245-0025- (b) (4) (empagliflozin 25 mg): Acute myocardial infarction

A 64 year old female with past medical history of T2DM, dyslipidemia, chronic pyelonephritis, cerebrovascular disease, and hypertension was randomized to empagliflozin 25 mg. On day 154 since randomization, she suffered an acute myocardial infarction and died that same day.

Patient 1245-0025- (b) (4) (empagliflozin 25 mg): Death

A 52 year old female with a past medical history of T2DM, cerebrovascular disease, hypertension, coronary artery disease s/p myocardial infarction, stent, bypass, peripheral vascular disease, and pulmonary tuberculosis. On day 57 since randomization, she was hospitalized for a leg ulcer. She initially developed pain and gangrene ultimately leading to hospitalization on day 69. The toe was amputated. Evaluation for possible revascularization did not find her to be a good candidate for intravascular intervention. Above the knee amputation was performed on day 87. She was discharged on day 92, but was readmitted with sepsis. On day 123, her condition deteriorated and she died.

Patient 1245-0025- (b) (4) (empagliflozin 25 mg): Cerebrovascular accident

A 63 year old male was randomized to empagliflozin 25 mg. He had a past medical history of T2DM, hypertension, dyslipidemia, smoking, coronary artery disease s/p myocardial infarction and bypass surgery. He experienced a cerebrovascular accident on day 44 since randomization. Study drug was stopped that same day. On day 50, he died. No further detailed information is known.

Reviewer Comment: This appears to be an early cardiovascular event.

(b) (4)

Table 71 Incidence of Fatal Cardiovascular Events – Safety Grouping 5

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	3630			4602			8400			3522			4676		
Total exposure (patient-years)	3258.2			4448.1			7827.8			2758.1			4184.4		
System Organ Class – Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Cardiac disorders	(b) (4)														
– Acute myocardial infarction															
– Cardiorespiratory arrest															
– Cardiac arrest															
– Cardiac failure															
– Cardiogenic shock															
– Left ventricular failure															
– Myocardial infarction															
– Ventricular fibrillation															
– Acute left ventricular failure															
– Cardiac failure congestive															
– Cardiac tamponade															
– Cardiovascular disorder															
– Myocardial ischemia															
General disorders and administration site conditions															
– Sudden death															
– Death															
– Cardiac death															
– Multi-organ failure															
– Sudden cardiac death															
Nervous system disorders															
– Cerebrovascular accident															
– Hemorrhagic stroke															
– Ischemic stroke															
Vascular disorders															
– Hypertension															

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; Per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files, and individual study reports

Table 72 Incidence of Fatal Cardiovascular Events – Safety Grouping 5, Excluding Study 1245.25

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1799			2759			4962			1741			2893		
Total exposure (patient-years)	1114.3			2302.0			3536.5			1067.3			2434		
System Organ Class – Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Cardiac disorders	1	0.06	0.09	3	0.11	0.13	4	0.08	0.11	6	0.34	0.56	8	0.28	0.33
– Cardiorespiratory arrest	0	0.00	0.00	2	0.07	0.09	2	0.04	0.06	1	0.06	0.09	1	0.03	0.04
– Acute myocardial infarction	1	0.06	0.09	0	0.00	0.00	1	0.02	0.03	0	0.00	0.00	1	0.03	0.04
– Cardiac arrest	0	0.00	0.00	1	0.04	0.04	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
– Acute left ventricular failure	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.09	1	0.03	0.04
– Cardiac tamponade	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04
– Cardiogenic shock	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.09	1	0.03	0.04
– Cardiovascular disorder	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.09	1	0.03	0.04
– Myocardial infarction	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.09	1	0.03	0.04
– Myocardial ischemia	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.09	1	0.03	0.04
General disorders and administration site conditions	1	0.06	0.09	2	0.07	0.09	3	0.06	0.08	1	0.06	0.09	2	0.07	0.08
– Sudden death	1	0.06	0.09	1	0.04	0.04	2	0.04	0.06	0	0.00	0.00	0	0.00	0.00
– Multi-organ failure	0	0.00	0.00	1	0.04	0.04	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
– Death	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04
– Sudden cardiac death	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.09	1	0.03	0.04
Vascular disorders	1	0.06	0.09	0	0.00	0.00	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
– Hypertension	1	0.06	0.09	0	0.00	0.00	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
Nervous system disorders	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.09	1	0.03	0.04
– Hemorrhagic stroke	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.09	1	0.03	0.04

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; Per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files, and individual study reports

Table 73 Incidence of Fatal Cardiovascular Events – Safety Grouping 5, Completed Studies Only

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1798			2000			4421			1740			2112		
Total exposure (patient-years)	909.1			1080.1			2108.0			884.0			1019.0		
System Organ Class – Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Cardiac disorders	1	0.06	0.11	3	0.15	0.28	4	0.09	0.19	6	0.34	0.68	6	0.28	0.59
– Cardiorespiratory arrest	0	0.00	0.00	2	0.10	0.19	2	0.05	0.09	1	0.06	0.11	1	0.05	0.10
– Acute myocardial infarction	1	0.06	0.11	0	0.00	0.00	1	0.02	0.05	0	0.00	0.00	0	0.00	0.00
– Cardiac arrest	0	0.00	0.00	1	0.05	0.09	1	0.02	0.05	0	0.00	0.00	0	0.00	0.00
– Acute left ventricular failure	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.11	1	0.05	0.10
– Cardiogenic shock	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.11	1	0.05	0.10
– Cardiovascular disorder	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.11	1	0.05	0.10
– Myocardial infarction	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.11	1	0.05	0.10
– Myocardial ischemia	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.11	1	0.05	0.10
Vascular disorders	1	0.06	0.11	0	0.00	0.00	1	0.02	0.05	0	0.00	0.00	0	0.00	0.00
– Hypertension	1	0.06	0.11	0	0.00	0.00	1	0.02	0.05	0	0.00	0.00	0	0.00	0.00
Nervous system disorders	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.11	1	0.05	0.10
– Hemorrhagic stroke	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.11	1	0.05	0.10

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; Per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files, and individual study reports

7.3.5.1.2 Nonfatal Serious Adverse Events:

The SOC with the greatest incidence of nonfatal SAEs in the empagliflozin-treated patients was “Cardiac disorders”, though this SOC was not reported at a higher frequency than the placebo or comparator-treated patients. (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Table 74 Incidence of Nonfatal Cardiovascular Serious Adverse Events – Safety Grouping 5

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	3630			4602			8400			3522			4676		
Total exposure (patient-years)	3258.2			4448.1			7827.8			2758.1			4184.4		
System Organ Class	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
– Preferred Term															
Cardiac disorders	(b) (4)														
– Angina unstable															
– Acute myocardial infarction															
– Angina pectoris															
– Myocardial infarction															
– Coronary artery disease															
– Cardiac failure															
– Atrial fibrillation															
– Cardiac failure congestive															
– Acute coronary syndrome															
– Atrial flutter															
– Coronary artery occlusion															
– Myocardial ischemia															
– Arteriosclerosis coronary artery															
– Coronary artery stenosis															
– Atrioventricular block															
– Palpitations															
– Sinus bradycardia															
Nervous system disorders	(b) (4)														
– Cerebrovascular accident															
– Transient ischemic attack	4	0.11	0.13	14	0.30	0.31	18	0.21	0.23	9	0.26	0.32	10	0.21	0.24
– Syncope	6	0.17	0.19	8	0.17	0.18	14	0.17	0.18	3	0.09	0.11	3	0.06	0.07
– Ischemic stroke	(b) (4)														
– Dizziness	4	0.11	0.13	3	0.07	0.07	7	0.08	0.09	1	0.03	0.04	1	0.02	0.02
– Carotid artery stenosis	3	0.08	0.10	3	0.07	0.07	6	0.07	0.08	3	0.09	0.11	3	0.06	0.07
– Cerebral infarction	(b) (4)														
– Convulsion	1	0.03	0.03	3	0.07	0.07	4	0.05	0.05	2	0.06	0.07	3	0.06	0.07

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	3630			4602			8400			3522			4676		
Total exposure (patient-years)	3258.2			4448.1			7827.8			2758.1			4184.4		
System Organ Class – Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Vascular disorders	21	0.58	0.67	36	0.78	0.81	57	0.68	0.72	38	1.08	1.37	40	0.86	0.95
– Peripheral arterial occlusive disease	7	0.19	0.22	7	0.15	0.16	14	0.17	0.18	3	0.09	0.11	4	0.09	0.09
– Femoral arterial stenosis	0	0.00	0.00	5	0.11	0.11	5	0.06	0.06	0	0.00	0.00	0	0.00	0.00
– Arteriosclerosis	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	2	0.06	0.07	2	0.04	0.05
– Hypertensive crisis	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	0	0.00	0.00	0	0.00	0.00
– Peripheral ischemia	1	0.03	0.03	2	0.04	0.04	3	0.04	0.04	3	0.09	0.11	3	0.06	0.07
General disorders and administration site conditions	16	0.44	0.51	33	0.72	0.74	50	0.60	0.64	24	0.68	0.87	30	0.64	0.71
– Chest pain	5	0.14	0.16	15	0.33	0.34	21	0.25	0.27	13	0.37	0.47	15	0.32	0.36
– Chest discomfort	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	1	0.03	0.04	1	0.02	0.02

Empa 10 = empagliflozin 10 mg; Empa 25 = Empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; Per 100 = events per 100 patient-years

Source: Table 5.7.5.1 (Integrated Summary of Safety)

Table 75 Incidence of Nonfatal Cardiovascular Serious Adverse Events – Safety Grouping 5, Excluding Study 1245.25

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1799			2759			4962			1741			2893		
Total exposure (patient-years)	1114.3			2302.0			3536.5			1067.3			2434.0		
System Organ Class – Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Cardiac disorders	22	1.22	1.97	28	1.01	1.22	54	1.09	1.53	41	2.35	3.84	57	1.97	2.34
– Atrial fibrillation	2	0.11	0.18	5	0.18	0.22	7	0.14	0.20	3	0.17	0.28	3	0.10	0.12
– Coronary artery disease	4	0.22	0.36	3	0.11	0.13	7	0.14	0.20	4	0.23	0.37	8	0.28	0.33
– Angina unstable	2	0.11	0.18	4	0.14	0.17	6	0.12	0.17	3	0.17	0.28	4	0.14	0.16
– Myocardial infarction	2	0.11	0.18	2	0.07	0.09	6	0.12	0.17	4	0.23	0.37	4	0.14	0.16
– Acute myocardial infarction	1	0.06	0.09	2	0.07	0.09	4	0.08	0.11	5	0.29	0.47	9	0.31	0.37
– Cardiac failure	2	0.11	0.18	1	0.04	0.04	3	0.06	0.08	3	0.17	0.28	3	0.10	0.12
Nervous system disorders	15	0.83	1.35	35	1.27	1.52	51	1.03	1.44	21	1.21	1.97	37	1.28	1.52
– Cerebrovascular accident	4	0.22	0.36	9	0.33	0.39	13	0.26	0.37	1	0.06	0.09	2	0.07	0.08
– Syncope	3	0.17	0.27	2	0.07	0.09	5	0.10	0.14	0	0.00	0.00	0	0.00	0.00

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1799			2759			4962			1741			2893		
Total exposure (patient-years)	1114.3			2302.0			3536.5			1067.3			2434.0		
System Organ Class – Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
– Transient ischemic attack	0	0.00	0.00	4	0.14	0.17	5	0.10	0.14	3	0.17	0.28	4	0.14	0.16
– Dizziness	2	0.11	0.18	2	0.07	0.09	4	0.08	0.11	1	0.06	0.09	1	0.03	0.04
– Carotid artery stenosis	1	0.06	0.09	2	0.07	0.09	3	0.06	0.08	1	0.06	0.09	1	0.03	0.04
– Cerebral infarction	0	0.00	0.00	3	0.11	0.13	3	0.06	0.08	0	0.00	0.00	2	0.07	0.08
– Ischemic stroke	1	0.06	0.09	2	0.07	0.09	3	0.06	0.08	1	0.06	0.09	2	0.07	0.08
General disorders and administration site conditions	3	0.17	0.27	18	0.65	0.78	22	0.44	0.62	7	0.40	0.66	13	0.45	0.53
– Chest pain	1	0.06	0.09	4	0.14	0.17	6	0.12	0.17	4	0.23	0.37	6	0.21	0.25
– Chest discomfort	2	0.11	0.18	1	0.04	0.04	3	0.06	0.08	0	0.00	0.00	0	0.00	0.00
Vascular disorders	4	0.22	0.36	8	0.29	0.35	12	0.24	0.34	11	0.63	1.03	13	0.45	0.53
– Peripheral arterial occlusive disease	2	0.11	0.18	1	0.04	0.04	3	0.06	0.08	0	0.00	0.00	1	0.03	0.04

Empa 10 = empagliflozin 10 mg; Empa 25 = Empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; Per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files, and individual study reports

Table 76 Incidence of Nonfatal Cardiovascular Nonfatal Adverse Events = Safety Grouping 5, Completed Studies Only

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1798			2000			4421			1740			2112		
Total exposure (patient-years)	909.1			1080.1			2108.0			884.0			1019.0		
System Organ Class – Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Cardiac disorders	16	0.89	1.76	19	0.95	1.76	39	0.88	1.85	27	1.55	3.05	28	1.33	2.75
– Atrial fibrillation	2	0.00	0.22	4	0.00	0.37	6	0.00	0.28	2	0.00	0.23	2	0.00	0.20
– Myocardial infarction	2	0.00	0.22	2	0.00	0.19	6	0.00	0.28	3	0.00	0.34	3	0.00	0.29
– Acute myocardial infarction	0	0.00	0.00	2	0.00	0.19	3	0.00	0.14	2	0.00	0.23	2	0.00	0.20
– Angina unstable	2	0.00	0.22	1	0.00	0.09	3	0.00	0.14	3	0.00	0.34	3	0.00	0.29
– Coronary artery disease	2	0.00	0.22	1	0.00	0.09	3	0.00	0.14	2	0.00	0.23	2	0.00	0.20
Nervous system disorders	13	1.00	1.43	20	1.00	1.85	33	1.00	1.57	14	1.00	1.58	14	1.00	1.37
– Cerebrovascular accident	3	0.00	0.33	5	0.00	0.46	8	0.00	0.38	1	0.00	0.11	1	0.00	0.10
– Transient ischemic attack	0	0.00	0.00	4	0.00	0.37	4	0.00	0.19	2	0.00	0.23	2	0.00	0.20

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1798			2000			4421			1740			2112		
Total exposure (patient-years)	909.1			1080.1			2108.0			884.0			1019.0		
System Organ Class	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
– Preferred Term															
– Cerebral infarction	0	0.00	0.00	3	0.00	0.28	3	0.00	0.14	0	0.00	0.00	0	0.00	0.00
– Syncope	2	0.00	0.22	1	0.00	0.09	3	0.00	0.14	0	0.00	0.00	0	0.00	0.00
General disorders and administration site conditions	3	0.00	0.33	9	0.00	0.83	13	0.00	0.62	6	0.00	0.68	6	0.00	0.59
– Chest pain	1	0.00	0.11	2	0.00	0.19	4	0.00	0.19	4	0.00	0.45	4	0.00	0.39
Vascular disorders	2	0.00	0.22	8	0.00	0.74	10	0.00	0.47	10	1.00	1.13	10	0.00	0.98

Empa 10 = empagliflozin 10 mg; Empa 25 = Empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; Per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files, and individual study reports

Table 77 Incidence of Events in the “Ischemic Cerebrovascular Conditions” Standardized Medical Dictionary for Regulatory Activities Query – Safety Grouping 5

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	3630			4602			8400			3522			4676		
Total exposure (patient-years)	3112.30			4226.01			7458.30			2556.83			3935.99		
Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Cerebrovascular accident	(b) (4)														
Transient ischemic attack	4	0.11	0.13	14	0.30	0.31	18	0.21	0.23	9	0.26	0.32	10	0.21	0.24
Ischemic stroke	(b) (4)														
Carotid artery stenosis	3	0.08	0.10	3	0.07	0.07	6	0.07	0.08	3	0.09	0.11	3	0.06	0.07
Cerebral infarction	(b) (4)														
Cerebrovascular disorder	(b) (4)														
Carotid artery occlusion	(b) (4)														
Carotid artery thrombosis	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
Cerebellar infarction	(b) (4)														
Cerebral ischemia	(b) (4)														
Brain stem infarction	(b) (4)														

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	3630			4602			8400			3522			4676		
Total exposure (patient-years)	3112.30			4226.01			7458.30			2556.83			3935.99		
Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Carotid artery disease	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
Carotid endarterectomy	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
Embolic cerebral infarction	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
Vertebrobasilar insufficiency	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.02	0.02
Total	27	0.74	0.83	49	1.06	1.10	76	0.90	0.97	33	0.94	1.20	40	0.86	0.86

Empa 10 = empagliflozin 10 mg; Empa 25 = Empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; Per 100 = events per 100 patient-years

Source: Table 5.7.5.1 (Integrated Summary of Safety)

Table 78 Incidence of Events in the “Ischemic Cerebrovascular Conditions” Standardized Medical Dictionary for Regulatory Activities Query – Safety Grouping 5, Excluding Study 1245.25

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1799			2759			4962			1741			2893		
Total exposure (patient-years)	1114.3			2302			3536.5			1067.3			2434		
Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
Cerebrovascular accident	4	0.22	0.36	9	0.33	0.39	13	0.26	0.37	1	0.06	0.09	2	0.07	0.08
Transient ischemic attack	0	0.00	0.00	4	0.14	0.17	5	0.10	0.14	3	0.17	0.28	4	0.14	0.16
Carotid artery stenosis	1	0.06	0.09	2	0.07	0.09	3	0.06	0.08	1	0.06	0.09	1	0.03	0.04
Cerebral infarction	0	0.00	0.00	3	0.11	0.13	3	0.06	0.08	0	0.00	0.00	2	0.07	0.08
Ischemic stroke	1	0.06	0.09	2	0.07	0.09	3	0.06	0.08	1	0.06	0.09	2	0.07	0.08
Lacunar infarction	1	0.06	0.09	1	0.04	0.04	2	0.04	0.06	0	0.00	0.00	0	0.00	0.00
Brain stem infarction	0	0.00	0.00	1	0.04	0.04	1	0.02	0.03	0	0.00	0.00	1	0.03	0.04
Carotid artery occlusion	0	0.00	0.00	1	0.04	0.04	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
Carotid artery thrombosis	0	0.00	0.00	1	0.04	0.04	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00
Cerebrovascular disorder	0	0.00	0.00	1	0.04	0.04	1	0.02	0.03	0	0.00	0.00	0	0.00	0.00

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1799			2759			4962			1741			2893		
Total exposure (patient-years)	1114.3			2302			3536..5			1067.3			2434		
Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
Carotid artery disease	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.09	1	0.03	0.04
Carotid endarterectomy	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.09	1	0.03	0.04
Cerebral ischemia	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.09	1	0.03	0.04
Vertebrobasilar insufficiency	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04
Total	7	0.39	0.63	25	0.91	1.09	33	0.67	0.93	9	0.52	0.84	16	0.55	0.66

Empa 10 = empagliflozin 10 mg; Empa 25 = Empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; Per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files, and individual study reports

Table 79 Incidence of Events in the “Ischemic Cerebrovascular Conditions” Standardized Medical Dictionary for Regulatory Activities Query – Safety Grouping 5, Completed Studies Only

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	1798			2000			4421			1740			2112		
Total exposure (patient-years)	909.1			1080.1			2108			884			1019		
Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Cerebrovascular accident	3	0.17	0.33	5	0.25	0.46	8	0.18	0.38	1	0.06	0.11	1	0.05	0.04
Transient ischemic attack	0	0.00	0.00	4	0.20	0.37	4	0.09	0.19	2	0.11	0.23	2	0.09	0.09
Brain stem infarction	0	0.00	0.00	1	0.05	0.09	1	0.02	0.05	0	0.00	0.00	0	0.00	0.00
Cerebral infarction	0	0.00	0.00	3	0.15	0.28	3	0.07	0.14	0	0.00	0.00	0	0.00	0.00
Carotid artery stenosis	1	0.06	0.11	1	0.05	0.09	2	0.05	0.09	1	0.06	0.11	1	0.05	0.04
Lacunar infarction	1	0.06	0.11	1	0.05	0.09	2	0.05	0.09	0	0.00	0.00	0	0.00	0.00
Carotid artery occlusion	0	0.00	0.00	1	0.05	0.09	1	0.02	0.05	0	0.00	0.00	0	0.00	0.00
Carotid artery thrombosis	0	0.00	0.00	1	0.05	0.09	1	0.02	0.05	0	0.00	0.00	0	0.00	0.00
Ischemic stroke	1	0.06	0.11	0	0.00	0.00	1	0.02	0.05	1	0.06	0.11	1	0.05	0.04
Embolic cerebral infarction	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.11	1	0.05	0.04
Carotid endarterectomy	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.06	0.11	1	0.05	0.04
Total	6	0.33	0.66	17	0.85	1.57	23	0.52	1.09	7	0.40	0.79	7	0.33	0.69

Empa 10 = empagliflozin 10 mg; Empa 25 = Empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; Per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files, and individual study reports

Summaries of Selected Cardiovascular Nonfatal Serious Adverse Event Narratives:

Patient 1245-0009-009464 (empagliflozin 5 mg): Myocardial infarction

A 77 year old female with a past medical history of coronary artery disease (diagnosed thirteen days before starting study drug) and hypertension experienced a myocardial infarction on day five following hard physical labor the previous day. Diagnosis was made based on ECG changes, and she was hospitalized for the event. Further information is not available.

Reviewer Comment: This is an early CV event.

(b) (4)

Patient 1245-0009-009883 (empagliflozin 5 mg): Myocardial infarction

A 68 year old male with past medical history of hypertension experienced an event of acute myocardial infarction on day 43 of study drug treatment. He presented to the emergency room with shortness of breath and diaphoresis. He was hospitalized and angioplasty was performed. He was discharged on day 48, but was readmitted on day 50 with similar symptoms. Work-up at that time did not identify another myocardial infarction. Last dose of study medication was day 42.

Reviewer Comment: This is an early CV event.

(b) (4)

Patient 1245-0010-005811 (empagliflozin 25 mg): Coronary artery disease

A 70 year old male with past medical history of hypertension and coronary artery disease (for approximately twelve years) experienced worsening of coronary artery disease on day nine. Exertional pain was reported leading to the diagnosis. On day 52 he was hospitalized for cardiac catheterization with stent placement.

Reviewer Comment: This is an early CV event.

(b) (4)

Patient 1245-0010-006063 (empagliflozin 5 mg): MI

A 68 year old male with past medical history of dyslipidemia and hypertension experienced the event of myocardial infarction on day 81 of study treatment.

Reviewer Comment: This is an early CV event.

(b) (4)

Patient 1245-0015-010538 (empagliflozin 1 mg): TIA

A 66 year old female experienced an event of possible TIA 61 days after starting study treatment. Study treatment had been completed on day 28 (as planned per protocol). Decreased hematocrit had been noted at end-of-study visit. At follow-up on day 61, this had returned to baseline. On the way home, she experienced loss of consciousness with fall. No hypoglycemia was reported. Neurology work-up included cerebrovascular angiography showing arteriosclerotic change but no stenosis. She was started on daily aspirin therapy.

Reviewer Comment: Though this is an early cerebrovascular event, given the occurrence of the event > 30 days after last dose of study drug this event is unlikely to be related to study treatment.

Patient 1245-0019-010820 (empagliflozin 25 mg): Myocardial ischemia

A 48 year old female with past medical history of gastritis and intermittent atypical chest pain experienced an event of myocardial ischemia on day three of study treatment. She reported chest pains similar to what she previously experienced. Stress test was concerning for myocardial ischemia. Additional testing did not identify any cardiac disease (normal angiography, normal echocardiogram). Angiography was complicated by hematoma and infection.

Reviewer Comment: This does not appear to be a case of myocardial ischemia/CV disease as angiography did not show coronary artery disease.

Patient 1245-0019-010941 (empagliflozin 25 mg): Cerebral infarct

A 58 year old female with past medical history of hypertension experienced a cerebral infarct on day 27 of study treatment. She developed slurred speech, and facial droop. She was brought to the hospital. MRI showed acute infarct of the left pons with focal stenosis of the basilar artery.

Reviewer Comment: This is an early stroke event.

(b) (4)

Patient 1245-0020-020064 (empagliflozin 10 mg): Stroke

A 61 year old male with a past medical history of stroke, hypertension, and dyslipidemia experienced an event of stroke on day 165 of study treatment. He presented with aphasia, hemianopsia, and nystagmus. Magnetic resonance imaging (MRI) showed a recent infarct.

Reviewer Comment: This stroke event occurred in a patient with two prior strokes. The role of study treatment on the event is unclear. (b) (4)

Patient 1245-0023-032200 (empagliflozin 10 mg): Lacunar infarction

A 52 year old female with past medical history of hypertension and dyslipidemia experienced a lacunar infarct on day 50 of study treatment. She reported dizziness, blurred vision, nausea, and vomiting. Detailed information is not available.

Reviewer Comment: This is an early stroke event. (b) (4)

Patient 1245-0024-004135 (empagliflozin 100 mg): Ischemic stroke

A 68 year old male with past medical history of hypertension and metabolic syndrome experienced an ischemic stroke on day 177. He experienced aphasia and right-sided paralysis. No action was taken with regard to the study medication. He had initially been on blinded therapy with empagliflozin 100 mg, but at the time of the events was on open-label therapy (unknown dose).

Reviewer Comment: This is a stroke event. (b) (4)

Patient 1245-0024-005730 (empagliflozin 25 mg): TIA

A 61 year old male experienced an event of TIA on day 88. He had reported loss of consciousness leading to hospitalization. An MRI was performed and reported as normal.

Reviewer Comment: This is concerning for an early cerebrovascular event. (b) (4)

Patient 1245-0023-032310 (empagliflozin 25): Gastroenteritis

A 60 year old male with past medical history of hypertension experienced an event of gastroenteritis requiring hospitalization on day 252 of study treatment.

Reviewer Comment: Included in this narrative is discussion of an episode of dizziness requiring hospitalization on day 368. This led to diagnosis of cerebral infarction. This event does not appear to have been reported.

Patient 1245-0024-005811 (empagliflozin 25 mg): Coronary artery disease

A 70 year old male with past medical history of dyslipidemia, hypertension, and CAD experienced worsening of CAD on day eleven of study drug treatment. He reported experiencing chest pain, and an exercise stress test was performed showing ischemia. Angiography was performed on day 113 showing stenosis. Repeat angiography was performed on day 527 with placement of stent.

Reviewer Comment: This is an early CV event.

(b) (4)

Patient 1245-0024-008271 (empagliflozin 10 mg): Visual acuity reduced, dizziness, nausea

A 59 year old female with a past medical history of hypothyroidism and Sjogren's syndrome experienced the event of dizziness on day 17, and the events of reduced visual acuity, nausea and tachycardia on day 23. Work-up for transient visual loss included CT, MRI, and cerebrovascular ultrasound. No findings were reported.

Reviewer comment: The reported symptoms may be consistent with a TIA which would be concerning for an early cerebrovascular event.

(b) (4)

Patient 1245-0024-008329 (empagliflozin 25 mg): MI

A 51 year old male with past medical history of dyslipidemia experienced an event of myocardial infarction on day 47 of study treatment. He was hospitalized for the event and had cardiac catheterization with stent placement.

Reviewer Comment: This is an early CV event.

(b) (4)

Patient 1245-0033-004661 (empagliflozin 10 mg): Cerebrovascular accident (CVA)

A 73 year old male with past medical history of osteoarthritis experienced a stroke on day 174 of study treatment. He had acute onset confusion and inability to concentrate. A CT scan showed changes in the occipital horn indicative of acute ischemia.

Reviewer Comment: This is a stroke event.

(b) (4)

Patient 1245-0033-005066 (empagliflozin 25 mg): Cerebral infarct

A 70 year old female with past medical history of hypertension, dyslipidemia, metabolic syndrome, and CAD experienced cerebral artery infarct on day 192. She developed decreased mental status and was diagnosed with cerebral artery infarct. This was confirmed on MRI. Following this, unintentional weight loss was noted. A recurrent cerebral artery infarct occurred on day 210 as well as severe hypoglycemia.

Reviewer Comment: This is a stroke event.

(b) (4)

Patient 1245-0038-801013 (empagliflozin 25 mg): Cerebral infarction

A 69 year old male with past medical history (PMH) of hypertension, dyslipidemia experienced a stroke on day 71 of study treatment. He had difficulty walking and riding his bike. Symptoms persisted and CT scan showed lacunar infarction. Study drug was discontinued.

Reviewer Comment: This is an early stroke event.

(b) (4)

7.3.5.1.3 Dropout/Discontinuations:

The second most common SOC leading to discontinuation was “Cardiac disorders”. The incidence of discontinuation in this SOC was lower in the empagliflozin-treated patients than comparator-treated patients. While there was a similar incidence of events between the empagliflozin-treated patients and the comparator-treated patients in the “Nervous system disorders” SOC leading to discontinuation, there was a greater frequency of empagliflozin-treated patients with the PTs “Dizziness” and “Cerebrovascular accident” (particularly for the Empa 25 group) than in placebo or comparator-treated patients.

Table 80 Incidence of Discontinuation Due to Adverse Events in the “Cardiac Disorders” and “Nervous System Disorders” System Organ Class – Safety Grouping 5

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
Treated	3630	100	4602	100	8400	100	3522	100	4676	100
System Organ Class – Preferred Term	N	%	N	%	N	%	N	%	N	%
Cardiac disorders	23	0.6	25	0.5	51	0.6	37	1.1	43	0.9
– Acute myocardial infarction	5	0.1	6	0.1	12	0.1	8	0.2	9	0.2
– Myocardial infarction	4	0.1	2	0.0	7	0.1	11	0.3	11	0.2
Nervous system disorders	14	0.4	32	0.7	46	0.6	17	0.5	24	0.5

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
Treated	3630	100	4602	100	8400	100	3522	100	4676	100
System Organ Class	N	%	N	%	N	%	N	%	N	%
– Preferred Term										
– Dizziness	4	0.1	7	0.2	11	0.1	2	0.1	4	0.1
– Cerebrovascular accident	3	0.1	7	0.2	11	0.1	1	0.0	1	0.0

Empa 10 = empagliflozin 10 mg; Empa 25 = Empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; CMQ = customized MedDRA query

Source: Table 2.1.1.2: 1 (Summary of Clinical Safety)

7.3.5.1.4 Analysis of Cardiovascular Safety

As recommended in the 2008 “Guidance for Industry: Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes”, the Applicant has performed a meta-analysis of their phase 2 and phase 3 studies to show that the upper bound of the two-sided 95% confidence interval for the estimated risk is < 1.8. This meta-analysis included data from completed randomized, double-blind studies with a treatment duration above twelve weeks, and interim data from the ongoing randomized, double-blind studies with preplanned interim analyses (Table 81). This resulted in a total of 10,036 treated patients for analysis.

Table 81 Studies Included in the Cardiovascular Meta-Analysis

Completed Studies	Description
1245.19	Efficacy and safety as add-on to pioglitazone +/- metformin compared to placebo
1245.20	Efficacy and safety as monotherapy compared to placebo and compared to sitagliptin
1245.23	Efficacy and safety as add-on to metformin and as add-on to metformin+sulfonylurea compared to placebo
1245.36	Efficacy and safety as add-on to any background therapy compared to placebo in patients with renal impairment
1245.33	Efficacy and safety as add-on to basal insulin with or without concomitant metformin +/- sulfonylurea compared to placebo
Studies with interim data	
1245.25 - cut-off date: June 22, 2012	CV safety compared to placebo in patients with T2DM and increased CV risk
1245.28 - cut-off date: July 31, 2012	Efficacy and safety as add-on to metformin compared to glimepiride
1245.31 - cut-off date: May 29, 2012	Extension of Studies 1245.19, 1245.20, and 1245.23

CV = cardiovascular; T2DM = type 2 diabetes mellitus

Source: Tables 6.2.1: 1 and 6.2.1: 2 (Interim cardiovascular safety meta-analysis)

The primary endpoint of this meta-analysis was time to first occurrence of any component of 4-point MACE¹. The components of 4-point MACE are:

1. CV death (including fatal stroke and fatal myocardial infarction (MI))
2. Nonfatal MI
3. Nonfatal stroke (ischemic or hemorrhagic)
4. Hospitalization for unstable angina

Secondary endpoints included 3-point MACE² (CV death, nonfatal MI, nonfatal stroke), 5-point MACE (CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, and hospitalization for congestive heart failure), and 7-point MACE (CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina, hospitalization for congestive heart failure, transient ischemic attack, and coronary revascularization procedures). Again, time to first occurrence was calculated.

Tertiary endpoints were time to first occurrence of the individual components of 7-point MACE and of all-cause mortality. Additional endpoints were time to first MI (fatal and nonfatal) and first stroke (fatal and nonfatal).

All events were adjudicated by an independent Clinical Events Committee (CEC) composed of five cardiologists and five neurologists. The committee reviewed all reported fatal events, and any events suspected to be a stroke, transient ischemic attack, myocardial ischemia, hospitalization for unstable angina or heart failure, or stent thrombosis and revascularization procedure. Two members reviewed and voted on each case with a third member reviewing and voting on cases if there was disagreement.

The main analysis included all CV events that occurred during the planned observational period and included events with an onset after study drug discontinuation. Events prior to the first intake of study drug were not included. Hazard ratios were based on Cox regression model for time to first event with treatment and study as stratification factors. Additional analyses were performed as sensitivity analyses (e.g. risk ratio based on Poisson regression model, odds-ratio based on exact test for a 2x2 contingency table, risk ratio based on Cochran-Mantel-Haenszel test, and time to event using Kaplan-Meier estimates).

¹Equivalent to MACE+ as described in the Guidance to Industry

²Equivalent to MACE as described in the Guidance to Industry

Of the 10,036 treated patients, 6,206 received empagliflozin. Two sets of patients were defined for analysis. The treated set (TS) was defined as the primary analysis set and includes all randomized patients who received at least one dose of study drug. The on-treatment set (OS) included all patients who received study drug for at least 30 days (not necessarily consecutively). Analysis included events that occurred up to four weeks after the last dose of study drug.

Baseline use of aspirin, lipid-lowering agents, and antihypertensive drugs was more common in the empagliflozin-treated patients than in the comparator-treated patients (particularly the active comparator-treated patients) (Table 82). Similarly, the active comparator group had a lower frequency of relevant medical diagnoses at screening (Table 83). This is likely due to the lack of an active comparator arm in Study 1245.25 which had patients with high risk for MACE and presumably more likely to be on aspirin, lipid-lowering drugs, and antihypertensive drugs, as well as a higher likelihood of having a relevant medical diagnosis. Though it is not explicitly stated in the protocol for Study 1245.25 or in the CV meta-analysis, randomization would presumably result in balance for these baseline factors between the arms in the ongoing CVOT.

Table 82 Baseline Use of Aspirin, Lipid-Lowering Drugs, and Antihypertensive Drugs - Treated Set

	Empa 10		Empa 25		All Empa		Placebo		Active Comp		All Comp	
	N	%	N	%	N	%	N	%	N	%	N	%
Number of patients	2619	100	3587	100	6206	100	2827	100	1003	100	3830	100
Aspirin	1641	62.7	1974	55.0	3615	58.3	1729	61.2	270	26.9	1999	52.2
Lipid-lowering drugs	1744	66.6	2257	62.9	4001	64.5	1814	64.2	448	44.7	2262	59.1
Antihypertensive drugs	2087	79.7	2739	76.4	4826	77.8	2252	79.7	559	55.7	2811	73.4

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator

Source: Table 7.3.4: 1 (Interim Cardiovascular safety Meta-Analysis)

Table 83 Frequency of Relevant Medical Diagnoses at Baseline – Treated Set

	Empa 10		Empa 25		All Empa		Placebo		Active Comp		All Comp	
	N	%	N	%	N	%	N	%	N	%	N	%
Number of patients	2657	100	3614	100	6271	100	2865	100	1003	100	3868	100
Hypertension	2058	78.6	2723	75.9	4781	77.0	2240	79.2	594	59.2	2834	74.0
Coronary artery disease	1331	50.8	1434	40.0	2765	44.6	1391	49.2	80	8.0	1471	38.4
Diabetic neuropathy	624	23.8	765	21.3	1389	22.4	698	24.7	69	6.9	767	20.0
Diabetic retinopathy	403	15.4	491	13.7	894	14.4	458	16.2	38	3.8	496	13.0
Cerebrovascular disease	385	14.7	457	12.7	842	13.6	425	15.0	30	3.0	455	11.9
Peripheral artery occlusive disease	298	11.4	348	9.7	646	10.4	317	11.2	17	1.7	334	8.7
Diabetic foot	85	3.2	115	3.2	200	3.2	115	4.1	5	0.5	120	3.1

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator

Source: Table 7.3.5: 1 (Interim cardiovascular safety meta-analysis)

Of the 10,036 patients, (b) (4) had events that qualified for adjudication. Of these, (b) (4) were confirmed, (b) (4) were not confirmed, and (b) (4) were not assessable. Review of randomly selected adjudication reports did not raise concern for misclassification of events.

For the primary endpoint of 4-point MACE, (b) (4) The majority of events occurred in ongoing CVOT (Study 1245.25), which was enriched with patients at high risk for these events. The hazard ratio for the overall meta-analysis was estimated as (b) (4) (95% CI [(b) (4)]) (Table 84). This upper bound is below the 1.8 margin discussed in the “Guidance for Industry”. Similar results are seen for the endpoints of 3-point MACE, 5-point MACE, and 7-point MACE. Sensitivity analyses by alternative statistical methods yielded similar results (not shown, see Table 7.5.1: 1 of the interim cardiovascular safety meta-analysis).

Looking separately at the events of “CV death”, “nonfatal myocardial infarction”, “nonfatal stroke”, “hospitalization for unstable angina”, “hospitalization for congestive heart failure”, “transient ischemic attack”, “coronary revascularization procedures”, and “all-cause (b) (4)

(b) (4)


Reviewer Comments on Cardiovascular Safety:

(b) (4)



Overall, the data presented in the meta-analysis and the interim results of the ongoing CVOT are reassuring that treatment with empagliflozin does not result in increased risk for MACE.

(b) (4)



7.3.5.1.5 Cardiovascular Safety – Four Month Safety Update

In the 4-month safety update, four cases of cardiovascular events were reported as serious unexpected suspected adverse reactions (SUSARs).

The first case was in a patient (1245-0025- (b) (4)) being treated with empagliflozin 25 mg. The patient was initially hospitalized on day 200 after randomization, for sepsis due to a urinary tract infection. During the hospitalization, multiple hypotensive episodes requiring pressor support occurred. Fatal cardiac arrest occurred on day 275 since randomization. Laboratory tests and ECGs did not suggest myocardial infarction. Cause of death was listed as urosepsis.

The next case was in a patient (1245-0025- (b) (4)) being treated with empagliflozin 10 mg. Myocardial infarction requiring hospitalization occurred on day 374 after starting empagliflozin. Empagliflozin therapy was stopped at that time. Acute renal insufficiency was reported 1 day after being hospitalized. The event was assessed as due to contrast agent use, and was assessed as resolved 5 days later.

The third case was in a patient (1245-0049-075427) being treated with empagliflozin 25 mg. Study drug was administered from 11/9/11 to 1/31/12. A 17 kg weight gain was reported over this period. On (b) (6) the patient was hospitalized with cardiac failure and cor pulmonale.

The last case was in a patient (1245-0052-0243007) being treated with empagliflozin 10 mg. Eight days after starting empagliflozin, the patient was hospitalized for acute myocardial infarction with ST-elevations. Study drug was stopped at that time. The investigator posited that the event may have been triggered by dehydration due to effects of the study drug.

No significant changes to the findings from the initially submitted data result from review of the 4-month safety update. No new safety concerns are raised by this update.

7.3.5.2 Liver Adverse Events/Hepatic Injury

During the review of dapagliflozin, concern was raised with regard to DILI. As a result, special attention is paid to the liver adverse events in the empagliflozin development program. The evaluation for hepatic injury was performed using the “Liver related investigations, signs and symptoms” SMQ (SMQ code 20000008), “Cholestasis and jaundice of hepatic origin” SMQ (SMQ code 20000009), “Hepatitis, non-infectious” SMQ (SMQ code 20000010), “Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions” SMQ (SMQ code 20000013), and by review of the laboratory values.

No imbalance was seen in SAF-5 for reported adverse events of hepatic injury using the CMQ (Table 94). The PT “Hyperbilirubinaemia” was reported with an increased incidence in the empagliflozin-treated patients compared to the placebo-treated patients. There was an imbalance in the number of patients with laboratory tests showing elevated liver enzymes, with more empagliflozin-treated patients than comparator-treated patients having elevated liver enzymes (eleven patients during treatment with empagliflozin vs. one during treatment with comparator (glimepiride); Table 95).

Table 94 Hepatic Injury Adverse Events (by Preferred Term) Occurring in ≥ 2 Patients - Safety Grouping 5, Treated Set

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	3630			4602			8400			3522			4676		
Total exposure (patient-years)	3257.0			4450.7			7833.9			2759.7			4187.9		
System Organ Class – Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Hepatic Injury SMQ	43	1.18	1.32	65	1.41	1.46	111	1.32	1.42	54	1.53	1.96	87	1.86	2.08
Gastrointestinal disorders	2	0.06	0.06	0	0.00	0.00	2	0.02	0.03	0	0.00	0.00	1	0.02	0.02
Hepatobiliary disorders	19	0.52	0.58	43	0.93	0.97	63	0.75	0.80	28	0.80	1.01	46	0.98	1.10
– Hepatic steatosis	8	0.22	0.25	24	0.52	0.54	32	0.38	0.41	13	0.37	0.47	21	0.45	0.50
– Hepatic function abnormal	1	0.03	0.03	4	0.09	0.09	5	0.06	0.06	3	0.09	0.11	4	0.09	0.10
– Hyperbilirubinemia	1	0.03	0.03	7	0.15	0.16	8	0.10	0.10	0	0.00	0.00	0	0.00	0.00
– Liver disorder	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	2	0.06	0.07	3	0.06	0.07
– Hepatitis	1	0.03	0.03	2	0.04	0.04	3	0.04	0.04	1	0.03	0.04	2	0.04	0.05
– Non-alcoholic steatohepatitis	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	3	0.09	0.11	4	0.09	0.10
– Hepatic cirrhosis	1	0.03	0.03	1	0.02	0.02	2	0.02	0.03	2	0.06	0.07	2	0.04	0.05
– Hepatomegaly	2	0.06	0.06	2	0.04	0.04	4	0.05	0.05	0	0.00	0.00	0	0.00	0.00
– Hepatitis acute	0	0.00	0.00	2	0.04	0.04	2	0.02	0.03	0	0.00	0.00	1	0.02	0.02
– Liver injury	2	0.06	0.06	0	0.00	0.00	2	0.02	0.03	0	0.00	0.00	1	0.02	0.02
– Hypertransaminasemia	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	2	0.06	0.07	2	0.04	0.05
– Hepatic fibrosis	0	0.00	0.00	2	0.04	0.04	2	0.02	0.03	0	0.00	0.00	0	0.00	0.00

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total (N)	3630			4602			8400			3522			4676		
Total exposure (patient-years)	3257.0			4450.7			7833.9			2759.7			4187.9		
System Organ Class – Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Investigations	22	0.61	0.68	25	0.54	0.56	49	0.58	0.63	30	0.85	1.09	47	1.01	1.12
– Alanine aminotransferase increased	14	0.39	0.43	8	0.17	0.18	22	0.26	0.28	13	0.37	0.47	21	0.45	0.50
– Aspartate aminotransferase increased	7	0.19	0.21	2	0.04	0.04	9	0.11	0.11	7	0.20	0.25	12	0.26	0.29
– Hepatic enzyme increased	5	0.14	0.15	6	0.13	0.13	11	0.13	0.14	5	0.14	0.18	9	0.19	0.21
– Gamma-glutamyl transferase increased	1	0.03	0.03	3	0.07	0.07	5	0.06	0.06	3	0.09	0.11	7	0.15	0.17
– Liver function test abnormal	0	0.00	0.00	3	0.07	0.07	4	0.05	0.05	5	0.14	0.18	5	0.11	0.12
– Transaminase increased	0	0.00	0.00	3	0.07	0.07	3	0.04	0.04	3	0.09	0.11	3	0.06	0.07

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; per 100 = events per 100 patient-years

Source: Table 2.1.5.2.1: 1(Summary of Clinical Safety)

Table 95 Subjects with Liver Enzyme Elevation – Safety Grouping 5

– ALT/AST $\geq 3\times$ ULRR w/ total bilirubin (T. Bili) $\geq 3\times$ ULRR, or ALT/AST $\geq 10\times$ ULRR

Subject Number	Age	Sex	Hy's Law? ¹	ALT/AST $\geq 3\times$ ULRR w/ T. Bili $\geq 2\times$ ULRR	ALT/AST $\geq 10\times$ ULRR	Alternative Etiology (from BI)
Empagliflozin 10 mg						
1245-0009-008963	57	F	N	Y	N	Bile duct cancer
1245-0025- (b) (4) ²	63	M	Y	N	Y	Sepsis
1245-0025- (b) (4)	62	M	Y	N	Y	Cholelithiasis
Empagliflozin 25 mg						
1245-0020-023063	49	M	Y	N	N	Hepatitis A
1245-0025- (b) (4)	64	M	N	N	Y	Other medication
1245-0028-082492	65	F	N	N	Y	Mirizzi syndrome w/ common bile duct obstruction, hepatic steatosis
1245-0028-084833 ²	48	M	Y	N	N	Cirrhosis, steatosis, alcohol
1245-0028-088530	66	M	N	N	Y	Other medication, alcohol
1245-0031-021141	55	M	Y	N	N	Bile duct cancer
1245-0033-004003	87	M	N	Y	Y	Other medication, supplement
1245-0038-817006	58	F	N	N	Y	Other medication, supplement
Glimepiride						
1245-0028-082414	57	M	N	Y	N	Tumor
Empagliflozin 25 mg post-treatment						
1245-0025- (b) (4)	66	M	N	Y	N	Hepatic neoplasm
1245-0033-004394	77	M	Y	N	N	Pancreatic carcinoma
Empagliflozin 100 mg post-treatment						
1245-0004-006059	40	M	N	N	Y	History of unspecified hepatitis, muscle related enzyme elevation
Placebo post-treatment						
1245-0048-016423	55	M	N	N	Y	No empagliflozin exposure

ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULRR = upper limit of reference range; T. Bili = total bilirubin; BI = Boehringer Ingelheim

¹ALT and/or AST $\geq 3\times$ ULRR w/ concomitant or subsequent T. Bili. $\geq 2\times$ ULRR, and alkaline phosphatase $< 2\times$ ULRR; ²Fatal event

Source: Table 2.1.5.2.2: 1 (Summary of Clinical Safety)

Cases of suspected DILI underwent independent adjudication by a committee consisting of four experts. Each event of concern was reviewed and voted on by two members. A third member reviewed and voted when another adjudicator was needed. Thirty-six cases that met prespecified criteria were reviewed, and 21 cases were adjudicated as unlikely, eight as possible, one as probable, and six as indeterminate. No irreversible hepatic failure requiring liver transplant was identified. Though five patients met the biochemical criteria for Hy's law, the Applicant and the adjudication committee felt that the alternative explanations could plausibly explain these findings.

Review of the supplied narratives for these cases is reassuring that the liver laboratory test abnormalities are unlikely to be due to empagliflozin treatment. In particular, the alternative explanations offered by the Applicant for the patients with biochemical findings consistent with Hy's law appear plausible. A summary of the empagliflozin patients treated with empagliflozin and with biochemical findings consistent with Hy's law, or with transaminase elevations $\geq 10\times$ ULRR follow:

Patient 1245-0025- (b) (4) (Empagliflozin 10 mg): Biochemical Hy's law, transaminase $\geq 10\times$ ULRR

A 62 year old male with a past medical history of T2DM with retinopathy and neuropathy, hypertension, coronary artery disease s/p stent/angioplasty, heart failure, hypothyroidism was noted to have elevated liver enzymes 465 days after initiation of study drug. Three days prior to this, he reported abdominal pain. On day 473 he was diagnosed with cholelithiasis, requiring hospitalization. He had surgery to remove obstructive gallstones and his gallbladder.

Reviewer Comment: The long duration of treatment and the diagnosis of cholelithiasis at the time of the event speak against this occurring as a result of treatment of empagliflozin.

Patient 1245-0025- (b) (4) (Empagliflozin 10 mg): Biochemical Hy's law, transaminase $\geq 10\times$ ULRR

A 63 year old male living in India with a past medical history of T2DM, coronary artery disease, and hypertension was hospitalized for sepsis on day 160 after randomization. Elevation in bilirubin and ALT were noted at that time. There was no report of alcohol use, or exposure to herbal supplements or non-steroidal anti-inflammatory drugs. Testing for HIV and hepatitis B were negative. Sepsis was believed to be a result of a urinary tract infection. He was treated with antibiotics, and recovered from the sepsis. He was discharged on day 167. Liver test elevations were improving at that time, and reportedly returned to normal by day 204.

Reviewer Comment: Sepsis appears to be a more likely cause of the liver test elevations rather than exposure to empagliflozin.

Patient 1245-0020-023063 (Empagliflozin 25 mg): Biochemical Hy's law:

A 49 year old male from India with a past medical history of T2DM and hypertension was diagnosed with infectious hepatitis on day 75. He reported nausea, vomiting, and loss of appetite at that time. Testing for hepatitis B and salmonella typhi was negative, and he was clinically diagnosed with hepatitis A. Ultrasound showed no evidence of biliary disease. On day 89, liver tests rose further, and study drug was stopped at that time. One week later (day 96), study drug was restarted. The event was considered resolved on day 166. The patient completed the study, and enrolled in the extension study.

Reviewer Comment: Though testing for infectious hepatitis was incomplete, this seems to be a plausible explanation as the patient is from a region where infectious hepatitis is endemic. Additionally, study drug was restarted quickly after it was stopped, and there was no reported recurrence of liver test elevations.

Patient 1245-0020-021141 (Empagliflozin 25 mg): Biochemical Hy's law

A 55 year old male with a past medical history of unspecified pancreatic disease and non-alcoholic steatohepatitis was found to have elevated liver enzymes at his baseline visit. On day 412 after starting study drug, he began to note itching of the whole body as well as abdominal discomfort. Liver dysfunction was diagnosed on day 415. Elevated tumor markers were noted on day 417 (increased CA-19-9, alpha fetoprotein, and carcinoembryonic antigen). A CT scan showed a bile duct tumor. He had a biliary drain placed and subsequently had surgical resection. Liver tests improved following surgery.

Reviewer Comment: This case is more likely a result of the bile duct cancer.

Patient 1245-0028-084833 (Empagliflozin 25 mg): Biochemical Hy's law

A 28 year old male from the Czech Republic with a past medical history of liver steatosis and a reported increase in alcohol consumption starting on day 206 of study drug treatment was hospitalized with renal insufficiency and liver failure on day 270 after starting study drug. Growing ascites and icterus were reported prior to hospitalization. Increases in transaminases were noted on laboratory tests done on day 262 with the elevation in AST > the elevation in ALT. Coagulopathy was reported and a gastrointestinal hemorrhage was reported during hospitalization. He subsequently died on day 276.

Reviewer Comment: While this case is of particular concern as it resulted in liver failure and death, it seems unlikely to be a result of treatment with empagliflozin. The long duration of treatment prior to the event is inconsistent with acute drug-induced liver injury, and the greater elevation in AST than in ALT is consistent with the Applicant's proposed alternative etiology of alcohol.

Patient 1245-0033-004003 (Empagliflozin 25 mg): Transaminase \geq 10x ULRR

An 87 year old male with a past medical history of T2DM with neuropathy, dyslipidemia, and metabolic syndrome was found to have elevations in liver enzymes on day 378 since starting study drug. Prior to this finding, he had been diagnosed with pneumonia on day 342 and started on antibiotics on day 344. The antibiotics were stopped on day 362. Evaluation of the liver enzyme elevations was negative for hepatitis A, hepatitis B, hepatitis E, and Epstein-Barr. Study drug was stopped on day 382. All other medications were stopped on day 384. Ultrasound performed on day 389 showed no pathologic findings, and liver biopsy was consistent with drug-related hepatitis. Liver enzymes were noted to be normal on day 431.

Reviewer Comment: Though the biopsy suggests drug-related hepatitis, there are several potential culprits. The antibiotics used to treat the pneumonia seem to be the most likely offender based on the timing. There was a long exposure to study drug before the event, and the antibiotics were the most recent addition to the patient's medication regimen.

Patient 1245-0028-082492 (Empagliflozin 25 mg): Transaminase \geq 10x ULRR

A 65 year old female with a past medical history of T2DM with neuropathy, dyslipidemia, hypertension, and prior cholecystectomy was diagnosed with acute hepatitis on day 77 after starting study drug. Ultrasound suggested pneumobilia. Serologic testing for hepatitis B and hepatitis C are reported as "unremarkable". Study drug was stopped on day 91. Significant elevations in alkaline phosphatase were noted which were slow to resolve following discontinuation of study drug. Bilirubin elevations were minimal and did not exceed 2x ULRR. Transaminases and bilirubin returned to normal by day 118. Subsequent imaging with CT and MRI did not demonstrate the pneumobilia.

Reviewer Comment: Though there is no clear etiology that can be identified from the supplied narrative information, the lack of a rise in bilirubin is reassuring that this is not the result of direct liver injury. The presence of pneumobilia is suggestive of a biliary tree problem, but it was apparently transient.

Patient 1245-0025- (b) (4) Empagliflozin 25 mg): Transaminase \geq 10x ULRR

A 64 year old male with a past medical history of T2DM w/ retinopathy, gout, hypothyroidism, coronary artery disease, morbid obesity, dyslipidemia, and renal insufficiency was noted to have an elevated ALT on day 269 of study drug treatment. He was diagnosed with a urinary tract infection on day 352 and started on antibiotic therapy. On day 361, he was diagnosed with drug-induced hepatitis based on elevated liver enzyme tests. Viral hepatitis serologies performed on day 324 for unclear reasons were negative. Study drug, antibiotic, and statin therapy were stopped. He was assessed as recovered from the event on day 393.

Reviewer Comment: The long exposure to study drug before the event occurred goes against the study drug being the causative agent. From a temporal perspective, the antibiotic appears to be a more likely causative factor.

Patient 1245-0038-817006 (Empagliflozin 25 mg): Transaminase \geq 10x ULRR

A 58 year old female with past medical history of T2DM, dyslipidemia, and obesity was diagnosed with liver dysfunction leading to hospitalization and discontinuation of study drug on day 251 of study drug treatment. Additional history included daily alcohol consumption with an increase in the amount consumed from day 231 to day 251. She was taking several concomitant medications, including a statin, a nonsteroidal anti-inflammatory drug, and several herbal supplements. She reported fatigue but jaundice was not noted. Ultrasound did not demonstrate findings consistent with acute hepatitis. Viral hepatitis tests were negative, though tests for hepatitis D and hepatitis E were not performed. All medications were stopped at the time of hospitalization. Values for AST, ALT, GGT, Alk Phos, and LDH were elevated but had normalized by day 280. Bilirubin was never elevated.

Reviewer Comment: No clear etiology can be identified from this case. The long duration of exposure to study drug prior to the event is reassuring that the study drug is not the causative agent. Other medications, and her recent increase in alcohol consumption could have contributed to the event.

Patient 1245-0033-004394 (Empagliflozin 25 mg): Biochemical Hy's law

A 74 year old male with a past medical history of T2DM w/ nephropathy, hypertension, dyslipidemia, and metabolic syndrome was found to have elevated amylase, lipase, and AST on day 470. Study drug was stopped on day 483. He was noted to be jaundiced on day 511 and laboratory tests showed elevated lipase, amylase, ALT, AST, and bilirubin. The tumor marker CA-19-9 was also elevated. Biliary drainage was performed on day 526, and biopsy performed on day 545 showed pancreatic adenocarcinoma.

Reviewer Comment: *The pancreatic cancer is the more likely cause of the liver enzyme elevation.*

Patient 1245-0004-006059 (Empagliflozin 100 mg): Transaminase \geq 10x ULRR

A 40 year old male was noted to have elevated AST and ALT on day 38 after starting study drug. Notably, this was ten days after the last dose of study drug. Only AST reached \geq 10x ULRR. A concomitant increase in creatine kinase was also noted (to \geq 40x ULRR). He reportedly had started a new strength training regimen.

Reviewer Comment: *The markedly elevated creatine kinase supports the possibility that the AST and ALT elevations originated from muscle injury. This can be seen with intense exercise.*

The incidence of ALT elevations \geq 5x, 10x, and 20x ULRR was slightly higher with empagliflozin vs. placebo or all comparators, and the incidence with the 25 mg dose was slightly higher than with the 10 mg dose (Table 96). There was a small numerical imbalance in the percentage of patients being treated with empagliflozin who had ALT \geq 3x ULRR with T. Bili \geq 2x ULRR and Alk Phos $<$ 2x ULRR. While these small imbalances are suggestive, there is no convincing evidence of an increased likelihood of drug-induced liver injury with empagliflozin treatment. Cases with elevations $>$ 10x ULRR are discussed in narratives above; review of these cases did not support empagliflozin-induced liver injury.

Table 96 Incidence of Categorical Increases in Liver Laboratory Tests

SAF-5										
	Empa 10		Empa 25		All Empa		Placebo		All Comp	
Total (N)	3630		4602		8400		3522		4676	
	n	%	n	%	n	%	n	%	n	%
ALT \geq 3x ULRR	17	0.47	24	0.52	43	0.51	23	0.65	37	0.79
ALT \geq 5x ULRR	6	0.17	10	0.22	16	0.19	2	0.06	3	0.06
ALT \geq 10x ULRR	2	0.06	5	0.11	7	0.08	0	0.00	0	0.00
ALT \geq 20x ULRR	0	0.00	1	0.02	1	0.01	0	0.00	0	0.00
AST \geq 3x ULRR	9	0.25	17	0.37	27	0.32	17	0.48	20	0.43
AST \geq 5x ULRR	4	0.11	7	0.15	12	0.14	4	0.11	5	0.11
AST \geq 10x ULRR	0	0.00	3	0.07	4	0.05	1	0.03	1	0.02
AST \geq 20x ULRR	0	0.00	1	0.02	1	0.01	0	0.00	0	0.00

SAF-5										
	Empa 10		Empa 25		All Empa		Placebo		All Comp	
Total (N)	3630		4602		8400		3522		4676	
ALT \geq 3x ULRR and T. Bili \geq 2x ULRR	1	0.03	3	0.07	4	0.05	0	0.00	1	0.02
- w/ Alk Phos < 2x ULRR	0	0.00	3	0.07	3	0.04	0	0.00	0	0.00
- w/ Alk Phos \geq 2x ULRR	1	0.03	0	0.00	1	0.01	0	0.00	1	0.02
Completed studies from SAF-5										
	Empa 10		Empa 25		All Empa		Placebo		All Comp	
Total (N)	1798		2000		4421		1740		2112	
	n	%	n	%	n	%	n	%	n	%
ALT \geq 3x ULRR	8	0.44	18	0.90	28	0.63	14	0.80	20	0.95
ALT \geq 5x ULRR	1	0.06	7	0.35	8	0.18	2	0.11	2	0.09
ALT \geq 10x ULRR	0	0.00	3	0.15	3	0.07	0	0.00	0	0.00
ALT \geq 20x ULRR	0	0.00	1	0.05	1	0.02	0	0.00	0	0.00
AST \geq 3x ULRR	4	0.22	10	0.50	15	0.34	9	0.52	10	0.47
AST \geq 5x ULRR	1	0.06	3	0.15	5	0.11	4	0.23	4	0.19
AST \geq 10x ULRR	0	0.00	2	0.10	3	0.07	1	0.06	1	0.05
AST \geq 20x ULRR	0	0.00	1	0.05	1	0.02	0	0.00	0	0.00
ALT \geq 3x ULRR and T. Bili \geq 2x ULRR	1	0.06	3	0.15	4	0.09	0	0.00	0	0.00
w/ Alk Phos < 2x ULRR	0	0.00	2	0.10	2	0.05	0	0.00	0	0.00
w/ Alk Phos \geq 2x ULRR	1	0.06	0	0.00	1	0.02	0	0.00	0	0.00

SAF-5 = Safety Grouping 5; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; ALT = alanine aminotransferase; ULRR = upper limit of reference range; AST = aspartate aminotransferase; T. Bili = total bilirubin; Alk Phos = alkaline phosphatase
Source: Table 6.4.5.5 (Integrated Summary of Safety)

Based on the available data there does not appear to be evidence of severe, acute drug-induced liver injury as a result of treatment with empagliflozin.

The Office of Surveillance and Epidemiology (OSE) was consulted for an opinion on the imbalance in liver enzyme elevations and empagliflozin's potential for DILI. Additional data for use in the Evaluation of Drug-Induced Serious Hepatotoxicity (eDISH) tool were requested and were submitted by the Applicant on August 12, 2013 (NDA-204629, SD-15, eCTD-0012). Review of the submitted data by Dr. John R. Senior led him to conclude that there is "no indication that empagliflozin is likely to cause serious liver injury or dysfunction." For details of his consult, see his premarket safety review submitted to the Document Archiving, Reporting and Regulatory Tracking System (DARRTS) on October 20, 2013.

Reviewer Comments on Liver Safety:

Based on my review of the narratives, plausible alternative explanations are offered for the identified cases meeting the biochemical criteria for Hy's Law, and I am not overly concerned that there is a risk for severe acute drug-induced liver injury with empagliflozin. There are two cases (Patient 1245-0020-023063 and Patient 1245-0028-084833) in which the submitted narrative leaves room for questioning of the proposed alternative etiology (discussed above). In the first, I am reassured by the rechallenge and absence of recurrent liver enzyme elevations. In the second, the late onset of the event is reassuring that this is not an acute event. I am further reassured by the conclusions from the independent adjudication of potential hepatic events.

7.3.5.2.1 Liver Adverse Events/Hepatic Injury – Four Month Safety Update

In the 4 month safety update, one case of a liver adverse event was reported.

In this case, a patient (1245-0052-281002) was being treated with empagliflozin 10 mg and reported drug-induced hepatic disorder. Abnormal liver laboratory tests were reported on day 192 after randomization. On day 206, treatment was stopped and discontinuation procedures were initiated. Work-up for abnormal liver laboratory tests were negative for Epstein-Barr infection, viral hepatitis, primary biliary cirrhosis, and cholecystolithiasis (by ultrasound). No elevation in bilirubin was ever documented. Despite the absence of a typical drug-induced liver injury pattern, the event was reported as a drug-induced hepatic disorder due to improvement in liver laboratory tests with discontinuation of empagliflozin. An additional suspect drug was solifenacin which had been started 23 days before the event.

No significant changes to the findings from the initially submitted data result from review of the 4 month safety update. No new safety concerns are raised by this update.

7.3.5.3 Fractures

Fractures were evaluated using a CMQ created by the Applicant. The PTs in the CMQ are:

- | | | |
|----------------------------|-------------------------|-------------------------------|
| • Acetabulum fracture | • Humerus fracture | • Traumatic fracture |
| • Ankle fracture | • Ilium fracture | • Cervical vertebral fracture |
| • Clavicle fracture | • Jaw fracture | • Lumbar vertebral fracture |
| • Complicated fracture | • Multiple fractures | • Thoracic vertebral fracture |
| • Compression fracture | • Open fracture | • Fracture of penis |
| • Elevation skull fracture | • Osteoporotic fracture | • Comminuted fracture |
| • Facial bones fracture | • Patella fracture | • Epiphyseal fracture |

- | | | |
|-------------------------------|-------------------------------|--------------------------------------|
| • Femoral neck fracture | • Pathological fracture | • Fractured zygomatic arch elevation |
| • Femur fracture | • Radius fracture | • Pelvic fracture |
| • Fibula fracture | • Rib fracture | • Skull fracture |
| • Foot fracture | • Scapula fracture | • Upper limb fracture |
| • Forearm fracture | • Skull fractured base | • Lower limb fracture |
| • Fracture | • Spinal compression fracture | • Tooth fracture |
| • Fractured ischium | • Spinal fracture | • Torus fracture |
| • Fractured maxilla elevation | • Sternal fracture | • Avulsion fracture |
| • Fractured sacrum | • Stress fracture | • Impacted fracture |
| • Fractured skull depressed | • Tibia fracture | • Periprosthetic fracture |
| • Greenstick fracture | • Ulna fracture | • Pubis fracture |
| • Hand fracture | • Wrist fracture | • Atypical femur fracture |
| • Hip fracture | • Fractured coccyx | |

Based on the CMQ, there was no increase in fracture adverse events with empagliflozin treatment (1.63% Empa 10 vs. 1.15% Empa 25 vs. 1.99% placebo; Table 97). The most frequent PT was “Traumatic fracture”. Review of the available narratives does not indicate that any of these events were clearly the result of hypotension, syncope, or hypoglycemia. While a few PTs were seen with a slightly greater incidence in the empagliflozin-treated patient vs. comparator, no clear imbalance in fractures was seen. Grouping fractures into upper extremity and lower extremity fractures also did not demonstrate an increased risk for either grouping with empagliflozin treatment.

Table 97 Incidence of Fractures by Preferred Term - Safety Grouping 5

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Number of patients	3630			4602			8400			3522			4676		
	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Patients with bone fracture	59	1.63	1.81	51	1.11	1.15	110	1.31	1.41	55	1.56	1.99	72	1.54	1.72
- Traumatic fracture	21	0.58	0.64	14	0.30	0.31	35	0.42	0.45	20	0.57	0.73	22	0.47	0.53
- Foot fracture	2	0.06	0.06	5	0.11	0.11	7	0.08	0.09	5	0.14	0.18	8	0.17	0.19
- Tooth fracture	4	0.11	0.12	8	0.17	0.18	12	0.14	0.15	3	0.09	0.11	3	0.06	0.07
- Rib fracture	5	0.14	0.15	4	0.09	0.09	9	0.11	0.11	5	0.14	0.18	6	0.13	0.14
- Hand fracture	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	2	0.06	0.07	8	0.17	0.19
- Tibia fracture	2	0.06	0.06	4	0.09	0.09	6	0.07	0.08	3	0.09	0.11	3	0.06	0.07
- Ankle fracture	3	0.08	0.09	2	0.04	0.04	5	0.06	0.06	1	0.03	0.04	2	0.04	0.05
- Fibula fracture	1	0.03	0.03	3	0.07	0.07	4	0.05	0.05	2	0.06	0.07	3	0.06	0.07
- Radius fracture	1	0.03	0.03	2	0.04	0.04	3	0.04	0.04	4	0.11	0.15	4	0.09	0.10
- Wrist fracture	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	3	0.09	0.11	4	0.09	0.10
- Pathological fracture	1	0.03	0.03	2	0.04	0.04	3	0.04	0.04	3	0.09	0.11	3	0.06	0.07
- Clavicle fracture	1	0.03	0.03	1	0.02	0.02	2	0.02	0.03	3	0.09	0.11	3	0.06	0.07
- Humerus fracture	1	0.03	0.03	1	0.02	0.02	2	0.02	0.03	2	0.06	0.07	3	0.06	0.07
- Upper limb fracture	4	0.11	0.12	1	0.02	0.02	5	0.06	0.06	0	0.00	0.00	0	0.00	0.00
- Facial bones fracture	2	0.06	0.06	2	0.04	0.04	4	0.05	0.05	0	0.00	0.00	0	0.00	0.00
- Ulna fracture	3	0.08	0.09	0	0.00	0.00	3	0.04	0.04	1	0.03	0.04	1	0.02	0.02
Upper extremity ¹	13	0.36	0.40	6	0.13	0.13	19	0.23	0.24	12	0.34	0.44	20	0.43	0.48
Lower extremity ²	8	0.22	0.25	14	0.30	0.31	22	0.26	0.28	11	0.31	0.40	16	0.34	0.38

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Number of patients	3630			4602			8400			3522			4676		
	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; per 100 = events per 100 patient-years

¹ includes the terms “Ulna fracture”, “Upper limb fracture”, “Humerus fracture”, “Wrist fracture”, “Radius fracture” and “Hand fracture”; ² includes the terms “Fibula fracture”, “Ankle fracture”, “Tibia fracture”, and “Foot fracture”

Source: Table 2.1.5.6: 1 (Summary of Clinical Safety)

Changes in laboratory tests related to bone health were also analyzed (Table 98). Serum calcium, phosphate, and alkaline phosphatase were available for all of the studies. Additional data with regard to 25-hydroxy cholecalciferol (25-OH vitamin D), intact parathyroid hormone (iPTH), and urine N-terminal telopeptide to creatinine ratio (U NTX:Cr) were available from Studies 1245.20, 1245.28, 1245.33, and 1245.38.

No changes in median values of serum calcium, phosphate, or alkaline phosphatase were seen. Further discussion of electrolytes can be found in Section 7.4.2.2. Median values for 25-OH vitamin D rose in the patients treated with empagliflozin 25 mg compared to placebo-treated patients. Intact PTH rose slightly with empagliflozin 10mg treatment compared to placebo. There was a small increase in U NTX:Cr for the empagliflozin-treated patients, which exhibited a suggestion of dose dependence. There were no striking differences in categorical shifts for iPTH or 25-OH vitamin D between the empagliflozin treated patients and the comparator treated patients (Table 99). A greater percentage of patients treated with empagliflozin 10 mg went from WRR to < LLRR for 25-OH vitamin D compared to placebo and to all comparators, while a greater percentage of patients treated with empagliflozin 25 mg went from WRR to > ULRR. For iPTH, a greater percentage of patients went from WRR to < LRR compared to either empagliflozin dose. The significance of these changes is not clear. As noted above, the incidence of fractures was not increased with empagliflozin treatment.

Table 98 Change in Laboratory Markers of Bone Health – Safety Grouping 5

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3
25-OH vitamin D (nmol/L)	N=307		N=983		N=1508		N=291		N=1175	
- Baseline	74.7	54.7, 99.7	79.7	54.7, 105.7	79.7	54.7, 105.7	71.7	50.4, 94.7	79.7	54.7, 104.7
- LVOT	79.7	54.7, 104.7	89.7	59.7, 119.7	88.7	59.7, 118.5	71.7	49.7, 99.7	84.7	54.7, 109.7
- Change	0.0	-20.0, 21.3	5.0	-10.0, 25.0	8.5	-10.0, 25.0	0.0	-20.0, 25.0	4.3	-15.0, 20.0
iPTH (ng/L)	N=308		N=962		N=1488		N=285		N=1162	
- Baseline	39.2	30.0, 51.8	32.7	23.2, 45.8	35.5	26.0, 47.7	39.1	29.8, 52.5	32.7	22.3, 46.4
- LVOT	40.9	31.3, 50.0	31.7	21.3, 44.0	36.4	25.1, 47.3	37.3	27.9, 51.5	30.8	20.4, 44.0
- Change	1.9	-6.9, 9.1	-0.9	-8.5, 7.5	0.0	-7.5, 7.5	-0.9	-10.4, 5.5	-1.9	-10.4, 6.6
Calcium (mmol/L)	N=3058		N=3975		N=7629		N=3233		N=4354	
- Baseline	2.4	2.4, 2.5	2.4	2.4, 2.5	2.4	2.4, 2.5	2.4	2.4, 2.5	2.4	2.4, 2.5
- LVOT	2.4	2.4, 2.5	2.4	2.4, 2.5	2.4	2.4, 2.5	2.4	2.4, 2.5	2.4	2.4, 2.5
- Change	0.0	-0.1, 0.0	0.0	-0.1, 0.0	0.0	-0.1, 0.0	0.0	-0.1, 0.0	0.0	-0.1, 0.0
Phosphate (mmol/L)	N=3033		N=3950		N=7531		N=3204		N=4325	
- Baseline	1.2	1.1, 1.2	1.2	1.1, 1.2	1.2	1.1, 1.2	1.2	1.1, 1.2	1.2	1.1, 1.2
- LVOT	1.2	1.1, 1.3	1.2	1.1, 1.3	1.2	1.1, 1.3	1.2	1.1, 1.3	1.2	1.1, 1.3
- Change	0.0	0.0, 0.1	0.0	0.0, 0.1	0.0	0.0, 0.1	0.0	0.0, 0.1	0.0	0.0, 0.1
Alk phos (U/L)	N=3173		N=4097		N=7866		N=3354		N=4475	
- Baseline	60	45, 80	60	45, 80	61	46, 80	60	45, 80	60	45, 81
- LVOT	60	45, 80	60	45, 81	60	46, 80	60	45, 81	60	45, 82
- Change	0.0	0.0, 0.1	0.0	0.0, 0.1	0.0	0.0, 0.1	0.0	0.0, 0.1	0.0	0.0, 0.1
U NTX: Cr (nM/mM Cr)	N=295		N=865		N=1370		N=280		N=1053	
- Baseline	37	26, 49	29	20, 42	33	23, 46	37	25, 51	30	21, 44
- LVOT	39	25, 54	33	24, 47	37	26, 54	34	24, 49	27	19, 41
- Change	3	-6, 12	5	-4, 14	5	-4, 14	-2	-10, 5	-2	-11, 6

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator; Mdn = median; Q1 = first quartile; Q3 = third quartile; LVOT = last value on treatment; iPTH = intact parathyroid hormone; Alk Phos = alkaline phosphatase; U NTX: Cr = urine N-telopeptide to creatinine ratio

Source: Table 2.1.5.6: 2 (Summary of Clinical Safety)

Table 99 Categorical Shifts for Intact Parathyroid Hormone and 25-Hydroxy Cholecalciferol – Safety Grouping 5

Baseline	N at baseline	Last Value on Treatment					
		Below LLRR		WRR		Above ULRR	
		N	%	N	%	N	%
25-OH vitamin D							
Placebo							
Below LLRR	11	3	23.1	9	69.2	1	7.7
WRR	275	6	2.2	264	96.0	5	1.8
Above ULRR	3	0	0.0	2	66.7	1	33.3
Empa 10							
Below LLRR	9	3	33.3	6	66.7	0	0
WRR	297	17	5.7	275	92.6	5	1.7
Above ULRR	1	0	0.0	1	100	0	0.0
Empa 25							
Below LLRR	48	16	33.3	31	64.6	1	2.1
WRR	904	18	2.0	853	94.4	33	3.7
Above ULRR	31	0	0.0	16	51.6	15	48.4
All Empa							
Below LLRR	59	19	32.2	39	66.1	1	1.7
WRR	1413	35	2.5	1334	94.4	44	3.1
Above ULRR	36	0	0.0	19	52.8	17	47.2
All Comp							
Below LLRR	59	17	28.8	40	67.8	2	3.4
WRR	1071	28	2.6	1017	95.0	26	2.4
Above ULRR	45	0	0.0	25	55.6	20	4.4
iPTH							
Placebo							
Below LLRR	5	1	20.0	4	80.0	0	0.0
WRR	237	9	3.8	212	89.5	16	6.8
Above ULRR	43	0	0.0	23	53.5	20	46.5
Empa 10							
Below LLRR	1	1	100	0	0.0	0	0.0
WRR	262	3	1.1	241	92.0	18	6.9
Above ULRR	45	0	0.0	24	53.3	21	46.7
Empa 25							
Below LLRR	30	10	33.3	20	66.7	0	0
WRR	846	24	2.8	774	91.5	48	5.7
Above ULRR	86	0	0.0	50	58.1	36	41.9
All Empa							
Below LLRR	31	11	35.5	20	64.55	0	0.0
WRR	1299	27	2.1	1194	91.9	78	6.0
Above ULRR	158	0	0.0	83	52.5	75	47.5
All Comp							
Below LLRR	58	21	36.2	37	63.8	0	0.0
WRR	966	33	3.4	894	92.5	39	4.0
Above ULRR	138	0	0.0	80	58.0	58	42.0

LLRR = lower limit of reference range; WRR = within reference range; ULRR = upper limit of reference range; 25-OH vitamin D = 25-hydroxy cholecalciferol; iPTH = intact parathyroid hormone; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators

Source: Table 6.1.5.1 (Integrated Summary of Safety)

7.3.5.3.1 Fractures – Four Month Safety Update

In the 4-month safety update, an additional thirteen fracture events (0.12%) are noted with twelve of these events due to trauma¹. The overall incidence of fractures was low. Treatment remains blinded for these events. No additional safety concerns are raised by this information.

7.3.5.4 Volume Depletion

Due to the diuretic effect of empagliflozin, the development of volume depletion is a theoretical concern. To explore the incidence of volume depletion, the Applicant used a CMQ with the following PTs:

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

Based on the CMQ, there was no difference between the empagliflozin-treated patients and the comparator-treated patients in the incidence of volume depletion events (Table 100). Individual terms seen with a higher incidence in the empagliflozin-treated patients include “Syncope”, “Orthostatic hypotension”, and “Dehydration”. While renal failure can be seen as a result of volume depletion, PTs related to renal failure are not included in this CMQ. They are discussed separately in 7.3.5.6.

Table 100 Volume Depletion Events - Safety Grouping 5

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
Treated	3630		4602		8400		3522		4676	
	N	%	N	%	N	%	N	%	N	%
Volume depletion CMQ	52	1.43	67	1.46	119	1.42	49	1.39	57	1.22
Rate per 100 patient-years	1.60		1.51		1.52		1.78		1.36	
Preferred Term										
Hypotension	22	0.61	25	0.54	47	0.56	28	0.80	32	0.68
Syncope	16	0.44	22	0.48	38	0.45	11	0.31	14	0.30
Orthostatic hypotension	8	0.22	11	0.24	19	0.23	6	0.17	6	0.13
Dehydration	9	0.25	8	0.17	17	0.20	4	0.11	6	0.13
Hypovolemia	0	0.00	1	0.02	1	0.01	2	0.06	2	0.04
Blood pressure decreased	0	0.00	2	0.04	2	0.02	1	0.03	1	0.02

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; CMQ = customized MedDRA query

Source: Table 2.1.5.7: 1 (Summary of Clinical Safety)

¹From review of listing C.1.2: 1 of 4MSU

The use of diuretic medications at baseline resulted in an increase in volume depletion events for both empagliflozin and placebo (Table 101). The incidence in the empagliflozin-treated patients was slightly higher than in placebo-treated patients. When added to loop diuretics, there was a more noticeable increased incidence of these events with empagliflozin treatment compared to placebo.

Table 101 Incidence of Volume Depletion Events With and Without Baseline Diuretic Use – Safety Grouping 5, Treated Set

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	N	%	N	%	N	%	N	%	N	%
Without diuretics at baseline	2528		3228		5910		2400		3333	
- w/ volume depletion	24	0.9	30	0.9	54	0.9	24	1.0	28	0.8
- per 100 patient-years	1.07		0.96		0.99		1.32		0.95	
With diuretics at baseline	1102		1374		2490		1122		1343	
- w/ volume depletion	28	2.5	37	2.7	65	2.6	25	2.2	29	2.2
- per 100 patient-years	2.76		2.83		2.78		2.64		2.35	
Without loop diuretic at baseline	3363		4236		7766		3181		4316	
- w/ volume depletion	39	1.2	56	1.3	95	1.2	39	1.2	47	1.1
- per 100 patient-years	1.29		1.36		1.31		1.59		1.22	
With loop diuretic at baseline	267		366		634		341		360	
- w/ volume depletion	13	4.9	11	3.0	24	3.8	10	2.9	10	2.8
- per 100 patient-years	5.63		3.45		4.35		3.35		3.11	

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparator

Source: Table 2.1.5.7: 2 (Summary of Clinical Safety)

Reviewer Comments on Volume Depletion Events:

While the incidence of events for the CMQ was not different, it is notable that there were three individual Preferred Terms with a higher incidence in the empagliflozin-treated patients compared to placebo. Volume depletion events should remain a concern with empagliflozin.

7.3.5.4.1 Volume Depletion Events – Four Month Safety Update

In the 4-month safety update, two cases of syncope are reported.

The first case occurred in a patient (1245-0025- (b) (4)) being treated with empagliflozin 25 mg. The patient experienced recurrent episodes of syncope and hypotension 19 days after initiating treatment. After the second episode, empagliflozin treatment was discontinued. Dehydration due to significant glucosuria was considered to be the cause for these events, though concomitant treatment with hydrocodone and methylprednisolone for neck pain may have contributed as well.

The second case occurred in a patient (1245-0049-076554) being treated with empagliflozin 10 mg. On day 84 of treatment, collapse with loss of consciousness occurred. The last dose of study drug was the same day. Prior to this event, the patient had reported a 10 kg weight loss which was attributed to study drug. The investigator assessed the initial event as probably related to the weight loss. After lying on the floor for three days (reason not provided), the patient was found by neighbors and taken to the hospital by ambulance. At the hospital, the patient was admitted and treated for rhabdomyolysis, presumably due to prolonged immobilization.

No significant changes to the findings from the initially submitted data result from review of the 4-month safety update. No new safety concerns are raised by this update.

7.3.5.5 Genital Infections/Urinary Tract Infections

Genital and urinary tract infections were explored using an Applicant-defined CMQ. Preferred Terms for the genital infections CMQ were:

- | | | |
|---|----------------------------|--|
| • Balanitis | • Vulval abscess | • Genitourinary tract infection |
| • Balanitis candida | • Vulval cellulitis | • Penile infection |
| • Balanoposthitis | • Vulvitis | • Genital infection female |
| • Bartholin's abscess | • Vulvovaginal candidiasis | • Scrotal infection |
| • Bartholinitis | • Vulvovaginitis | • Vaginitis bacterial |
| • Cervicitis | • Genital infection | • Uterine infection |
| • Cervicitis cystic | • Clitoris abscess | • Genital abscess |
| • Endometritis | • Scrotal abscess | • Genital infection male |
| • Epididymitis | • Vaginal abscess | • Parametric abscess |
| • Genital candidiasis | • Salpingo-oophoritis | • Uterine abscess |
| • Hydrocele male infected | • Fallopian tube abscess | • Spermatic cord funiculitis |
| • Oophoritis | • Prostate infection | • Testicular abscess |
| • Orchitis | • Erosive balanitis | • Vulvovaginal mycotic infection |
| • Ovarian abscess | • Myometritis | • Cellulitis of male external genital organ |
| • Parametritis | • Prostatovesiculitis | • Genital infection viral |
| • Pelvic abscess | • Vaginal cellulitis | • Urogenital infection fungal |
| • Pelvic inflammatory disease | • Perineal abscess | • Urogenital infection bacterial |
| • Pelvic inflammatory disease mycoplasmal | • Escherichia vaginitis | • Vulvovaginal human papilloma virus infection |
| • Penile abscess | • Tubo-ovarian abscess | • Perineal infection |

- | | | |
|---------------------------------------|-------------------------------|--------------------------------|
| • Posthitis | • Ovarian infection | • Vulvovaginitis streptococcal |
| • Prostatic abscess | • Intrauterine infection | • Cervicitis streptococcal |
| • Prostatitis | • Rectovaginal septum abscess | • Prostatitis Escherichia coli |
| • Pyometra | • Ovarian bacterial infection | • Cytolytic vaginosis |
| • Salpingitis | • Epididymal infection | • Balanoposthitis infective |
| • Scrotal gangrene | • Seminal vesicular infection | • Gangrenous balanitis |
| • Seminal vesiculitis | • Pelvic infection | • Bacterial prostatitis |
| • Toxic shock syndrome staphylococcal | • Vaginitis viral | • Candida cervicitis |
| • Toxic shock syndrome streptococcal | • Pelvic sepsis | • Pyospermia |
| • Vaginal infection | • Genital infection bacterial | • Genital herpes zoster |
| • Vaginitis gardnerella | • Genital infection fungal | |

Preferred Terms for the urinary tract infections CMQ were:

- | | | |
|-------------------------------------|---|--|
| • Bacteriuria | • Urethral papilloma | • Bladder candidiasis |
| • Bacteriuria in pregnancy | • Urethral stricture post infection | • Renal cyst infection |
| • Cystitis | • Urethritis | • Viral hemorrhagic cystitis |
| • Cystitis escherichia | • Urethritis chlamydial | • Bacterial pyelonephritis |
| • Cystitis gonococcal | • Urethritis gonococcal | • Genitourinary tract gonococcal infection |
| • Cystitis hemorrhagic | • Urethritis trichomonal | • Genitourinary tract infection |
| • Cystitis klebsiella | • Urethritis ureaplasma | • Ureter abscess |
| • Cystitis pseudomonal | • Urinary tract infection | • Urinary tract infection pseudomonal |
| • Fungal cystitis | • Urinary tract infection enterococcal | • Urinary tract infection staphylococcal |
| • Genitourinary chlamydia infection | • Urinary tract infection neonatal | • Urinary tract infection viral |
| • Kidney infection | • Urogenital trichomoniasis | • Cystitis viral |
| • Perinephric abscess | • Urosepsis | • Cystitis bacterial |
| • Pyelonephritis | • Urinary tract infection fungal | • Cystitis helminthic |
| • Pyelonephritis acute | • Pyelocystitis | • Pyelonephritis viral |
| • Pyelonephritis chronic | • Candiduria | • Pyelonephritis fungal |
| • Pyelonephritis mycoplasma | • Ureteritis | • Urogenital infection fungal |
| • Pyonephrosis | • Cytomegalovirus urinary tract infection | • Urogenital infection bacterial |
| • Renal abscess | • Urinary bladder abscess | • Urinary tract abscess |
| • Renal syphilis | • Escherichia urinary tract infection | • Emphysematous pyelonephritis |

- | | | |
|--|-------------------------------------|---|
| • Renal tuberculosis | • Urethral carbuncle | • Streptococcal urinary tract infection |
| • Tuberculosis bladder | • Urinary tract infection bacterial | • Acute focal bacterial nephritis |
| • Tuberculosis of genitourinary system | • Emphysematous cystitis | • Perinephritis |
| • Tuberculosis ureter | • Asymptomatic bacteriuria | |
| • Urethral abscess | • Adenoviral hemorrhagic cystitis | |

While the overall incidence of events in the CMQ for urinary tract infections was not higher in the empagliflozin-treated patients, there were some PTs that appeared with greater incidence in the empagliflozin-treated patients (Table 102). These were “Genitourinary tract infection”, “Urinary tract infection fungal”, and “Candiduria”. There was no increase in cases of sepsis resulting from a urinary tract infection or in cases of pyelonephritis (Table 103).

Events in the CMQ for genital infections occurred at a higher overall incidence in the empagliflozin-treated patients. This was true for the majority of PTs in the CMQ. Along with the higher incidence of genital infections seen with empagliflozin treatment, phimosis (not included in the CMQ) occurred with greater frequency in empagliflozin-treated patients (Table 105). This is important to note, as phimosis can occur as a complication of genital infections and may require surgical intervention for treatment.

Fungal infections were more common in the empagliflozin-treated patients (Table 104). This was true for both the urinary tract infections CMQ, the genital infections CMQ, and the combination of the two.

Table 102 Incidence of Urinary Tract Infections and Genital Infections - Safety Grouping 5

- Based on Applicant's CMQ

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Number of patients	3630			4602			8400			3522			4676		
Estimated exposure (patient-years)	3260.0			4450.7			7833.9			2759.7			4187.9		
Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Urinary tract infection CMQ	324	8.93	10.54	406	8.82	9.62	737	8.77	9.95	284	8.06	10.85	380	8.13	9.57
Urinary tract infection	276	7.60	8.89	352	7.65	8.27	632	7.52	8.45	236	6.70	8.92	325	6.95	8.11
Cystitis	20	0.55	0.61	29	0.63	0.65	52	0.62	0.66	17	0.48	0.61	21	0.45	0.50
Asymptomatic bacteriuria	10	0.28	0.30	14	0.30	0.31	24	0.29	0.30	12	0.34	0.43	14	0.30	0.33
Bacteriuria	6	0.17	0.18	4	0.09	0.09	10	0.12	0.13	4	0.11	0.14	5	0.11	0.12
Genitourinary tract infection	8	0.22	0.24	4	0.09	0.09	12	0.14	0.15	2	0.06	0.07	4	0.09	0.09
Urinary tract infection fungal	6	0.17	0.18	1	0.02	0.02	7	0.08	0.09	0	0.00	0.00	0	0.00	0.00
Candiduria	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	0	0.00	0.00	0	0.00	0.00
Cystitis hemorrhagic	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	2	0.06	0.07	2	0.04	0.05
Escherichia urinary tract infection	0	0.00	0.00	2	0.04	0.04	2	0.02	0.03	5	0.14	0.18	5	0.11	0.12
Pyelonephritis	0	0.00	0.00	4	0.09	0.09	5	0.06	0.06	3	0.09	0.11	4	0.09	0.09
Pyelonephritis acute	1	0.03	0.03	2	0.04	0.04	3	0.04	0.04	3	0.09	0.11	3	0.06	0.07
Pyelonephritis chronic	1	0.03	0.03	1	0.02	0.02	2	0.02	0.03	5	0.14	0.18	5	0.11	0.12
Urinary tract infection bacterial	3	0.08	0.09	0	0.00	0.00	3	0.04	0.04	0	0.00	0.00	0	0.00	0.00
Urosepsis	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	2	0.06	0.07	2	0.04	0.05
Cystitis bacterial	1	0.03	0.03	1	0.02	0.02	2	0.02	0.03	0	0.00	0.00	0	0.00	0.00
Cystitis eschericia	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
Cystitis pseudomonal	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
Kidney infection	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	1	0.03	0.04	1	0.02	0.02
Streptococcal urinary tract infection	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
Urethritis	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Number of patients	3630			4602			8400			3522			4676		
Estimated exposure (patient-years)	3260.0			4450.7			7833.9			2759.7			4187.9		
Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Urinary tract infection enterococcal	1	0.03	0.03	1	0.02	0.02	2	0.02	0.03	0	0.00	0.00	0	0.00	0.00
Urogenital infection fungal	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
Genital infections CMQ	160	4.41	5.02	218	4.74	5.05	386	4.60	5.07	35	0.99	1.27	52	1.11	1.24
Vulvovaginal mycotic infection	20	0.55	0.61	38	0.83	0.85	59	0.70	0.75	1	0.03	0.04	4	0.09	0.09
Balanitis	26	0.72	0.80	31	0.67	0.69	60	0.71	0.76	3	0.09	0.11	6	0.13	0.14
Genital infection fungal	17	0.47	0.52	26	0.56	0.58	43	0.51	0.55	2	0.06	0.07	2	0.04	0.05
Vulvovaginal candidiasis	22	0.61	0.67	29	0.63	0.65	52	0.62	0.66	4	0.11	0.14	6	0.13	0.14
Vaginal infection	14	0.39	0.43	22	0.48	0.49	36	0.43	0.46	4	0.11	0.14	5	0.11	0.12
Balanitis candida	13	0.36	0.40	10	0.22	0.22	23	0.27	0.29	2	0.06	0.07	2	0.04	0.05
Balanoposthitis	11	0.30	0.34	10	0.22	0.22	21	0.25	0.27	0	0.00	0.00	0	0.00	0.00
Genital candidiasis	7	0.19	0.21	3	0.07	0.07	10	0.12	0.13	0	0.00	0.00	0	0.00	0.00
Genital infection	8	0.22	0.24	11	0.24	0.25	19	0.23	0.24	3	0.09	0.11	3	0.06	0.07
Genitourinary tract infection	8	0.22	0.24	4	0.09	0.09	12	0.14	0.15	2	0.06	0.07	4	0.09	0.09
Prostatitis	7	0.19	0.21	8	0.17	0.18	16	0.19	0.20	6	0.17	0.22	7	0.15	0.17
Vulvitis	5	0.14	0.15	11	0.24	0.25	16	0.19	0.20	1	0.03	0.04	1	0.02	0.02
Vulvovaginitis	4	0.11	0.12	10	0.22	0.22	14	0.17	0.18	2	0.06	0.07	3	0.06	0.07
Cervicitis	2	0.06	0.06	4	0.09	0.09	6	0.07	0.08	2	0.06	0.07	3	0.06	0.07
Epididymitis	1	0.03	0.03	2	0.04	0.04	4	0.05	0.05	3	0.09	0.11	3	0.06	0.07
Penile infection	2	0.06	0.06	2	0.04	0.04	5	0.06	0.06	0	0.00	0.00	0	0.00	0.00
Vaginitis bacterial	2	0.06	0.06	4	0.09	0.09	6	0.07	0.08	0	0.00	0.00	2	0.04	0.05
Balanoposthitis infective	0	0.00	0.00	2	0.04	0.04	2	0.02	0.03	0	0.00	0.00	0	0.00	0.00
Cellulitis of male external genital organ	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
Genital infection bacterial	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Number of patients	3630			4602			8400			3522			4676		
Estimated exposure (patient-years)	3260.0			4450.7			7833.9			2759.7			4187.9		
Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Genital infection female	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
Orchitis	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	1	0.03	0.04	1	0.02	0.02
Pelvic inflammatory disease	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	2	0.04	0.05
Prostate infection	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
Scrotal abscess	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
Urogenital infection fungal	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
Vulval abscess	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00
Vulvovaginal human papilloma virus infection	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; per 100 = events per 100 patient-years

Source: Tables 2.1.5.3: 1 and 2.1.5.4: 1 (Summary of Clinical Safety), Tables 5.12.5.2 and 5.13.5.2 (Integrated Summary of Safety)

Table 103 Incidence of Pyelonephritis and Sepsis Due to Urinary Tract Infection – SAF-5

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Number of Patients	3630			4602			8400			3522			4676		
Estimated exposure (patient-years)	3260.0			4450.7			7833.9			2759.7			4187.9		
	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Acute pyelonephritis	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	2	0.06	0.07	2	0.04	0.05
Urosepsis	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	2	0.06	0.07	2	0.04	0.05
Sepsis (with urinary tract as possible source)	3	0.08	0.09	1	0.02	0.02	4	0.05	0.05	1	0.03	0.04	1	0.02	0.02
Total	7	0.19	0.21	3	0.07	0.07	10	0.12	0.13	5	0.14	0.18	5	0.11	0.12

Empa 10 = empagliflozin 10 mg; Empa 25 ; empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; per 100 = events per 100 patient-years

Source: Tables 2.1.5.3: 2 and 2.1.5.3: 4 (Summary of Clinical Safety)

Table 104 Incidence of Fungal Urinary Tract and Genital Infections – Safety Grouping 5

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Number of patients	3630			4602			8400			3522			4676		
Estimated exposure (patient-years)	3260.0			4450.7			7833.9			2759.7			4187.9		
	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
From urinary tract infection CMQ															
Urinary tract infection fungal	6	0.2	0.18	1	< 0.1	0.02	7	< 0.1	0.09	0	0.0	0.00	0	0.0	0.00
Candiduria	2	< 0.1	0.06	1	< 0.1	0.02	3	< 0.1	0.04	0	0.0	0.00	0	0.0	0.00
Urogenital infection fungal	1	< 0.1	0.03	0	0.0	0.00	1	< 0.1	0.01	0	0.0	0.00	0	0.0	0.00
Total	9	0.2	0.28	2	< 0.1	0.04	11	0.1	0.14	0	0.0	0.00	0	0.0	0.00
From genital infections CMQ															
Vulvovaginal mycotic infection	20	0.6	0.61	38	0.8	0.85	59	0.7	0.75	1	1	0.04	4	< 0.1	0.09
Genital infection fungal	17	0.5	0.52	26	0.6	0.58	43	0.5	0.55	2	< 0.1	0.07	2	< 0.1	0.05
Vulvovaginal candidiasis	22	0.6	0.67	29	0.6	0.65	52	0.6	0.66	4	< 0.1	0.14	6	0.1	0.14
Balanitis candida	13	0.4	0.40	10	0.2	0.22	23	0.3	0.29	2	< 0.1	0.07	2	< 0.1	0.05
Genital candidiasis	7	0.2	0.21	3	< 0.1	0.07	10	0.1	0.13	0	0	0.00	0	0.00	0.00
Urogenital infection fungal	1	< 0.1	0.03	0	0.0	0.00	1	< 0.1	0.01	0	0.0	0.00	0	0.0	0.00
Total	80	2.2	2.45	106	2.3	2.38	188	2.2	2.40	9	0.3	0.33	14	0.3	0.33
From combined urinary tract and genital infections CMQ¹															
Total	88	2.4	2.70	108	2.3	2.43	198	2.4	2.53	9	0.3	0.33	14	0.3	0.33

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; per 100 = events per 100 patient-years; CMQ = customized MedDRA query

¹Preferred Term “Urogenital infection fungal” only counted once

Source: Table 102

Table 105 Incidence of Phimosis – Safety Grouping 5

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Number of patients	3630			4602			8400			3522			4676		
Estimated exposure (patient-years)	3258.2			4448.1			7827.8			2758.1			4184.4		
Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
Phimosis	8	0.22	0.25	13	0.30	0.29	21	0.30	0.27	1	0.03	0.04	1	0.02	0.02
Acquired phimosis	1	0.03	0.03	3	0.10	0.07	4	0.05	0.05	0	0.00	0.00	0	0.00	0.00
Total	9	0.25	0.28	16	0.35	0.36	25	0.3	0.32	1	0.03	0.04	1	0.02	0.02

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files

Reviewer Comments on Genital Infections/Urinary Tract Infections:

There appears to be a predilection for fungal genitourinary infections with empagliflozin use. While undesirable, these were reported as treatable with standard therapy in the development program. It may be prudent to label cautious use for those patients at risk for systemic fungal infections (i.e. immunocompromised patients).

Though the cases of genitourinary infections were treatable, overuse of antibiotics and/or antifungals and development of resistance to these therapies is a theoretical concern. Adverse reactions with antifungal therapies can be serious, and include liver injury. These theoretical concerns should not preclude approval of empagliflozin.

7.3.5.5.1 Genital Infections/Urinary Tract Infections – Four Month Safety Update

In the 4-month safety update, there are an additional eleven genitourinary infection events (0.10%) noted in the ongoing studies that support the NDA¹. Of these, two (0.02%) are events of sepsis secondary to urinary tract infections, one (0.01%) is an event of pyelonephritis, and one (0.01%) is an event of phimosis. An additional case of pyelonephritis with sepsis is noted but not included in these numbers as these events were the result of an obstructive kidney stone.

The incidence is low and does not exceed that seen with placebo in SAF-5. Treatment remains blinded for these events. No additional safety concerns are raised by this additional information.

7.3.5.6 Decreased Renal Function

Analysis of decreased renal function was performed by review of adverse event reports, and by review of laboratory data. To evaluate this event of special interest by adverse event reports, the Applicant utilized the narrow SMQ for acute renal failure (SMQ code 20000003). To evaluate this event of special interest by laboratory data, the Applicant reviewed the laboratory data to identify cases where serum creatinine was $\geq 2x$ baseline and above the upper limit of normal.

Review of the reported adverse events did not reveal a difference in the incidence of decreased renal function between the empagliflozin-treated patients and the comparator-treated patients for the entire population (Table 106). Examination of patient subgroups did show some suggestions of populations that may be at greater risk for developing decreased renal function with empagliflozin treatment. These are discussed below and also in Sections 7.5.3.1, 7.5.3.2, 7.5.3.3, and 7.5.3.4.

¹From review of listing C.1.2: 1 (4MSU)

It is noted that nine patients had the reported event of “Epidermal growth factor receptor decreased” (Table 107). Measurement of epidermal growth factor receptor was not part of any of the study protocols, and I have difficulty determining a reason why this would be measured for any of these patients. I suspect that this PT was miscoded, and should have been coded as “Glomerular filtration rate decreased”, which is part of the “Acute renal failure” SMQ. Incorporating these patients into the numbers reported above does not significantly change the above findings (Table 108).

Based on the serum creatinine criteria defined by the Applicant, there was no increased incidence of empagliflozin-treated patients developing decreased renal function (Table 109).

Certain subgroups appeared to be at greater risk for decreased renal function events. Older patients (i.e. ≥ 75 years of age) appeared to develop decreased renal function more frequently than with placebo, particularly with the 25 mg dose (Table 110). Female patients and Hispanic/Latino patients also appeared to more frequently develop decreased renal function, though there is no plausible explanation for this observation. Subjects with lower baseline eGFR by MDRD also appeared to have slightly increased risk for developing decreased renal function. None of these differences was statistically significant. The small numbers of patients with more severe renal impairment, particularly at the 10 mg dose, limit the ability to make more definitive statements regarding the role of baseline eGFR in identifying patients at risk for developing decreased renal function with empagliflozin treatment.

Table 106 Incidence of Decreased Renal Function Adverse Events – Safety Grouping 5

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Number of patients	3630			4602			8400			3522			4676		
Estimated exposure (patient-years) ¹	3260.0			4450.7			7833.9			2759.7			4187.9		
Preferred Term	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Acute renal failure SMQ	41	1.13	1.26	58	1.26	1.30	99	1.18	1.26	36	1.02	1.30	40	0.86	0.95
Oliguria	24	0.66	0.73	34	0.74	0.76	58	0.69	0.74	17	0.48	0.61	20	0.43	0.48
Renal impairment	7	0.19	0.21	12	0.26	0.27	19	0.23	0.24	11	0.31	0.40	12	0.26	0.28
Renal failure acute	9	0.25	0.27	10	0.22	0.22	19	0.23	0.24	8	0.23	0.29	8	0.17	0.19
Renal failure	0	0.00	0.00	3	0.07	0.07	3	0.04	0.04	0	0.00	0.00	0	0.00	0.00
Azotemia	1	0.03	0.03	0	0.00	0.00	1	0.01	0.01	0	0.00	0.00	0	0.00	0.00

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; per 100 = events per 100 patient-years; SMQ = standardized MedDRA query

Source: Table 2.1.5.1.1: 1 (Summary of Clinical Safety)

Table 107 Subjects with Preferred Term “Epidermal Growth Factor Receptor Decreased”

Subject ID	Treatment	Verbatim Term
1245-0019-011081	PLACEBO	REDUCED EGFR
1245-0028-080628	GLIMEPIRIDE	DECREASED EGFR
1245-0028-086455	GLIMEPIRIDE	LOW EPIDERMAL GROWTH FACTOR RECEPTOR
1245-0025- (b) (4)	EMPA 10	DECREASED EGFR
1245-0025- (b) (4)	EMPA 10	DECREASED EGFR
1245-0023-031546	EMPA 10	DECREASE IN EGFR < 60 ML/MIN/BSA
1245-0025- (b) (4)	EMPA 10	LOW EGFR
1245-0025- (b) (4)	EMPA 25	EGFR LOW
1245-0028-086862	EMPA 25	LOW EGFR

EMPA 10 = empagliflozin 10 mg; EMPA 25 = empagliflozin 25 mg

Source: Submitted AE xpt and DM xpt files

Table 108 Incidence for “Acute Renal Failure” Standardized Medical Dictionary for Regulatory Activities Query With and Without Patients from Table 107

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Number of patients	3630			4602			8400			3522			4676		
Estimated exposure (patient-years)	3260.0			4450.7			7833.9			2759.7			4187.9		
	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Acute renal failure SMQ - From Table 106	41	1.10	1.26	58	1.26	1.30	99	1.20	1.26	36	1.00	1.30	40	0.90	0.95
Acute renal failure SMQ - Including patients from Table 107	45	1.24	1.38	60	1.30	1.35	105	1.25	1.34	37	1.05	1.34	43	0.92	1.03

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; per 100 = events per 100 patient-years; SMQ = standardized MedDRA query

Source: Table 106 and Table 107 of this review

Table 109 Incidence of Decreased Renal Function Based on Serum Creatinine \geq 2x Baseline and Above Upper Limit of Reference Range – Safety Grouping 5

Empa 10		Empa 25		All Empa		Placebo		All Comp	
3630		4602		8400		3522		4676	
N	%	N	%	N	%	N	%	N	%
11	0.3	13	0.3	24	0.3	8	0.2	11	0.2

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators

Source: Table 2.10.5.9 (Integrated Summary of Safety)

Table 110 Incidence of Decreased Renal Function Adverse Events – Safety Grouping 5, by Subgroups

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
≥ 75 years of age															
Number of patients	217			272			491			237			269		
Acute renal failure SMQ	2	0.92	1.06	6	2.21	2.47	8	1.63	1.84	4	1.69	1.93	4	1.49	1.59
Renal failure acute	1	0.46	0.53	3	1.10	1.22	4	0.81	0.91	1	0.42	0.48	1	0.37	0.39
Renal impairment	1	0.46	0.53	3	1.10	1.23	4	0.81	0.92	2	0.84	0.96	2	0.74	0.80
Renal failure	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.42	0.48	1	0.37	0.40
Female patients															
Number of patients	1285			1691			3046			1303			1800		
Acute renal failure SMQ	20	1.56	1.69	21	1.24	1.29	41	1.35	1.43	7	0.54	0.70	8	0.44	0.49
Renal impairment	12	0.93	1.01	11	0.65	0.67	23	0.76	0.80	1	0.08	0.10	2	0.11	0.12
Renal failure acute	5	0.39	0.42	7	0.41	0.43	12	0.39	0.42	5	0.38	0.50	5	0.28	0.31
Renal failure	3	0.23	0.25	3	0.18	0.18	6	0.20	0.21	1	0.08	0.10	1	0.06	0.06
Azotemia	0	0.00	0.00	1	0.06	0.06	1	0.03	0.03	0	0.00	0.00	0	0.00	0.00
Hispanic/Latino															
Number of patients	452			572			1050			417			605		
Acute renal failure SMQ	6	1.33	1.73	8	1.40	1.54	14	1.33	1.60	3	0.72	0.97	5	0.83	0.96
Renal impairment	2	0.44	0.57	6	1.05	1.16	8	0.76	0.91	2	0.48	0.64	4	0.66	0.77
Renal failure	2	0.44	0.57	1	0.17	0.19	3	0.29	0.34	0	0.00	0.00	0	0.00	0.00
Renal failure acute	2	0.44	0.57	2	0.35	0.38	4	0.38	0.45	1	0.24	0.32	1	0.17	0.19
By eGFR (MDRD, ml/min/1.73 m²)															
≥ 90															
Number of patients	1079			1406			2592			956			1428		
Acute renal failure SMQ	2	0.19	0.20	3	0.21	0.22	5	0.19	0.21	3	0.31	0.42	3	0.21	0.23
Renal failure acute	0	0.00	0.00	1	0.07	0.07	1	0.04	0.04	2	0.21	0.28	2	0.14	0.20
Renal failure	1	0.09	0.10	1	0.07	0.07	2	0.08	0.08	0	0.00	0.00	0	0.00	0.00
Renal impairment	1	0.09	0.10	1	0.07	0.07	2	0.08	0.08	1	0.10	0.14	1	0.07	0.08

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
60 to < 90															
Number of patients	1991			2391			4439			1798			2442		
Acute renal failure SMQ	15	0.75	0.83	15	0.63	0.63	30	0.68	0.71	8	0.44	0.58	11	0.45	0.50
Renal impairment	8	0.40	0.44	12	0.50	0.51	20	0.45	0.47	5	0.28	0.36	7	0.29	0.32
Renal failure	4	0.20	0.22	1	0.04	0.04	5	0.11	0.12	1	0.06	0.07	1	0.04	0.05
Oliguria	1	0.05	0.06	0	0.00	0.00	1	0.02	0.02	0	0.00	0.00	0	0.00	0.00
30 to < 60															
Number of patients	548			743			1295			714			750		
Acute renal failure SMQ	22	4.01	4.69	33	4.44	5.02	55	4.25	4.87	19	2.66	3.01	20	2.67	2.97
Renal impairment	14	2.55	2.96	19	2.56	2.86	33	2.55	2.89	9	1.26	1.42	10	1.33	1.47
Renal failure	4	0.73	0.83	7	0.94	1.04	11	0.85	0.95	6	0.84	0.94	6	0.80	0.88
Renal failure acute	4	0.73	0.83	6	0.81	0.89	10	0.77	0.86	4	0.56	0.63	4	0.53	0.59
Azotemia	0	0.00	0.00	2	0.27	0.30	2	0.15	0.17	0	0.00	0.00	0	0.00	0.00
< 30															
Number of patients	7			56			63			52			52		
Acute renal failure SMQ	2	28.57	30.11	7	12.50	17.25	9	14.29	19.06	6	11.54	14.40	6	11.54	14.40
Renal failure acute	1	14.29	13.81	3	5.36	7.03	4	6.35	8.02	3	5.77	6.83	3	5.77	6.83
Renal impairment	1	14.29	14.02	2	3.57	4.68	3	4.76	6.01	2	3.85	4.62	2	3.85	4.62
Renal failure	0	0.00	0.00	1	1.79	2.35	1	1.59	1.99	1	1.92	2.35	1	1.92	2.35
Azotemia	0	0.00	0.00	1	1.79	2.31	1	1.59	1.96	0	0.00	0.00	0	0.00	0.00

Empa 10 = empagliflozin 10 mg; Empa 25 = Empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; per 100 = events per 100 patient-years; SMQ = standardized MedDRA query; eGFR = estimated glomerular filtration rate; MDRD = modification of diet in renal disease formula
Source: Tables 5.10.5.1, 5.10.5.2, 5.10.5.3, 5.10.5.5, and 5.10.5.8 (Integrated Summary of Safety)

In addition to examining serum creatinine, changes in eGFR as calculated by the MDRD equation were analyzed. Decreases in eGFR were greater with empagliflozin treatment, both numerically and by percent change (Table 111). The change in eGFR to from baseline to the last value on treatment (LVOT) was greater with the 25 mg dose than with the 10 mg dose, which in turn had a greater change than placebo. This suggests that the changes in eGFR are dependent on dose. Recovery from these changes was examined by analysis of follow-up data from Studies 1245.33, 1245.36, and 1245.48 (Table 112, Table 113, and Table 114). As was seen with the overall safety grouping SAF-5, there was a greater decrease in eGFR from baseline to LVOT with 25 mg than with 10 mg, which in turn had a greater decrease than with placebo (numerically and by percent change). Results of eGFR calculated at follow-up following cessation of empagliflozin therapy suggested that these changes were reversible.

Table 111 Change in Estimated Glomerular Filtration Rate by Modification of Diet in Renal Disease Formula – Safety Grouping 5, Treated Set

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
N	3306		4280		8186		3520		4672	
Baseline										
Mean; SD	79.82	21.63	79.28	22.53	80.25	22.02	77.22	22.83	79.82	22.13
Median; Q1, Q3	78.38	65.56, 92.94	79.06	65.52, 93.40	79.46	66.39, 94.04	76.91	62.28, 91.80	79.57	66.15, 93.86
Last value on treatment										
Mean; SD	79.11	22.66	78.17	22.98	79.32	22.71	76.74	23.34	79.05	22.39
Median; Q1, Q3	78.06	63.83, 93.07	78.34	63.57, 92.95	78.92	64.75, 93.59	76.77	61.39, 91.68	78.96	65.13, 93.20
Change from baseline to last value on treatment										
Mean; SD	-0.95	11.52	-1.49	11.79	-1.28	11.64	-0.65	11.28	-1.01	11.55
Median; Q1, Q3	-1.09	-7.44, 5.20	-1.38	-7.98, 5.34	-1.29	-7.75, 5.17	-0.33	-6.76, 5.52	-0.57	-7.35, 5.47
% change (mean) ¹	-1.19		-1.88		-1.60		-0.84		-1.27	
% change (median) ²	-1.39		-1.75		-1.62		-0.43		-0.72	

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; SD = standard deviation; Q1 = first quartile; Q3 = third quartile

¹ % change (mean) = $\text{mean}_{(\text{change})} / \text{mean}_{(\text{baseline; or last value on treatment})} \times 100$; ² % change (median) = $\text{median}_{(\text{change})} / \text{median}_{(\text{baseline; or last value on treatment})} \times 100$

Source: Table 6.5.5.2 (Integrated Summary of Safety)

Table 112 Changes in Estimated Glomerular Filtration Rate from Baseline and After Cessation of Empagliflozin Therapy – 4 Week Follow-Up, Study 1245.33

	Empa 10		Empa 25		Placebo	
N	129		120		121	
Baseline						
Mean; SD	85.11	22.81	83.32	25.14	84.97	23
Median; Q1, Q3	83.83	70.66, 97.35	82.5	66.88, 97.99	84.58	67.71, 99.79
Last value on treatment						
Mean; SD	80.56	22.81	76.96	22.58	78.94	21.28
Median; Q1, Q3	80.15	65.34, 94.51	76.09	60.75, 89.73	75.84	63.51, 94.82
Change from baseline to last value on treatment						
Mean; SD	-4.79	12.09	-5.67	13.35	-6.26	12.99
Median; Q1, Q3	-3.4	-12.38, -0.14	-5.31	-12.15, 1.19	-5.48	-12.1, -0.29
% change (mean)	-5.63		-6.81		-7.37	
% change (median)	-4.06		-6.44		-6.48	
4 week follow-up						
Mean; SD	83.74	21.7	81.35	21.8	78.36	21.4
Median; Q1, Q3	85.09	68.09, 97.24	80.4	66.48, 95.60	76.59	62.17, 92.28
Change from baseline to 4 week follow-up						
Mean; SD	-1.88	13.02	-0.79	12	-6.66	12.06
Median; Q1, Q3	-0.87	-11.2, 6.31	-0.49	-8.25, 6.25	-5.35	-13.73, -0.08
% change (mean)	-2.21		-0.95		-7.84	
% change (median)	-1.04		-0.59		-6.33	
Change from last value on treatment to 4 week follow-up						
Mean; SD	2.66	11.88	3.89	11.63	-0.18	9.51
Median; Q1, Q3	1.47	-0.04, 8.95	5.28	-0.03, 9.09	-0.03	-6.39, 6.42
% change (mean)	3.3		5.05		-0.23	
% change (median)	1.83		6.94		-0.04	

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; SD = standard deviation; Q1 = first quartile; Q3 = third quartile

Source: Table 15.3.3.1: 5 (Study 1245.33 study report)

Table 113 Changes in Estimated Glomerular Filtration Rate from Baseline and After Cessation of Empagliflozin Therapy, by Degree of Baseline Renal Impairment – 3 Week Follow-Up, Study 1245.36

- Using eGFR as calculated by MDRD formula

	Empa 10		Empa 25		Placebo	
Mild (eGFR 60 to < 90)						
N	41		38		32	
Baseline						
Mean; SD	68.42	8.23	72.01	10.84	72.24	12.68
Median; Q1, Q3	69.14	63.49, 73.03	71.36	65.39, 80.11	70.39	62.86, 81.03
Last value on treatment						
Mean; SD	68.07	11.36	66.25	13.00	70.34	11.42
Median; Q1, Q3	69.35	60.59, 77.13	67.13	61.61, 73.57	68.73	64.63, 78.95
Change from baseline to last value on treatment						
Mean; SD	-0.76	9.42	-5.67	10.37	-1.89	11.14
Median; Q1, Q3	0.13	-6.42, 5.29	-4.03	-12.45, 0.89	0.63	-6.96, 4.58
% change (mean)	-1.11		-7.87		-2.62	
% change (median)	0.19		-5.65		0.90	
Value at 3 week follow-up						
Mean; SD	69.84	11.3	73.38	13.7	68.2	11.2
Median; Q1, Q3	69.58	63.53, 78.45	73.56	65.93, 81.08	69.88	59.22, 76.40
Change from baseline to 3 week follow-up						
Mean; SD	2.06	8.91	1.28	8.89	-3.84	11.63
Median; Q1, Q3	0.09	-5.3, 8.36	3.16	-2.42, 7.15	-2.7	-6.54, 4.6
% change (mean)	3.01		1.78		-5.32	
% change (median)	0.13		4.43		-3.84	
Change from last value on treatment to 3 week follow-up						
Mean; SD	1.86	6.45	6.94	7.6	-2.17	7.04
Median; Q1, Q3	2.72	-1.90, 7.42	7.84	1.05, 11.79	-1.7	-1.7, 0.91
% change (mean)	2.73		10.48		-3.09	
% change (median)	3.92		11.68		-2.47	
Moderate (eGFR 30 to < 60)						
N			105		104	
Baseline						
Mean; SD			43.84	8.7	43.35	10.39
Median; Q1, Q3			43.07	37.75, 49.93	42.89	35.67, 49.71
Last value on treatment						
Mean; SD			40.58	10.26	43.7	11.08
Median; Q1, Q3			38.93	33.13, 48.10	44.62	34.64, 50.15
Change from baseline to last value on treatment						
Mean; SD			-3.55	6.63	0.04	7.16
Median; Q1, Q3			-3.94	-7.48, -0.12	0.62	-4.5, 4.33
% change (mean)			-8.1		0.09	
% change (median)			-9.15		1.45	
Value at 3 week follow-up						
Mean; SD			45.39	11.3	42.99	12.7
Median; Q1, Q3			43.77	37.58, 53.59	42.81	34.19, 49.20
Change from baseline to 3 week follow-up						
Mean; SD			1.48	6.7	0.16	9.14
Median; Q1, Q3			1.34	-2.9, 4.05	0.27	-3.31, 3.97
% change (mean)			3.38		0.37	
% change (median)			3.11		0.63	

	Empa 10		Empa 25		Placebo	
Change from last value on treatment to 3 week follow-up						
Mean; SD			5.16	4.49	0.21	7.2
Median; Q1, Q3			5.94	2.42, 8.52	-0.16	-3.16, 3.77
% change (mean)			12.72		0.48	
% change (median)			15.26		-0.36	
Severe (eGFR < 30)						
N			21		18	
Baseline						
Mean; SD			24.22	3.99	22.9	3.44
Median; Q1, Q3			23.42	22.18, 27.07	23	20.98, 24.40
Last value on treatment						
Mean; SD			20.23	5.86	21.8	6.36
Median; Q1, Q3			19.79	17.07, 23.92	21.48	18.91, 25.19
Change from baseline to last value on treatment						
Mean; SD			-3.98	5.8	-1.17	5.82
Median; Q1, Q3			-1.95	-7.10, 0.98	-0.29	-3.94, 0.93
% change (mean)			-16.43		-5.11	
% change (median)			-8.33		-1.26	
Value at 3 week follow-up						
Mean; SD			23.63	7.4	21.42	6.6
Median; Q1, Q3			21.18	19.53, 26.73	21.47	16.98, 24.81
Change from baseline to 3 week follow-up						
Mean; SD			-0.59	6.76	-1.48	6.03
Median; Q1, Q3			-0.45	-3.22, 2.69	-0.95	-5.36, 0.66
% change (mean)			-2.44		-6.46	
% change (median)			-1.92		-4.13	
Change from last value on treatment to 3 week follow-up						
Mean; SD			3.39	6.22	-0.34	1.34
Median; Q1, Q3			2.34	1.50, 3.25	-0.44	-1.33, 0.84
% change (mean)			16.76		-1.56	
% change (median)			11.82		-2.05	

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; SD = standard deviation; Q1 = first quartile; Q3 = third quartile; eGFR = estimated glomerular filtration rate

Source: Table 15.3.3.3.2: 4 (Study 1245.36 study report)

Table 114 Change in Estimated Glomerular Filtration Rate from Baseline and After Cessation of Empagliflozin Therapy – 2 Week Follow-Up, Study 1245.48

	Empa 10		Empa 25		Placebo	
N	241		244		238	
Baseline						
Mean; SD	83.01	16.43	83.97	17.85	84.47	17.06
Median; Q1, Q3	80.51	71.58, 92.77	82.32	72.70, 94.28	82.40	72.45, 96.26
Last value on treatment						
Mean; SD	82.7	17.11	81.24	17.61	84.16	17.95
Median; Q1, Q3	81.86	70.50, 93.69	79.30	69.67, 92.53	81.11	70.49, 96.44
Change from baseline to last value on treatment						
Mean; SD	-0.2	8.99	-2.6	9.98	-0.27	9.18
Median; Q1, Q3	-0.01	-6.02, 5.37	-2.03	-8.33, 3.86	-0.07	-6.42, 5.11
% change (mean)	-0.24		-3.1		-0.32	
% change (median)	-0.01		-2.47		-0.08	

	Empa 10		Empa 25		Placebo	
N	241		244		238	
Value at follow-up						
Mean; SD	86.25	17.1	86.6	18.2	83.52	17.4
Median; Q1, Q3	85.35	73.72, 95.92	85.54	72.25, 96.06	81.59	71.35, 94.41
Change from baseline to 2 week follow-up						
Mean; SD	3.06	10.05	2.75	9.71	-0.82	9.62
Median; Q1, Q3	3.28	-2.73, 8.22	2.65	-2.67, 7.87	-0.13	-6.05, 5.20
% change (mean)	3.69		3.27		-0.97	
% change (median)	4.07		3.22		-0.16	
Change from last value on treatment to 2 week follow-up						
Mean; SD	3.32	9.75	5.54	9.44	-0.52	9.39
Median; Q1, Q3	3.90	-2.46, 9.43	5.49	-0.02, 11.58	-1.03	-5.68, 5.21
% change (mean)	4.01		6.82		-0.62	
% change (median)	4.76		6.92		-1.27	

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; SD = standard deviation; Q1 = first quartile; Q3 = third quartile
Source: Table 15.3.3.3: 8 (Study 1245.48 study report)

Reviewer Comments on Decreased Renal Function:

Though no notable difference was seen in the reported adverse events or by elevations in serum creatinine, examination of the changes in eGFR calculated by MDRD suggests that there is a decrease in renal function with empagliflozin, particularly with the 25 mg dose (mean decrease of 1 to 6 ml/min/1.73 m², mean % decrease from 1 to 8% depending on dose and demographics). This change appears to be reversible with discontinuation of empagliflozin therapy. While a decrease in renal function in a population already at risk for renal dysfunction is clinically concerning, this apparent reversibility is reassuring that there is no direct renal toxicity from empagliflozin. Examination of subgroups suggests that there is a numerically increased incidence of renal failure adverse events for patients with age ≥ 75 years old (incidence increases from 1.26% from the overall safety population to 2.21%) and for eGFR from 30 to < 60 with the 25 mg dose (incidence increases from 1.26% from the overall safety population to 4.44%). Given this finding, caution should be exercised in using the 25 mg dose in these subgroups.

7.3.5.6.1 Decreased Renal Function – Four Month Safety Update

In the 4-month safety update, two cases concerning for decreased renal function are included in the SUSARs.

The first case was in a patient (1245-0025-^{(b) (4)}) being treated with empagliflozin 25 mg. Gradual decline in eGFR was noted following initiation of treatment with empagliflozin. At screening, eGFR was 59 ml/min/1.73 m². Twenty-nine days after initiating study drug, eGFR was noted to be 48 ml/min/1.73 m² and an event of renal insufficiency was reported. Three hundred thirty-two days after randomization, the patient was hospitalized with urinary tract

infection and worsening renal insufficiency. The calculated eGFR at that time was 31 ml/min/1.73 m². Study drug was stopped at that time. After treatment of the urinary tract infection, laboratory tests showed the eGFR to be 47 ml/min/1.73 m², and empagliflozin therapy was restarted on day 349. On day 365, eGFR was 50 ml/min/1.73 m².

The second case was in a patient (1245-0025 (b) (4)) being treated with empagliflozin 25 mg. Five hundred sixty days after randomization, a 2.2x increase from baseline creatinine was reported. No treatment was reported, and renal function remained stable at this level. The event was reported as recovered with sequelae (i.e. new diagnosis of chronic renal insufficiency). Obstructive nephrolithiasis was reported on day 632. Study drug was stopped that same day. With the obstructive nephrolithiasis, acute decrease in renal function was seen as well as development of sepsis from urinary tract infection. Both of these resolved following treatment with antibiotics, decompression, and intravenous (IV) fluids.

From review of the adverse event listing for the studies that support the NDA (Table C.1.2: 1 in the 4MSU), there are an additional ten events (0.09%) that could be considered decreased renal function events. The incidence from these studies does not exceed that seen with placebo for SAF-5. Treatment remains blinded. No additional safety concerns are raised by this additional information.

7.3.5.7 Hypoglycemic Events

Hypoglycemic events were assessed based on information recorded in the case report forms. Events did not need to be coded to the PT “Hypoglycemia” to be considered a hypoglycemic event, and investigators were instructed to record additional information on events considered to be a hypoglycemic event. Additional information collected for hypoglycemic events included the plasma glucose, symptoms, and whether external assistance was needed.

A confirmed hypoglycemic event was defined by the Applicant as an event with typical hypoglycemic symptoms and an associated plasma glucose \leq 70 mg/dL, or requiring assistance of another person. An asymptomatic hypoglycemic event was defined by the Applicant as plasma glucose between 54 mg/dL and 70 mg/dL without symptoms of hypoglycemia, and was recorded separately from the adverse events. Comparing the incidence of hypoglycemic events in SAF-5 did not demonstrate an imbalance between the empagliflozin-treated patients and the comparator-treated patients for number of events, number of severe events, minimum glucose value, time to first episode, or number of events per patient (Table 115). The Applicant has categorized hypoglycemic events by the number of episodes per patient, intensity of the worst

episode, plasma glucose range (i.e. < 70 mg/dL or < 54 mg/dL), presence or absence of symptoms, time of onset, and whether the event led to premature discontinuation. Hypoglycemic events were also analyzed by age categories, gender, race, ethnicity, and baseline renal function, and there was no apparent increase in the incidence of hypoglycemic events with empagliflozin treatment compared to placebo when considering these factors (not shown, see Tables 5.14.5.5, 5.14.5.6, 5.14.5.7, 5.14.5.8, 5.14.5.9, 5.14.5.10, 5.14.5.11, 5.14.5.12, 5.14.5.17, and 5.14.5.18 of the Integrated Summary of Safety).

For the safety grouping SAF-3, the incidence of hypoglycemic events was slightly higher with empagliflozin than with placebo (Table 116). There were no severe hypoglycemic events in any treatment arm. The majority of events were mild in intensity, and none required hospitalization.

Table 115 Incidence of Hypoglycemic Events - Safety Grouping 5, Treated Set

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	N	%	N	%	N	%	N	%	N	%
Total number of patients	3630	100	4602	100	8400	100	3522	100	4676	100
# w/ hypoglycemia	766	21.1	899	19.5	1672	19.9	771	21.9	1009	21.6
- Symptomatic	415	11.4	489	10.6	909	10.8	406	11.5	580	12.4
- Asymptomatic, reported as AE	153	4.2	157	3.4	311	3.7	151	4.3	186	4.0
- Asymptomatic, not reported as AE	524	14.4	614	13.3	1139	13.6	544	15.4	642	13.7
Severity (worst episode)										
- Requiring assistance (Severe)	12	0.3	16	0.3	28	0.3	14	0.4	15	0.3
- Symptomatic, PG < 54 mg/dL, no assistance	158	4.4	205	4.5	364	4.3	177	5.0	227	4.9
- Symptomatic, 54 mg/dL ≤ PG ≤ 70 mg/dL, no assistance	201	5.5	207	4.5	411	4.9	171	4.9	269	5.8
- Symptomatic, PG > 70 mg/dL (Relative)	19	0.5	23	0.5	42	0.5	24	0.7	35	0.7
- Symptomatic, no PG	25	0.7	38	0.8	64	0.8	21	0.6	35	0.7
- Asymptomatic, PG ≤ 70 mg/dL	348	9.6	410	8.9	760	9.0	362	10.3	426	9.1
Minimum glucose (mg/dL)										
- < 54	265	7.3	299	6.5	565	6.7	282	8.0	344	7.4
- ≥ 54, ≤ 70	462	12.7	543	11.8	1010	12.0	446	12.7	602	12.6
- > 70	25	0.7	22	0.5	47	0.6	22	0.6	33	0.7
- Not measured	14	0.4	35	0.8	50	0.6	21	0.6	30	0.6
Time to first episode (days)										
- ≤ 7	136	3.7	136	3.0	275	3.3	122	3.5	140	3.0
- > 7, ≤ 28	163	4.5	212	4.6	380	4.5	162	4.6	180	3.8
- > 28, ≤ 84	191	5.3	230	5.0	421	5.0	202	5.7	276	5.9
- > 84	276	7.6	321	7.0	596	7.1	285	8.1	413	8.8

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	N	%	N	%	N	%	N	%	N	%
Total number of patients	3630	100	4602	100	8400	100	3522	100	4676	100
# events per patient										
- 1 or 2	362	10.0	399	8.7	768	9.1	354	10.1	490	10.5
- 3 or 4	117	3.2	155	3.4	271	3.2	120	3.4	159	3.4
- 5 to 9	117	3.2	159	3.5	277	3.3	134	3.8	175	3.7
- ≥ 10	170	4.7	186	4.0	356	4.2	163	4.6	185	4.0

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; AE = adverse event; PG = plasma glucose

Source: Table 5.14.5.3 (Integrated Summary of Safety)

Table 116 Incidence of Hypoglycemic Events – Safety Grouping 3, Treated Set

	Empa 10		Empa 25		All Empa		Placebo		Sitagliptin	
	N	%	N	%	N	%	N	%	N	%
Total number of patients	830	100	822	100	1652	100	825	100	223	100
# w/ hypoglycemia	115	13.9	99	12.0	214	13.0	75	9.1	3	1.3
- Symptomatic	61	7.3	51	6.2	112	6.8	42	5.1	1	0.4
- Asymptomatic, reported as AE	15	1.8	14	1.7	29	1.8	9	1.1	0	0.0
- Asymptomatic, not reported as AE	71	8.6	58	7.1	129	7.8	47	5.7	2	0.9
Severity (worst episode)										
- Requiring assistance (Severe)	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
- Symptomatic, PG < 54 mg/dL, no assistance	15	1.8	10	1.2	25	1.5	13	1.6	0	0.0
- Symptomatic, 54 mg/dL ≤ PG ≤ 70 mg/dL, no assistance	34	4.1	27	3.3	61	3.7	18	2.2	1	0.4
- Symptomatic, PG > 70 mg/dL (Relative)	5	0.6	5	0.6	10	0.6	5	0.6	0	0.0
- Symptomatic, no PG	7	0.8	9	1.1	16	1.0	6	0.7	0	0.0
- Asymptomatic, PG ≤ 70 mg/dL	53	6.4	48	5.8	101	6.1	33	4.0	2	0.9
Minimum glucose (mg/dL)										
- < 54	23	2.8	14	1.7	37	2.2	18	2.2	0	0.0
- ≥ 54, ≤ 70	82	9.9	72	8.8	154	9.3	48	5.8	3	1.3
- > 70	5	0.6	6	0.7	11	0.7	4	0.6	0	0.0
- Not measured	5	0.6	7	0.9	12	0.7	5	0.6	0	0.0
Time to first episode (days)										
- ≤ 7	8	1.0	7	0.9	15	0.9	9	1.1	0	0.0
- > 7, ≤ 28	17	2.0	16	1.9	33	2.0	10	1.2	0	0.0
- > 28, ≤ 84	25	3.0	24	2.9	49	3.0	14	1.7	0	0.0
- > 84	65	7.8	52	6.3	117	7.1	42	5.1	3	1.3

	Empa 10		Empa 25		All Empa		Placebo		Sitagliptin	
	N	%	N	%	N	%	N	%	N	%
Total number of patients	830	100	822	100	1652	100	825	100	223	100
# events per patient										
- 1 or 2	74	8.9	62	7.5	136	8.2	46	5.6	2	0.9
- 3 or 4	21	2.5	18	2.2	39	2.4	6	0.7	0	0.0
- 5 to 9	9	1.1	10	1.2	19	1.2	13	1.6	0	0.0
- ≥ 10	11	1.3	9	1.1	20	1.2	10	1.2	1	0.4

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; AE = adverse event; PG = plasma glucose

Source: Table 5.14.3.3 (Integrated Summary of Safety)

Given that concomitant use of other antidiabetic medications would be predicted to impact the incidence of hypoglycemia, the Applicant has also evaluated hypoglycemic events by baseline background antidiabetic medication (Table 117). The incidence of hypoglycemic events increased when the background therapy included sulfonylureas or insulin, and the addition of empagliflozin appeared to increase the frequency of hypoglycemic events when added to metformin + sulfonylurea background vs. placebo. As there was no evidence of an increased incidence in the patients treated with metformin only, one can infer that it is the addition of empagliflozin to a sulfonylurea that results in the increased risk for hypoglycemia.

Table 117 Incidence of Hypoglycemia in Phase 3 Studies by Background Therapy

Background	Study	Glucose (mg/dL)	Empa 10		Empa 25		Placebo	
			n/N	%	n/N	%	n/N	%
None	1245.20	≤ 70	1/224	0.4	1/223	0.4	1/229	0.4
		< 54	0/224	0.0	0/223	0.0	0/229	0.0
	1245.31 _{mono}	≤ 70	2/224	0.9	2/223	0.9	2/229	0.9
		< 54	0/224	0.0	0/223	0.0	1/229	0.4
Metformin	1245.23 _{met}	≤ 70	4/217	1.8	3/214	1.4	1/206	0.5
		< 54	3/217	1.4	1/214	0.5	1/206	0.5
	1245.31 _{met}	≤ 70	6/217	2.8	4/214	1.9	3/206	1.5
		< 54	3/217	1.4	1/214	0.5	3/206	1.5
	1245.28	≤ 70	NA	NA	15/765	2.0	NA	NA
		< 54	NA	NA	10/765	1.3	NA	NA
Pioglitazone +/- metformin	1245.19	≤ 70	2/165	1.2	4/168	2.4	3/165	1.8
		< 54	2/165	1.2	1/168	0.6	1/165	0.6
	1245.31 _{pio+/-met}	≤ 70	3/165	1.8	5/168	3.0	4/165	2.4
		< 54	2/165	1.2	1/168	0.6	2/165	1.2
Metformin + sulfonylurea	1245.23 _{met+SU}	≤ 70	36/224	16.1	25/217	11.5	19/225	8.4
		< 54	13/224	5.8	9/217	4.1	7/225	3.1
	1245.31 _{met+SU}	≤ 70	45/224	20.1	33/217	15.2	27/225	12.0
		< 54	17/224	7.6	11/217	5.1	12/225	5.3

Background	Study	Glucose (mg/dL)	Empa 10		Empa 25		Placebo	
			n/N	%	n/N	%	n/N	%
Basal insulin +/- metformin/SU	1245.33	≤ 70	61/169	36.1	56/155	36.1	60/170	35.3
		< 54	37/169	21.9	36/155	23.2	39/170	22.9
		Assistance	0/169	0.0	2/155	1.3	0/170	0.0
Any background	1245.25	≤ 70	291/1623	17.9	274/1632	16.8	246/1619	15.2
		< 54	160/1623	9.9	150/1632	9.2	147/1619	9.1
		Assistance	11/1623	0.7	9/1632	0.6	88/1619	0.5
	1245.36	≤ 70	26/98	26.5	88/321	27.4	88/319	27.6
		< 54	18/98	18.4	61/321	19.0	56/319	17.6
		Assistance	1/98	1.0	5/321	1.6	6/319	1.9
	1245.48	≤ 70	18/276	6.5	17/276	6.2	13/272	4.8
		< 54	12/276	4.3	12/276	4.3	7/272	2.6

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; NA = not applicable; SU = sulfonylurea
Source: Table 2.1.5.5: 1 (Summary of Clinical Safety)

7.3.5.7.1 Hypoglycemic Events – Four Month Safety Update

No additional information on hypoglycemic events is reported in the 4-month safety update.

7.3.5.8 Malignancy Events

The Applicant explored malignancy events using a CMQ which included the “Malignant and unspecified tumors” SMQ (SMQ code 20000091) and the “Malignancy related conditions” SMQ (SMQ code 20000092), excluding the PT “Acanthosis nigricans”. Malignancy events were analyzed for all malignancy events, and for events occurring after six months for patients treated for greater than six months. Given that malignancies typically have a long latency period for development, examining the malignancy events occurring after six months of treatment in patients treated for greater than six months may give a more accurate perspective of the risk for malignancy events associated with empagliflozin use. A slight increase in the overall incidence of all malignancy events and in the incidence of malignancy events occurring after six months of treatment was noted (Table 118). For the safety grouping SAF-3, there was only a small number of malignancy events occurring after six months of treatment (0.2% for Empa 10; 0.6% for Empa 25; 0.2% for placebo; 0.4% for sitagliptin) with no single Preferred Term was reported more than once. The focus of this section will be on SAF-5 where the larger number of patients and events allows for a more credible comparison.

Table 118 Incidence of Malignancy Events – Safety Grouping 5

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	N	%	N	%	N	%	N	%	N	%
Number of patients	3630	100	4602	100	8400	100	3522	100	4676	100
All malignancies	37	1.02	51	1.11	89	1.06	32	0.91	42	0.90
Malignancies with onset \geq 6 months after initiation of study drug	22	0.61	25	0.54	49	0.58	16	0.45	25	0.53

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators

Source: Tables 5.17.5.1 and 5.17.5.2 (Integrated Summary of Safety)

While there was only a slight difference in the overall incidence of malignancy events between groups, there were notable imbalances for specific types of malignancies. Using MedDRA High Level Terms (HLTs), there were more events in the “Skin melanomas (excl ocular)” and “Respiratory tract and pleural neoplasm malignant cell type unspecified NEC” HLT for the empagliflozin-treated patients compared to the comparator-treated patients (six vs. zero for “Skin melanomas (excl ocular)”, five vs. zero for “Respiratory tract and pleural neoplasm malignancy cell type unspecified NEC”) (Table 119).

Other HLTs for which there were no cases in the all comparator group were “Bile duct neoplasm malignant”, “Oropharyngeal, nasopharyngeal and tonsillar neoplasms malignant and unspecified”, “Bladder neoplasms malignant”, and “Thyroid neoplasm malignant”. For each of these terms, there were only two cases in the All Empa group compared to none in the all comparator group, making it more difficult to exclude chance as a cause for the imbalance.

Table 119 Incidence of Selected Malignancy Events (by High Level Term and Preferred Term) Occurring After ≥ 6 Months of Treatment – Safety Grouping 5

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
N	3630			4602			8400			3522			4676		
HLT - PT	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100	N	%	Per 100
Any malignancy	22	0.61	1.34	25	0.54	1.05	49	0.58	1.19	16	0.45	1.11	25	0.53	1.05
Skin melanomas (excl ocular)	2	0.06	0.12	4	0.09	0.17	6	0.07	0.15	0	0.00	0.00	0	0.00	0.00
- Malignant melanoma	2	0.06	0.12	3	0.07	0.13	5	0.06	0.12	0	0.00	0.00	0	0.00	0.00
- Malignant melanoma in situ	0	0.00	0.00	1	0.02	0.04	1	0.01	0.02	0	0.00	0.00	0	0.00	0.00
Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	2	0.06	0.12	2	0.04	0.00	5	0.06	0.05	0	0.00	0.00	0	0.00	0.00
- Lung neoplasm malignant	2	0.06	0.12	1	0.02	0.04	3	0.04	0.07	0	0.00	0.00	0	0.00	0.00
- Bronchial carcinoma	0	0.00	0.00	1	0.02	0.04	1	0.01	0.02	0	0.00	0.00	0	0.00	0.00
- Lung cancer metastatic	0	0.00	0.00	0	0.00	0.00	1	0.01	0.02	0	0.00	0.00	0	0.00	0.00
Bladder neoplasms malignant	1	0.03	0.06	0	0.00	0.00	2	0.02	0.02	0	0.00	0.00	0	0.00	0.00
- Bladder cancer	1	0.03	0.06	0	0.00	0.00	2	0.02	0.05	0	0.00	0.00	0	0.00	0.00
Bile duct neoplasms malignant	1	0.03	0.06	1	0.02	0.04	2	0.02	0.05	0	0.00	0.00	0	0.00	0.00
- Bile duct cancer	1	0.03	0.06	1	0.02	0.04	2	0.02	0.05	0	0.00	0.00	0	0.00	0.00
Oropharyngeal, nasopharyngeal and tonsillar neoplasm malignant and unspecified	1	0.03	0.06	1	0.02	0.04	2	0.02	0.05	0	0.00	0.00	0	0.00	0.00
- Nasopharyngeal cancer	1	0.03	0.06	1	0.02	0.04	2	0.02	0.05	0	0.00	0.00	0	0.00	0.00
Thyroid neoplasms malignant	0	0.00	0.00	2	0.04	0.08	2	0.02	0.05	0	0.00	0.00	0	0.00	0.00
- Thyroid cancer	0	0.00	0.00	2	0.04	0.08	2	0.02	0.05	0	0.00	0.00	0	0.00	0.00

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; HLT = MedDRA High Level Term; PT = MedDRA Preferred Term; per 100 = events per 100 patient-years
Source: Table 2.1.5.8: 1 (SCS) and Table 5.17.5.17 (ISS)

There is no clear mechanistic explanation for the observed imbalance in lung neoplasms or melanomas. The Applicant suggests that the increased incidence of these malignancy events is due to factors other than exposure to empagliflozin. Further discussion of the lung neoplasm and melanoma cases follows.

Lung neoplasms:

Review of the submitted AE.xpt files identifies two additional cases in which there was an onset of a lung cancer adverse event after six months from randomization that were not included in the Applicant's summary. The first case (patient 1245-0033-004331) appears to have been excluded as the defined TS and treatment-emergent adverse event (TEAE) period was for up to seven days after last dose of study medication. Additionally, the patient was not exposed to study drug for greater than six months, which the Applicant used as a criteria for identifying cases. This patient had discontinuation at day 167 (just shy of six months), and the lung cancer event occurred at day 193. The second case (patient 1245-0023-034564) fell into a separate HLT ("Non-small cell neoplasms malignant of the respiratory tract cell type specified"). Inclusion of these cases brings the total number of cases to seven.

Table 120 Subjects with Lung Neoplasm Diagnosis > 6 Months after Randomization – Safety Grouping 5

Patient ID	Treatment Arm	Days since Randomization	Preferred Term	Diagnosis on Pathology Report
1245-0020-020704	Empa 25	472	Bronchial carcinoma	Invasive squamous cell carcinoma
1245-0023-034564 ¹	Empa 25	371	Lung squamous cell carcinoma stage unspecified	Small cell lung cancer
1245-0025-(b) (4)	Empa 10	241	Lung neoplasm malignant	Poorly differentiated squamous cell carcinoma
1245-0025-(b) (4)	Empa 25	427	Lung neoplasm malignant	Keratinizing squamous epithelium carcinoma
1245-0033-004331 ²	Empa 10	193	Lung neoplasm malignant	Undifferentiated bronchial adenocarcinoma
1245-0033-006859	Empa 10	461	Lung neoplasm malignant	Carcinoma, pavement cell in situ
1245-0038-809006 ³	Empa 10	194	Lung cancer metastatic	NA
Empa 25 = empagliflozin 25 mg; Empa 10 = empagliflozin 10 mg; NA = not applicable ¹ Not included in Applicant's Table 2.1.5.8: 4 or in Table 119 above as this was coded to the "Non-small cell neoplasms malignant of the respiratory tract cell type specified" High Level Term; ² Not included in Applicant's Table 2.1.5.8: 4 as lung cancer event occurred > 7 days after last dose of study medication and the patient was only exposed to study drug for 167 days; ³ Was not a case of lung cancer, but was a case of colon cancer that was metastatic to the lung Source: Table 2.1.5.8: 4 (Summary of Clinical Safety), and submitted AE xpt and DM xpt files, Additional information submitted in the Sponsor's August 16, 2013 Response to Information Request (NDA-204629, SD-18, eCTD-0016)				

Reviewing the supplied narratives for these cases provides some additional information. One patient (patient 1245-0038-809006) appears to be misclassified. Though coded as a case of metastatic lung cancer, review of the narrative reveals that it to be a case of colon cancer with metastases to the lung. Another patient (Patient 1245-0023-034564) had a baseline history of squamous cell lung cancer treated with surgical resection five years before randomization to empagliflozin. The adverse event was a recurrence of prior disease 371 days after randomization.

From review of the supplied narratives and from additional information provided by the Applicant on August 16, 2013 in response to a request for information, all of the patients (excluding Patient 1245-0038-006859) had baseline risk factors for the development of lung cancer (Table 121). All of the patients were either current or prior smokers. One case (Patient 1245-0023-034564) had a prior history of lung cancer. One case (Patient 1245-0020-020704) had a history of asbestos exposure and a family history of lung cancer. Additionally, there was no consistent single cellular type across all of these patients. This also speaks against the lung cancers being a result of empagliflozin treatment.

Table 121 Lung Cancer Risk Factors

Patient ID	Risk factors
1245-0020-020704	Smoker, asbestos exposure, family history of lung cancer
1245-0023-034564	Smoker, prior history of squamous cell lung cancer
1245-0025- (b) (4)	Prior smoker
1245-0025- (b) (4)	Prior smoker
1245-0033-004331	Smoker
1245-0033-006859	Smoker

Note: Subject 1245-0038-809066 not included. Event was colon cancer with metastasis to lungs.

Source: August 16, 2013 Response to Information Request (NDA-204629, SD-18, eCTD-0016)

Assuming that this additional history provides an alternative explanation that is sufficient to exclude empagliflozin as the causative factor, there remain no patients in the empagliflozin-treated arms resulting in no imbalance.

Melanomas:

For melanoma, there were six patients with events occurring greater than six months after randomization (Table 122).

Table 122 Subjects with Melanoma Diagnosis > 6 Months after Randomization – Safety Grouping 5

Patient ID	Treatment Arm	Days since randomization	Preferred Term
1245-0010-003402	Empa 25	238	Malignant melanoma
1245-0025- (b) (4)	Empa 10	236	Malignant melanoma
1245-0025- (b) (4)	Empa 25	216	Malignant melanoma
1245-0025- (b) (4)	Empa 10	345	Malignant melanoma
1245-0028-080040	Empa 25	351	Malignant melanoma in situ
1245-0036-001815	Empa 25	233	Malignant melanoma

Empa 25 = empagliflozin 25 mg; Empa 10 = empagliflozin 10 mg

Source: Table 2.1.5.8: 4 (Summary of Clinical Safety), and submitted AE xpt and DM xpt files

From review of the supplied narratives and from additional information provided by the Applicant on August 16, 2013 in response to a request for information, the majority of these patients had baseline risk factors for the development of melanoma (Table 123).

Table 123 Melanoma Risk Factors

Patient ID	Risk factors
1245-0010-003402	Prior melanoma
1245-0025- (b) (4)	Prior melanoma, prior basal cell carcinoma
1245-0025- (b) (4)	History of sun damaged skin
1245-0025- (b) (4)	None
1245-0028-080040	Prior basal cell carcinoma, prior squamous cell carcinoma, family history of basal cell carcinoma, history of acute lymphoblastic leukemia
1245-0036-001815	None

Source: August 16, 2013 Response to Information Request (NDA-204629, SD-18, eCTD-0016)

Assuming that this additional history provides an alternative explanation that is sufficient to exclude empagliflozin as the causative factor, there remain two patients in the empagliflozin-treated arms compared to zero in the comparator-treated arms. From these amended numbers it is difficult to conclude that empagliflozin treatment resulted in the development of melanoma. Additionally, there are no data (either clinical or preclinical) to suggest that there is increased phototoxicity associated with empagliflozin use. As discussed above for lung neoplasm, the small number of events taken in conjunction with a lack of plausible mechanism does not support a causative role for empagliflozin in the development of melanomas.

The Office of Hematology and Oncology Products were consulted regarding the imbalance in lung cancers and melanomas. In the consult response by Dr. Jennie Chang, she notes that the

cases of lung cancer occurred in high-risk individuals. The incidence of 150 cases per 100,000 patient-years is higher than the 61.4 cases per 100,000 patient-years in the general population but less than the 600 cases per 100,000 patient-years expected in a high-risk population. For melanoma, Dr. Chang again notes that the cases of melanoma occurred in high-risk individuals. The incidence of 120 cases per 100,000 patient-years is higher than the 21.1 cases per 100,000 patient-years for the general population. The incidence in high-risk individuals is not known. She concludes that that it is unclear whether these events are truly associated with empagliflozin and makes recommendations regarding additional postmarketing surveillance and nonclinical studies (Figure 24).

Figure 24 Excerpt from Dr. Jennie Chang's Consult Review

IV. CONCLUSION

In conclusion, whether the cases of melanoma and lung cancer associated with administration of empagliflozin is a true signal or a chance finding is unclear. Considering the uncertainties in the data available to assess the risk of developing melanoma and NSCLC in patients exposed to empagliflozin, we recommend the following:

1. Boehringer Ingelheim should collect data in a clinical trial on the relative risk and risk difference of lung cancer and melanoma in patients exposed to empagliflozin versus placebo in a clinical trial setting with a median duration of follow up of at least 5 years, in which risk factors are collected. Detailed information on the histopathological diagnosis and molecular characteristics of all observed cases of lung cancer and melanoma should be collected.
2. Consider a consultation with Office of Surveillance and Epidemiology (OSE) for a pharmacovigilance review of the data on empagliflozin exposure and lung cancer and melanoma in the postmarketing setting. A pharmacovigilance review should also be conducted for comparison for canagliflozin as it is in the same therapeutic class as empagliflozin.
3. Boehringer Ingelheim should consider conducting mechanistic studies to better understand the potential risk of empagliflozin-induced malignant transformation.

For details of her consult, see Dr. Chang's consult review submitted to DARRTS on October 17, 2013.

7.3.5.8.1 Malignancies – Four Month Safety Update

In the 4-month safety update, additional cases of malignancy events are reported. Two additional case of lung cancer are reported, and two additional cases of melanoma are reported. Treatment remains blinded for these patients, but the small number of additional cases for these malignancies does not raise any additional safety concerns.

Other malignancies reported in more than two patients from this update include prostate cancer (n=10; 0.09%), renal carcinoma (n=7; 0.06%), basal cell carcinoma (n=6; 0.05%), bladder cancer (n=4; 0.04%), and breast cancer (n=3; 0.03%)¹. Treatment remains blinded for these cases. The overall incidence for each of these is low and not markedly different from the reported incidence for placebo in SAF-5 (0.09% for prostate “Prostatic neoplasms malignant” HLT; “0.06% for “Renal neoplasms malignant” HLT; 0.06% for “Basal cell carcinoma” PT; 0.00% for “Bladder neoplasms malignant” HLT; 0.03% for “Breast and nipple neoplasms malignant” HLT)². No additional safety concerns are raised from this data.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

In the safety grouping SAF-5, the overall incidence of treatment-emergent adverse events (TEAEs) was similar for all groups (68.1% Empa 10; 69.5% Empa 25; 68.6% placebo; Table 124). The most common PTs were “Nasopharyngitis”, “Urinary tract infection”, “Hypoglycaemia”, and “Hyperglycaemia”. For the safety grouping SAF-3, the overall incidence of TEAEs was similar between all groups (71.8% Empa 10; 70.1% Empa 25; 74.1% placebo; Table 125). The PT “Hypoglycaemia” was reported with a higher incidence in the empagliflozin-treated patients than in the placebo-treated patients.

In SAF-5, the SOC of “Renal and urinary disorder” and “Reproductive system and breast disorder” were reported more frequently in the empagliflozin-treated patients than in the patients treated with comparators (Table 126). PTs occurring in $\geq 1\%$ of empagliflozin-treated patients with a greater frequency than in comparators were “Thirst”, “Pollakiuria”, “Polyuria”, and “Vulvovaginal pruritus”.

¹From review of listing C.1.2: 1 of the 4MSU

²From review of table 2.1.5.8: 1 (SCS)

For SAF-3, the SOC's of "Skin and subcutaneous disorders", "Renal and urinary disorders", "Gastrointestinal disorders", "Nervous system disorders", Reproductive system and breast disorders", and "Respiratory, thoracic and mediastinal disorders" were reported more frequently in the empagliflozin-treated patients than in the placebo-treated patients (Table 127). Preferred Terms reported with a greater frequency in the empagliflozin-treated patients were "Hypoglycaemia", "Pollakiuria", "Toothache", "Muscle spasms", "Hypercholesterolaemia", "Vulvovaginal pruritus", "Thirst", "Hypertriglyceridaemia", "Paraesthesia", "Polyuria", and "Weight decreased".

Given the mechanism of action for empagliflozin, the increased frequency of some of these terms (e.g. "Thirst", "Polyuria", "Pollakiuria", "Hypoglycemia") in the empagliflozin patients could be plausibly attributed to empagliflozin treatment.

Table 124 Adverse Events (by Preferred Term), Occurring in > 5% of Any Group – Safety Grouping 5, Treated Set

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
# of patients (N)	3630			4602			8400			3522			4676		
System Organ Class - Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
# of patients w/ AE	2472	68.1	174.6	3199	69.5	169.0	5785	68.9	173.7	2418	68.6	211.6	3291	70.4	194.1
Infections and infestations	1152	31.7	46.0	1569	34.1	46.7	2765	32.9	46.5	1059	30.1	49.4	1495	32.0	47.0
- Nasopharyngitis	288	7.9	9.3	348	7.6	8.2	660	7.9	8.9	233	6.6	8.8	342	7.3	8.6
- Urinary tract infections	276	7.6	8.9	352	7.6	8.3	632	7.5	8.5	236	6.7	8.9	325	7.0	8.1
Metabolism and nutrition disorders	809	22.3	30.1	979	21.3	26.1	1807	21.5	27.6	971	27.6	45.1	1384	29.6	42.8
- Hypoglycemia	489	13.5	16.8	546	11.9	13.5	1043	12.4	14.7	476	13.5	19.4	662	14.2	17.9
- Hyperglycemia	155	4.3	4.9	215	4.7	5.0	372	4.4	4.9	364	10.3	14.1	525	11.2	13.5

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; per 100 = events per 100 patient-years; AE = adverse event

Source: Table 2.1.1.1: 1 (Summary of Clinical Safety) and Table 5.2.5.2 (Integrated Summary of Safety)

Table 125 Adverse Events (by Preferred Term), Occurring in > 5% of Any Group – Safety Grouping 3, Treated Set

	Empa 10			Empa 25			Placebo			Sitagliptin		
# of patients (N)	830			822			825			223		
System Organ Class - Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
# of patients w/ AE	596	71.8	179.52	576	70.1	169.31	611	74.1	204.86	145	65.0	144.07
Infections and infestations	298	35.9	51.48	298	36.3	52.28	303	36.7	58.11	65	29.1	40.86
- Nasopharyngitis	91	11.0	12.59	75	9.1	10.47	80	9.7	12.22	21	9.4	11.26
- Urinary tract infections	90	10.8	12.31	67	8.2	9.24	81	9.8	12.23	14	6.3	7.27
- Upper respiratory tract infection	34	4.1	4.44	56	6.8	7.61	55	6.7	8.19	13	5.8	6.75

	Empa 10			Empa 25			Placebo			Sitagliptin		
# of patients (N)	830			822			825			223		
System Organ Class - Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
Metabolism and nutrition disorders	190	22.9	28.62	163	19.8	24.58	266	32.2	47.85	44	19.7	25.03
- Hyperglycemia	46	5.5	5.99	37	4.5	4.95	179	21.7	29.15	24	10.8	12.80
- Hypoglycemia	64	7.7	8.64	50	6.1	6.87	44	5.3	6.48	1	0.4	0.50
- Dyslipidemia	42	5.1	5.51	34	4.1	4.54	39	4.7	5.69	6	2.7	3.03

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; per 100 = events per 100 patient-years; AE = adverse event

Source: Table 2.1.1.1: 3 (Summary of Clinical Safety) and Table 5.2.3.2 (Integrated Summary of Safety)

Table 126 Treatment-Emergent Adverse Events (by System Organ Class and Preferred Term), Occurring in $\geq 1\%$ of Patients of the All Empagliflozin Group and Occurring More Frequently Among Empagliflozin-Treated Patients than Among Placebo-Treated Patients - Safety Grouping 5, Treated Set

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total number of patients	3630			4602			8400			3522			4676		
Estimated exposure	3258.2			4448.1			7827.8			2758.1			4184.4		
System Organ Class - Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
Metabolism and nutrition disorders	885	24.4	77.5	1084	23.6	74.9	1969	23.4	75.1	1115	31.7	122.2	1115	23.9	104.9
Infections and infestations	1653	45.5	60.7	2265	49.2	61.0	3918	46.6	60.9	1455	41.3	61.9	1455	31.1	58.2
- Nasopharyngitis	289	8.0	11.1	360	7.8	10.3	679	8.1	10.9	238	6.8	10.7	346	7.4	10.6
- Urinary tract infection	259	7.1	10.9	328	7.1	9.5	594	7.1	10.0	228	6.5	10.7	313	6.7	9.6
- Sinusitis	45	1.2	1.5	56	1.2	1.5	103	1.2	1.5	35	1.0	1.4	51	1.1	1.3
- Pharyngitis	36	1.0	1.3	54	1.2	1.3	93	1.1	1.3	28	0.8	1.1	54	1.2	1.5
Gastrointestinal disorders	734	20.2	24.2	982	21.3	23.7	1716	20.4	24.2	702	19.9	28.5	702	15.0	27.6
- Vomiting	49	1.4	1.8	58	1.3	1.4	108	1.3	1.6	37	1.1	1.6	55	1.2	1.5
- Gastritis	35	1.0	1.1	62	1.4	1.5	100	1.2	1.4	30	0.9	1.2	50	1.1	1.3
- Abdominal pain upper	41	1.1	1.4	43	0.9	1.1	88	1.1	1.3	33	0.9	1.3	53	1.1	1.4

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total number of patients	3630			4602			8400			3522			4676		
Estimated exposure	3258.2			4448.1			7827.8			2758.1			4184.4		
System Organ Class - Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
Musculoskeletal and connective tissue disorders	665	18.3	21.9	931	20.2	22.4	1596	19.0	22.2	654	18.6	25.6	654	14.0	25.9
- Osteoarthritis	44	1.2	1.5	50	1.1	1.2	95	1.1	1.3	38	1.1	1.4	61	1.3	1.6
Nervous system disorders	504	13.9	20.1	691	15.0	18.7	1195	14.2	19.3	515	14.6	23.2	515	11.0	22.2
General disorders and administration site conditions	355	9.8	13.0	478	10.4	12.2	833	9.9	12.7	412	11.7	16.8	412	8.8	15.3
- Thirst	35	1.0	1.2	62	1.4	1.5	105	1.3	1.5	2	0.1	0.1	4	0.1	0.1
- Fatigue	53	1.5	1.9	50	1.1	1.2	103	1.2	1.5	41	1.2	1.6	66	1.4	1.7
Renal and urinary disorders	351	9.7	11.3	447	9.7	10.5	798	9.5	11.1	266	7.6	9.9	266	5.7	8.2
- Pollakiuria	83	2.3	2.7	101	2.2	2.4	203	2.4	2.7	31	0.9	1.1	40	0.9	1.0
- Polyuria	40	1.1	1.3	48	1.0	1.1	93	1.1	1.2	9	0.3	0.3	12	0.3	0.3
Investigations	344	9.5	11.3	389	8.5	9.2	733	8.7	10.2	380	10.8	14.4	380	8.1	12.6
Skin and subcutaneous tissue disorders	250	6.9	8.4	425	9.2	10.6	675	8.0	9.9	259	7.4	10.6	259	5.5	9.6
- Pruritus	33	0.9	1.0	58	1.3	1.4	96	1.1	1.3	27	0.8	1.3	38	0.8	1.1
Injury, poisoning and procedural complications	293	8.1	9.2	394	8.6	9.5	687	8.2	9.5	313	8.9	12.2	313	6.7	11.5
Respiratory, thoracic and mediastinal disorders	231	6.4	7.8	320	7.0	7.6	551	6.6	7.7	346	9.8	13.7	346	7.4	12.0
Cardiac disorders	221	6.1	7.1	283	6.2	7.0	504	6.0	7.0	345	9.8	13.1	345	7.4	9.7
Vascular disorders	186	5.1	6.1	274	6.0	6.6	460	5.5	6.4	254	7.2	10.0	254	5.4	9.3
Reproductive system and breast disorders	197	5.4	6.8	248	5.4	6.1	445	5.3	6.4	81	2.3	3.0	81	1.7	3.1
- Vulvovaginal pruritus	35	1.0	1.2	49	1.1	1.2	85	1.0	1.2	3	0.1	0.1	6	0.1	0.1
Eye disorders	154	4.2	5.0	221	4.8	5.3	375	4.5	5.2	173	4.9	6.7	173	3.7	6.2
Psychiatric disorders	115	3.2	3.7	155	3.4	3.6	270	3.2	3.6	139	4.0	5.6	139	3.0	5.6
Blood and lymphatic system disorders	91	2.5	2.8	106	2.3	2.5	197	2.4	2.6	120	3.4	4.6	120	2.6	3.9

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total number of patients	3630			4602			8400			3522			4676		
Estimated exposure	3258.2			4448.1			7827.8			2758.1			4184.4		
System Organ Class - Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	76	2.1	2.4	94	2.0	2.2	170	2.0	2.3	67	1.9	2.4	67	1.4	2.3
Ear and labyrinth disorders	58	1.6	1.8	102	2.2	2.5	160	1.9	2.2	64	1.8	2.3	64	1.4	2.5
Hepatobiliary disorders	43	1.2	1.4	86	1.9	2.0	129	1.5	1.7	55	1.6	2.0	55	1.2	2.2
Surgical and medical procedures	42	1.2	1.3	44	1.0	1.1	86	1.0	1.2	42	1.2	1.6	42	0.9	1.2

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files, and individual study reports

Table 127 Treatment-Emergent Adverse Events (by System Organ Class and Preferred Term), Occurring in $\geq 1\%$ of Patients of the All Empagliflozin Group and Occurring More Frequently Among Empagliflozin-Treated Patients than Among Placebo-Treated Patients - Safety Grouping 3, Treated Set

	Empa 10			Empa 25			All Empa			Placebo			Sitagliptin		
Total number of patients	830			822			1652			825			223		
Estimated exposure	783.9			761.7			1546.5			699.2			199.4		
System Organ Class - Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
Infections and infestations	298	35.9	51.48	298	36.3	52.28	596	36.1	51.88	303	36.7	58.11	65	29.1	40.86
- Nasopharyngitis	91	11.0	12.59	75	9.1	10.47	166	10.0	11.53	80	9.7	12.22	21	9.4	11.26
- Urinary tract infection	90	10.8	12.31	67	8.2	9.24	157	9.5	10.78	81	9.8	12.23	14	6.3	7.27
- Upper respiratory infection	34	4.1	4.44	56	6.8	7.61	90	5.4	5.99	55	6.7	8.19	13	5.8	6.75
- Bronchitis	22	2.7	2.84	17	2.1	2.25	39	2.4	2.55	19	2.3	2.73	6	2.7	3.06
- Sinusitis	15	1.8	1.92	11	1.3	1.45	26	1.6	1.69	8	1.0	1.14	6	2.7	3.05
- Influenza	15	1.8	1.93	20	2.4	2.66	35	2.1	2.29	17	2.1	2.44	3	1.3	1.50
- Gastroenteritis	13	1.6	1.67	12	1.5	1.58	25	1.5	1.63	13	1.6	1.86	3	1.3	1.51
- Pharyngitis	11	1.3	1.41	7	0.9	0.92	18	1.1	1.17	13	1.6	1.86	1	0.4	0.50

	Empa 10			Empa 25			All Empa			Placebo			Sitagliptin		
Total number of patients	830			822			1652			825			223		
Estimated exposure	783.9			761.7			1546.5			699.2			199.4		
System Organ Class – Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
– Asymptomatic bacteriuria	6	0.7	0.76	11	1.3	1.45	17	1.0	1.10	10	1.2	1.43	1	0.4	0.50
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	5	0.6	0.64	14	1.7	1.84	19	1.2	1.23	13	1.6	1.85	2	0.9	1.00
Blood and lymphatic system disorders	23	2.8	2.95	29	3.5	3.88	52	3.1	3.41	38	4.6	5.52	4	1.8	2.02
– Anemia	10	1.2	1.28	9	1.1	1.18	19	1.2	1.23	22	2.7	3.15	0	0.0	0.00
Endocrine disorders	8	1.0	1.02	8	1	1.05	16	1.0	1.04	7	0.8	1.00	4	1.8	2.01
Metabolism and nutrition disorders	190	22.9	28.62	163	19.8	24.58	353	21.4	26.6	266	32.2	47.85	44	19.7	25.03
– Hyperglycemia	46	5.5	5.99	37	4.5	4.95	83	5.0	5.48	179	21.7	29.15	24	10.8	12.8
– Hypoglycemia	64	7.7	8.64	50	6.1	6.87	114	6.9	7.76	44	5.3	6.48	1	0.4	0.5
– Dyslipidemia	42	5.1	5.51	34	4.1	4.54	76	4.6	5.03	39	4.7	5.69	6	2.7	3.03
– Hypercholesterolemia	10	1.2	1.28	10	1.2	1.31	20	1.2	1.30	3	0.4	0.43	4	1.8	2.01
– Hyperlipidemia	8	1.0	1.02	12	1.5	1.58	20	1.2	1.30	11	1.3	1.57	3	1.3	1.51
– Hypertriglyceridemia	5	0.6	0.64	10	1.2	1.32	16	1.0	1.04	0	0.0	0.00	1	0.4	0.5
Psychiatric disorders	23	2.8	2.97	22	2.7	2.93	45	2.7	2.95	23	2.8	3.32	10	4.5	5.1
Nervous system disorders	94	11.3	13.01	108	13.1	15.63	202	12.2	14.29	91	11.0	14.00	16	7.2	8.31
– Dizziness	24	2.9	3.12	35	4.3	4.70	59	3.6	3.90	26	3.2	3.77	6	2.7	3.02
– Headache	32	3.9	4.17	30	3.6	4.03	62	3.8	4.10	30	3.6	4.36	3	1.3	1.51
– Paraesthesia	7	0.8	0.89	9	1.1	1.18	16	1.0	1.04	1	0.1	0.14	1	0.4	0.50
Eye disorders	35	4.2	4.54	20	2.4	2.66	55	3.3	3.61	32	3.9	4.65	6	2.7	3.04
Ear and labyrinth disorders	20	2.4	2.58	13	1.6	1.71	33	2.0	2.15	13	1.6	1.86	8	3.6	4.11
– Vertigo	12	1.4	1.54	5	0.6	0.65	17	1.0	1.10	4	0.5	0.57	4	1.8	2.01
Cardiac disorders	26	3.1	3.35	35	4.3	4.66	61	3.7	4.00	35	4.2	5.06	8	3.6	4.08
Vascular disorders	39	4.7	5.11	29	3.5	3.87	68	4.1	4.50	40	4.8	5.85	18	8.1	9.53
– Hypertension	22	2.7	2.84	16	1.9	2.12	38	2.3	2.48	30	3.6	4.36	10	4.5	5.15
Respiratory, thoracic and mediastinal disorders	49	5.9	6.52	42	5.1	5.67	91	5.5	6.10	40	4.8	5.85	17	7.6	8.95
– Cough	20	2.4	2.59	12	1.5	1.58	32	1.9	2.09	13	1.6	1.85	4	1.8	2.01

	Empa 10			Empa 25			All Empa			Placebo			Sitagliptin		
Total number of patients	830			822			1652			825			223		
Estimated exposure	783.9			761.7			1546.5			699.2			199.4		
System Organ Class – Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
Gastrointestinal disorders	145	17.5	21.12	112	13.6	16.3	257	15.6	18.71	123	14.9	19.48	35	15.7	19.45
– Diarrhea	29	3.5	3.76	19	2.3	2.52	48	2.9	3.15	25	3.0	3.62	5	2.2	2.52
– Constipation	13	1.6	1.67	7	0.9	0.92	20	1.2	1.30	17	2.1	2.44	9	4.0	4.59
– Nausea	21	2.5	2.72	11	1.3	1.45	32	1.9	2.09	14	1.7	2.00	1	0.4	0.50
– Toothache	16	1.9	2.05	7	0.9	0.92	23	1.4	1.49	7	0.8	1.00	0	0.0	0.00
– Vomiting	12	1.4	1.54	10	1.2	1.31	22	1.3	1.43	9	1.1	1.29	1	0.4	0.50
– Dyspepsia	11	1.3	1.41	9	1.1	1.18	20	1.2	1.30	8	1.0	1.14	2	0.9	1.00
– Gastritis	11	1.3	1.41	8	1.0	1.05	19	1.2	1.23	10	1.2	1.43	3	1.3	1.50
Hepatobiliary disorders	9	1.1	1.15	15	1.8	1.98	24	1.5	1.55	17	2.1	2.45	4	1.8	2.01
Skin and subcutaneous disorders	53	6.4	7.05	72	8.8	9.97	125	7.6	8.48	43	5.2	6.33	17	7.6	9.03
– Pruritus	11	1.3	1.41	14	1.7	1.84	25	1.5	1.62	8	1.0	1.14	3	1.3	1.51
Musculoskeletal and connective tissue disorders	124	14.9	17.56	137	16.7	20.26	261	15.8	18.88	127	15.4	20.5	44	19.7	25.84
– Back pain	30	3.6	3.89	29	3.5	3.89	59	3.6	3.89	30	3.6	4.38	12	5.4	6.20
– Arthralgia	29	3.5	3.76	23	2.8	3.06	52	3.1	3.41	22	2.7	3.18	6	2.7	3.04
– Pain in extremity	12	1.4	1.53	10	1.2	1.31	22	1.3	1.43	13	1.6	1.86	6	2.7	3.04
– Myalgia	10	1.2	1.28	9	1.1	1.18	19	1.2	1.23	10	1.2	1.43	5	2.2	2.51
– Osteoarthritis	17	2.0	2.19	12	1.5	1.58	29	1.8	1.89	15	1.8	2.15	3	1.3	1.51
– Musculoskeletal pain	9	1.1	1.15	9	1.1	1.18	18	1.1	1.16	16	1.9	2.30	3	1.3	1.52
– Muscle spasms	9	1.1	1.15	12	1.5	1.58	21	1.3	1.36	7	0.8	1.00	1	0.4	0.50
Renal and urinary disorders	67	8.1	9.06	57	6.9	7.83	124	7.5	8.45	44	5.3	6.47	8	3.6	4.12
– Pollakiuria	16	1.9	2.07	13	1.6	1.72	29	1.8	1.9	4	0.5	0.57	1	0.4	0.50
– Polyuria	8	1	1.03	9	1.1	1.18	17	1.0	1.1	0	0.0	0.00	1	0.4	0.50
Reproductive system and breast disorders	41	4.9	5.4	38	4.6	5.12	79	4.8	5.26	25	3.0	3.63	4	1.8	2.01
– Vulvovaginal pruritus	10	1.2	1.28	9	1.1	1.18	19	1.2	1.23	3	0.4	0.43	0	0.0	0.00

	Empa 10			Empa 25			All Empa			Placebo			Sitagliptin		
Total number of patients	830			822			1652			825			223		
Estimated exposure	783.9			761.7			1546.5			699.2			199.4		
System Organ Class – Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
General disorders and administration site conditions	78	9.4	10.62	62	7.5	8.58	140	8.5	9.61	72	8.7	10.81	14	6.3	7.28
– Fatigue	20	2.4	2.58	7	0.9	0.92	27	1.6	1.76	12	1.5	1.71	2	0.9	1.00
– Asthenia	11	1.3	1.41	12	1.5	1.58	23	1.4	1.49	13	1.6	1.86	3	1.3	1.51
– Thirst	10	1.2	1.28	10	1.2	1.32	20	1.2	1.3	0	0.0	0.00	0	0.0	0.00
Investigations	68	8.2	9.07	70	8.5	9.61	138	8.4	9.33	96	11.6	14.75	15	6.7	7.78
– Weight decreased	3	0.4	0.38	13	1.6	1.71	16	1.0	1.04	2	0.2	0.28	0	0.0	0.00
Injury, poisoning and procedural complications	57	6.9	7.6	52	6.3	7.15	109	6.6	7.38	55	6.7	8.14	10	4.5	5.14

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; per 100 = events per 100 patient-years

Source: Table 5.2.3.1 (Integrated Summary of Safety)

As was done with the nonfatal SAEs, adverse events reported by patients in SAF-5 were evaluated in additional subsets that excluded patients in Study 1245.25, and that excluded patients from studies with interim data only.

Excluding those patients at high risk for CV events (i.e. the patients in Study 1245.25) from SAF-5 yielded results similar to what was seen with the entire SAF-5 population. The SOC “Renal and urinary disorder”, and “Reproductive system and breast disorder” were reported with greater frequency in the empagliflozin-treated patients (either 10 mg or 25 mg dose) than in the comparator-treated patients (Table 128). In addition to these SOC, the SOC “Infections and infestations” was reported with greater frequency in the empagliflozin-treated patients than in comparator-treated patients. The PTs “Thirst”, “Pollakiuria”, “Polyuria”, and “Vulvovaginal pruritus” were again reported with greater frequency in the empagliflozin-treated patients than in the comparator-treated patients (Table 128). In the SOC “Infections and infestations”, the increased incidence of this SOC in the empagliflozin-treated patients appears to be a results of several PTs, all relating to upper airway infections (i.e. “Nasopharyngitis”, “Sinusitis”, and “Pharyngitis”).

For the completed studies in SAF-5, the findings are again similar to the entire SAF-5 grouping. The events in the SOC of “Infections and infestations”, “Renal and urinary disorders” SOC, and “Reproductive system and breast disorder” were reported with a higher incidence in the empagliflozin-treated patients (either 10 mg or 25 mg dose) compared to the comparator-treated patients (Table 129). The increased incidence in the “Infections and infestations” SOC again appears to be due to upper airway infections (PTs “Nasopharyngitis”, “Sinusitis”, and “Pharyngitis”). The PT “Vulvovaginal pruritus” is not reported by $\geq 1\%$ of empagliflozin-treated patients, but the other terms (“Thirst”, “Pollakiuria”, and “Polyuria”) are again noted to be reported with a greater frequency in the empagliflozin-treated patients.

Table 128 Treatment-Emergent Adverse Events (by System Organ Class and Preferred Term), Occurring in $\geq 1\%$ of Patients of the All Empagliflozin Group and Occurring More Frequently Among Empagliflozin-Treated Patients than Among Placebo-Treated Patients - Safety Grouping 5 Excluding Study 1245.25

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total number of patients	1799			2759			4962			1741			2893		
Estimated exposure	1114.3			2302			3536.5			1067.3			2434		
System Organ Class – Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
Infections and infestations	978	54.4	107.1	1624	58.9	85.3	2675	53.9	91.4	822	47.2	92.3	1442	49.8	70.5
– Nasopharyngitis	223	12.4	25.8	297	10.8	16.9	550	11.1	20.0	173	9.9	20.8	281	9.7	15.2
– Urinary tract infection	148	8.2	18.2	222	8.1	12.1	377	7.6	13.8	145	8.3	17.8	230	8.0	12.2
– Bronchitis	39	2.2	4.3	64	2.3	3.3	106	2.1	3.6	39	2.2	4.0	85	2.9	4.1
– Gastroenteritis	28	1.6	3.1	51	1.9	2.4	83	1.7	2.6	30	1.7	3.0	56	1.9	2.5
– Sinusitis	31	1.7	3.1	45	1.6	2.4	78	1.6	2.6	18	1.0	1.7	34	1.2	1.5
– Pharyngitis	26	1.5	2.9	46	1.7	2.2	75	1.5	2.4	18	1.0	1.8	44	1.5	2.1
Metabolism and nutrition disorders	453	25.2	105.9	670	24.3	85.4	1143	23.0	89.5	598	34.4	152.4	1066	36.9	108.8
Gastrointestinal disorders	412	22.9	40.1	701	25.4	33.0	1166	23.5	35.6	372	21.4	39.2	706	24.4	32.3
– Nausea	43	2.4	4.2	73	2.7	3.5	119	2.4	3.7	36	2.1	3.8	59	2.0	2.7
– Vomiting	26	1.5	2.8	47	1.7	2.3	74	1.5	2.4	20	1.2	2.3	38	1.3	1.8
– Abdominal pain upper	26	1.5	2.4	34	1.2	1.7	64	1.3	2.0	15	0.9	1.6	35	1.2	1.6
– Gastritis	16	0.9	1.6	40	1.5	1.9	59	1.2	1.8	18	1.0	1.8	38	1.3	1.6
– Toothache	24	1.3	2.3	25	0.9	1.3	53	1.1	1.7	13	0.8	1.2	24	0.8	1.0
Musculoskeletal and connective tissue disorders	393	21.9	37.8	654	23.7	30.3	1075	21.7	32.5	353	20.3	35.6	694	24.0	31.0
– Back pain	80	4.5	7.6	129	4.7	6.0	216	4.4	6.5	69	4.0	7.0	135	4.7	6.1
– Arthralgia	60	3.3	6.2	80	2.9	4.0	144	2.9	4.7	60	3.5	6.1	120	4.2	5.6
– Pain in extremity	34	1.9	3.4	52	1.9	2.4	87	1.8	2.6	30	1.7	3.0	56	1.9	2.5
– Osteoarthritis	29	1.6	2.8	38	1.4	1.8	68	1.4	2.1	25	1.4	2.4	48	1.7	2.1
Nervous system disorders	264	14.7	33.9	465	16.9	24.1	754	15.2	27.2	259	14.9	32.2	473	16.4	26.0
– Headache	64	3.6	10.1	127	4.6	6.2	197	4.0	7.5	64	3.7	9.1	119	4.1	6.7

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
Total number of patients	1799			2759			4962			1741			2893		
Estimated exposure	1114.3			2302			3536.5			1067.3			2434		
System Organ Class – Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
General disorders and administration site conditions	194	10.8	22.2	313	11.3	15.9	528	10.6	18.0	183	10.5	19.7	325	11.2	16.0
– Thirst	31	1.7	3.1	50	1.8	2.3	89	1.8	2.7	1	0.1	0.1	3	0.1	0.1
– Asthenia	25	1.4	4.3	31	1.1	2.0	57	1.2	2.7	18	1.0	3.1	34	1.2	2.6
Renal and urinary disorders	191	10.6	17.9	283	10.3	12.6	504	10.2	14.7	131	7.5	12.6	198	6.8	8.4
– Pollakiuria	51	2.8	4.9	74	2.7	3.3	144	2.9	4.3	16	0.9	1.5	25	0.9	1.1
– Polyuria	28	1.6	2.6	31	1.1	1.4	64	1.3	1.9	2	0.1	0.2	5	0.2	0.2
Skin and subcutaneous tissue disorders	144	8.0	14.2	299	10.8	14.6	470	9.5	14.7	131	7.5	14.2	235	8.1	10.7
Investigations	198	11.0	19.7	254	9.2	11.5	469	9.5	14.3	219	12.6	22.0	346	12.0	15.0
Injury, poisoning and procedural complications	189	10.5	17.3	270	9.8	12.5	479	9.7	14.2	152	8.7	15.0	284	9.8	12.5
– Fall	26	1.5	2.3	32	1.2	1.7	61	1.2	1.9	15	0.9	1.6	24	0.8	1.1
Respiratory, thoracic and mediastinal disorders	110	6.1	11.0	217	7.9	10.1	335	6.8	10.3	169	9.7	17.4	278	9.6	12.6
Reproductive system and breast disorders	118	6.6	11.7	179	6.5	8.6	308	6.2	9.6	48	2.8	4.5	93	3.2	3.9
– Vulvovaginal pruritus	21	1.2	2.0	33	1.2	1.6	55	1.1	1.7	3	0.2	0.3	6	0.2	0.3
Eye disorders	84	4.7	8.0	164	5.9	7.5	254	5.1	7.6	85	4.9	8.7	153	5.3	6.9
Vascular disorders	78	4.3	7.5	145	5.3	6.9	233	4.7	7.1	115	6.6	12.0	220	7.6	9.9
Cardiac disorders	78	4.3	7.5	118	4.3	5.6	205	4.1	6.3	108	6.2	10.3	147	5.1	6.2
Psychiatric disorders	65	3.6	6.2	110	4.0	5.0	175	3.5	5.2	58	3.3	6.1	131	4.5	6.0
Blood and lymphatic system disorders	41	2.3	3.7	72	2.6	3.3	115	2.3	3.3	68	3.9	6.8	97	3.4	4.5
Ear and labyrinth disorders	32	1.8	2.9	74	2.7	3.3	109	2.2	3.2	34	2.0	3.2	69	2.4	3.0
Hepatobiliary disorders	26	1.5	2.5	63	2.3	2.8	90	1.8	2.6	32	1.8	3.1	66	2.3	2.8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	28	1.6	2.6	60	2.2	2.7	89	1.8	2.6	36	2.1	3.4	64	2.2	2.7

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files, and individual study reports

Table 129 Treatment-Emergent Adverse Events (by System Organ Class and Preferred Term), Occurring in $\geq 1\%$ of Patients of the All Empagliflozin Group and Occurring More frequently Among Empagliflozin-Treated Patients than Among Placebo-Treated Patients – Safety Grouping 5, Completed Studies Only

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
# of subjects	1798			2000			4421			1740			2112		
Estimated exposure	909.1			1080.1			2108			884			1019		
System Organ Class – Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
Infections and infestations	804	44.7	104.8	946	47.3	103.9	1823	41.2	102.1	662	38.1	87.2	782	37.0	89.0
– Nasopharyngitis	185	10.3	24.8	208	10.4	24.5	423	9.6	24.7	141	8.1	19.3	171	8.1	20.5
– Urinary tract infection	126	7.0	17.9	135	6.8	15.4	268	6.1	15.9	113	6.5	16.5	130	6.2	16.3
– Upper respiratory tract infection	73	4.1	10.0	100	5.0	11.9	175	4.0	10.5	77	4.4	11.5	89	4.2	11.2
– Bronchitis	27	1.5	3.4	38	1.9	4.1	68	1.5	3.7	27	1.6	3.4	40	1.9	4.3
– Sinusitis	24	1.3	2.9	25	1.3	2.8	51	1.2	2.8	15	0.9	1.7	20	1.0	2.0
– Pharyngitis	22	1.2	2.8	20	1.0	2.2	45	1.0	2.5	14	0.8	1.7	16	0.8	1.7
Metabolism and nutrition disorders	391	21.8	118.8	463	23.2	153.3	874	19.8	130.8	495	28.5	166.6	560	26.5	152.1
– Hypoglycemia	169	9.4	89.9	220	11.0	126.8	398	9.0	104.2	192	11.0	126.0	203	9.6	110.6
Gastrointestinal disorders	351	19.5	41.6	418	20.9	41.9	822	18.6	41.9	310	17.8	39.5	389	18.4	42.3
– Nausea	39	2.2	4.6	41	2.1	4.2	83	1.9	4.3	32	1.8	4.2	42	2.0	4.6
– Abdominal pain upper	22	1.2	2.5	21	1.1	2.3	47	1.1	2.5	11	0.6	1.5	14	0.7	1.7
– Vomiting	21	1.2	2.9	25	1.3	2.7	47	1.1	2.7	19	1.1	2.6	20	1.0	2.4
– Dyspepsia	17	1.0	2.1	25	1.3	2.7	44	1.0	2.4	16	0.9	1.8	22	1.0	2.2
Musculoskeletal and connective tissue disorders	317	17.6	37.1	370	18.5	36.2	715	16.2	35.9	306	17.6	36.9	361	17.1	38.4
– Back pain	62	3.5	7.0	77	3.9	7.7	146	3.3	7.3	60	3.5	7.4	71	3.4	7.7
– Pain in extremity	25	1.4	3.2	28	1.4	2.7	54	1.2	2.8	27	1.6	3.1	32	1.5	3.3
– Osteoarthritis	20	1.1	2.3	25	1.3	2.3	46	1.0	2.2	18	1.0	2.2	23	1.1	2.5
Nervous system disorders	216	12.0	35.1	270	13.5	29.1	511	11.6	31.4	226	13.0	34.3	261	12.4	33.2
– Headache	55	3.1	10.9	77	3.9	7.5	138	3.1	9.0	58	3.3	9.4	65	3.1	8.8

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
# of subjects	1798			2000			4421			1740			2112		
Estimated exposure	909.1			1080.1			2108			884			1019		
System Organ Class – Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
General disorders and administration site conditions	167	9.3	23.5	188	9.4	20.4	376	8.5	21.8	158	9.1	20.8	182	8.6	20.7
– Thirst	31	1.7	3.6	35	1.8	3.5	74	1.7	3.8	1	0.1	0.1	1	0.1	0.1
– Fatigue	30	1.7	4.3	16	0.8	1.6	46	1.0	2.7	19	1.1	2.4	25	1.2	2.9
Renal and urinary disorders	162	9.0	18.2	182	9.1	17.3	374	8.5	18.2	112	6.4	13.0	130	6.2	13.2
– Pollakiuria	49	2.7	5.5	53	2.7	5.2	121	2.7	6.0	16	0.9	1.8	18	0.9	1.8
– Polyuria	28	1.6	3.1	19	1.0	1.9	52	1.2	2.5	2	0.1	0.2	3	0.1	0.3
Investigations	175	9.7	21.2	172	8.6	16.8	364	8.2	18.6	181	10.4	21.5	214	10.1	22.1
Injury, poisoning and procedural complications	165	9.2	18.6	156	7.8	15.7	341	7.7	17.0	123	7.1	14.7	151	7.2	16.2
– Fall	24	1.3	2.6	18	0.9	2.1	45	1.0	2.4	14	0.8	1.8	15	0.7	1.7
Skin and subcutaneous tissue disorders	125	7.0	14.9	187	9.4	19.7	339	7.7	17.8	121	7.0	15.8	139	6.6	15.6
Respiratory, thoracic and mediastinal disorders	91	5.1	10.8	127	6.4	12.7	226	5.1	11.5	150	8.6	18.6	171	8.1	18.3
Reproductive system and breast disorders	106	5.9	12.8	93	4.7	9.3	210	4.8	10.8	36	2.1	4.1	47	2.2	4.6
Eye disorders	65	3.6	7.5	97	4.9	9.5	168	3.8	8.4	67	3.9	8.0	81	3.8	8.4
Cardiac disorders	68	3.8	7.7	79	4.0	7.9	156	3.5	7.8	92	5.3	10.6	104	4.9	10.4
Vascular disorders	61	3.4	7.3	79	4.0	7.9	150	3.4	7.6	103	5.9	12.9	127	6.0	13.7
Psychiatric disorders	56	3.1	6.6	58	2.9	5.6	114	2.6	5.7	52	3.0	6.6	64	3.0	6.9
Blood and lymphatic system disorders	31	1.7	3.4	48	2.4	4.6	81	1.8	3.9	58	3.3	6.7	64	3.0	6.4
Ear and labyrinth disorders	21	1.2	2.3	37	1.9	3.4	61	1.4	2.9	27	1.6	3.1	35	1.7	3.6
Hepatobiliary disorders	18	1.0	2.1	40	2.0	3.7	59	1.3	2.9	27	1.6	3.2	43	2.0	4.5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	25	1.4	2.9	32	1.6	3.1	58	1.3	2.9	28	1.6	3.2	34	1.6	3.3

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators; per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files, and individual study reports

In the proposed label, the Applicant presents the adverse reaction/clinical studies experience based on the pivotal studies (1245.19, 1245.20, 1245.23_{met}, and 1245.23_{met+SU}) at 24 weeks and the add-on to basal insulin study (1245.33) at 18 weeks rather than from the larger safety grouping SAF-5. While this grouping is smaller and covers a shorter exposure than SAF-5, the findings are consistent with that observed for the larger safety grouping. Looking at the aggregate of the treatment-emergent adverse events for this group of studies, the increased frequency of events in the “Renal and urinary disorder” and “Reproductive system and breast disorder” SOC with empagliflozin treatment is again apparent (Table 130). Individual PTs where there is an increase in frequency with empagliflozin treatment are “Pollakiuria”, “Polyuria”, “Thirst”, “Vulvovaginal pruritus”, “Hypoglycaemia”, “Urinary tract infection”, and “Dry mouth”.

Table 130 Treatment-Emergent Adverse Events (by System Organ Class and Preferred Term) in $\geq 1\%$ of Either Empagliflozin Dose and Occurring More Frequently Among Empagliflozin-Treated Patients than Among Placebo-Treated Patients – Pool of Pivotal Studies (at 24 Weeks) and Add-On to Basal Insulin Study (at 18 Weeks)

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
Number of patients	999		977		1976		995		1218	
Total with adverse events	625	62.56	609	62.33	1234	62.45	633	63.62	752	61.74
	N	%	N	%	N	%	N	%	N	%
System Organ Class										
– Preferred Term										
Infections and infestations	265	26.53	255	26.10	520	26.32	244	24.52	289	23.73
– Bronchitis	13	1.30	9	0.92	22	1.11	10	1.01	13	1.07
– Gastroenteritis	13	1.30	10	1.02	23	1.16	9	0.90	11	0.90
– Sinusitis	11	1.10	9	0.92	20	1.01	7	0.70	11	0.90
– Upper respiratory tract infection	31	3.10	39	3.99	70	3.54	38	3.82	48	3.94
– Urinary tract infection	82	8.21	60	6.14	142	7.19	58	5.83	69	5.67
Metabolism and nutrition disorders	186	18.62	162	16.58	348	17.61	230	23.12	261	21.43
– Dyslipidemia	39	3.90	28	2.87	67	3.39	34	3.42	40	3.28
– Hypoglycemia	78	7.81	79	8.09	157	7.95	63	6.33	64	5.25
Gastrointestinal disorders	124	12.41	97	9.93	221	11.18	107	10.75	128	10.51
– Constipation	14	1.40	8	0.82	22	1.11	12	1.21	21	1.72
– Dry mouth	3	0.30	10	1.02	13	0.66	1	0.10	1	0.08
– Nausea	23	2.30	11	1.13	34	1.72	14	1.41	14	1.15
– Toothache	10	1.00	3	0.31	13	0.66	5	0.50	5	0.41
Musculoskeletal and connective tissue disorders	96	9.61	111	11.36	207	10.48	110	11.06	140	11.49
– Arthralgia	24	2.40	22	2.25	46	2.33	22	2.21	26	2.13
General disorders and administration site conditions	64	6.41	59	6.04	123	6.22	61	6.13	73	5.99
– Asthenia	10	1.00	12	1.23	22	1.11	13	1.31	16	1.31
– Fatigue	19	1.90	6	0.61	25	1.27	11	1.11	13	1.07
– Thirst	15	1.50	12	1.23	27	1.37	0	0.00	0	0.00

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
Number of patients	999		977		1976		995		1218	
Total with adverse events	625	62.56	609	62.33	1234	62.45	633	63.62	752	61.74
	N	%	N	%	N	%	N	%	N	%
System Organ Class										
– Preferred Term										
Renal and urinary disorders	59	5.91	57	5.83	116	5.87	33	3.32	40	3.28
– Pollakiuria	19	1.90	15	1.54	34	1.72	5	0.50	6	0.49
– Polyuria	14	1.40	10	1.02	24	1.21	1	0.10	2	0.16
Skin and subcutaneous tissue disorders	45	4.50	57	5.83	102	5.16	48	4.82	63	5.17
Reproductive system and breast disorders	41	4.10	33	3.38	74	3.74	15	1.51	19	1.56
– Vulvovaginal pruritus	11	1.10	8	0.82	19	0.96	3	0.30	3	0.25
Respiratory, thoracic and mediastinal disorders	41	4.10	32	3.28	73	3.69	39	3.92	50	4.11
– Cough	14	1.40	12	1.23	26	1.32	11	1.11	11	0.90
Injury, poisoning and procedural complications	44	4.40	39	3.99	83	4.20	40	4.02	48	3.94
Psychiatric disorders	25	2.50	16	1.64	41	2.07	22	2.21	29	2.38

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators

Source: Table 15.3.2.1: 2 (Study 1245.19 study report), 15.3.2.1: 2 (Study 1245.20 study report, Tables 15.1.3.2.1: 2 and 15.2.3.2.1: 2 (Study 1245.23 study report), and 15.4.4: 2 (Study 1245.33 study report)

7.4.2 Laboratory Findings

Laboratory test data were analyzed based on the first treatment assignment. A “treated set” (TS) was defined as all patients with at least one dose of randomized study medication. A “treated set actual” was used for analysis of adverse events assessed as drug-related with the actual study medication taken at the time of the adverse event defining the treatment assignment.

Several differences in laboratory findings were noted in the empagliflozin development program and will be discussed further.

7.4.2.1 Increases in Hematocrit

There was a small increase in hematocrit from baseline to last value on treatment in the empagliflozin groups (Table 131). This was not seen in either the comparator or placebo groups. An effect on hematocrit with empagliflozin treatment was also seen when examining the proportion of patients with shifts in hematocrit from within the reference range (WRR) to above the upper limit of the reference range (ULRR) (Table 132). The increase in hematocrit with empagliflozin treatment appears reversible with discontinuation of treatment.

Table 131 Median Change from Baseline – Hematocrit, Treated Set

	Empa 10	Empa 25	All Empa	Placebo	All Comp
SAF-5					
# of patients with hematocrit data	3041	3964	7600	3219	4336
Baseline					
- Median	41.7	41.7	41.7	41.7	41.7
- Q1,Q3	38.6, 45.2	38.8, 45.2	38.8, 45.2	38.6, 44.6	38.8, 45.2
Last value on treatment					
- Median	44.5	44.5	44.5	41.7	41.7
- Q1, Q3	41.7, 48.1	41.7, 48.8	41.7, 48.8	37.4, 44.5	38.6, 44.5
Difference					
- Median	2.8	2.8	2.8	0.0	0.0
- Q1, Q3	0.0, 5.7	1.3, 5.7	0.7, 5.7	-2.6, 1.4	-2.8, 1.4
SAF-3					
# of patients with hematocrit data	802	787	1589	776	214
Baseline					
- Median	43.1	42.5	43.1	41.7	44.5
- Q1,Q3	38.8, 45.9	38.8, 45.2	38.8, 45.9	38.8, 45.9	41.2, 45.9
Last value on treatment					
- Median	44.5	44.5	44.5	41.7	42.5
- Q1, Q3	41.7, 47.3	41.7, 47.8	41.7, 47.8	38.6, 44.5	38.8, 45.9

	Empa 10	Empa 25	All Empa	Placebo	All Comp
Difference					
- Median	2.8	2.8	2.8	-1.3	-1.4
- Q1, Q3	0.0, 4.3	0.0, 5.7	0.0, 5.1	-2.8, 1.4	-2.8, 1.4

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = All randomized comparators; SAF-5 = Safety Grouping 5; Q1 = first quartile; Q3 = third quartile; SAF-3 = Safety Grouping 3
Source: Table 3.1: 1 (Summary of Clinical Safety) and Table 6.2.3.1 (Integrated Summary of Safety)

Table 132 Incidence of Selected Categorical Shifts – Hematocrit, SAF-5, Treated Set

Baseline value	Last Value on Treatment		
	Below LLRR	WRR	Above ULRR
	%	%	%
SAF-5			
Empa 10 (N=3310)			
- Below LLRR	34.4	65.6	0.0
- WRR	2.0	94.2	3.8
Empa 25 (N=4285)			
- Below LLRR	32.6	67.4	0.0
- WRR	2.1	93.5	4.4
All Empa (N=8196)			
- Below LLRR	33.6	66.4	0.0
- WRR	1.9	93.7	4.3
Placebo (N=3522)			
- Below LLRR	67.3	32.7	0.0
- WRR	6.4	93.1	0.5
All Comp (N=4676)			
- Below LLRR	64.7	35.3	0.0
- WRR	6.1	93.4	0.5
SAF-3			
Empa 10 (N=830)			
- Below LLRR	26.3	73.7	0.0
- WRR	0.5	98.3	1.2
Empa 25 (N=822)			
- Below LLRR	19.0	81.0	0.0
- WRR	0.5	98.6	0.8
All Empa (N=1652)			
- Below LLRR	22.5	77.5	0.0
- WRR	0.5	98.5	1.0

Baseline value	Last Value on Treatment		
	Below LLRR	WRR	Above ULRR
	%	%	%
Placebo (N=825)			
- Below LLRR	56.5	43.5	0.0
- WRR	2.6	97.0	0.4
Sitagliptin (N=223)			
- Below LLRR	50.0	50.0	0.0
- WRR	1.4	98.6	0.0

LLRR = lower limit of reference range; WRR = within reference range; ULRR = upper limit of reference range; Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = All randomized comparators; SAF-5 = Safety Grouping 5; SAF-3 = Safety Grouping 3
Source: Tables 6.1.3.1 and 6.1.5.1 (Integrated Summary of Safety)

While the laboratory data suggest that there is an increase in hematocrit with empagliflozin treatment, the significance of this change in hematocrit is unclear.

Possible complications from elevations in hematocrit are an increase in thromboembolic events and vascular events (e.g. stroke). For discussion of stroke events, see 7.3.5.1. Based on adverse event reports for the combination of the PTs “thrombosis”, “deep vein thrombosis”, “venous thrombosis”, “venous thrombosis limb”, and “pulmonary embolus” to explore potential effects of this change, no increase in thromboembolic events is seen with empagliflozin treatment (Table 133). No thromboembolic events were reported in SAF-3.

Table 133 Incidence of Thromboembolic Events - Safety Grouping 5

	Empa 10	Empa 25	All Empa	Placebo	All Comp
# of patients	3630	4602	8400	3522	4676
Exposure (days)					
- Mean	327.8	353	340.4	286	326.9
- SD	173.7	176.2	181.2	169.8	183.2
# with thromboembolic events¹, N (%)	3 (< 0.1)	4 (< 0.1)	7 (< 0.1)	8 (0.2)	8 (< 0.1)
Incidence rate/100 patient-years	0.09	0.09	0.09	0.29	0.19
Events by Preferred Term, N (%)					
- Deep vein thrombosis	0 (0.0)	3 (< 0.1)	3 (< 0.1)	3 (< 0.1)	3 (< 0.1)
- Pulmonary embolism	0 (0.0)	0 (0.0)	0 (0.0)	3 (< 0.1)	3 (< 0.1)
- Thrombosis	2 (< 0.1)	1 (< 0.1)	3 (< 0.1)	2 (< 0.1)	2 (< 0.1)
- Venous thrombosis	1 (< 0.1)	0 (0.0)	1 (< 0.1)	0 (0.0)	0 (0.0)
- Venous thrombosis limb	0 (0.0)	0 (0.0)	0 (0.0)	1 (< 0.1)	1 (< 0.1)

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = All randomized comparators; SD = standard deviation

¹includes the Preferred Terms (PTs) “Deep vein thrombosis”, “Pulmonary embolus”, “Thrombosis”, “Venous thrombosis”, and “Venous thrombosis limb”

Source: Table 3.1: 2 (Summary of Clinical Safety)

These findings are similar to those seen in the canagliflozin development program.

7.4.2.2 Electrolytes

For evaluation of electrolytes, changes in serum sodium, potassium, calcium, magnesium, chloride, phosphate, and bicarbonate were examined. No significant change in median values from baseline was noted for any of these laboratory tests (Table 134). Looking at shifts in laboratory value categories, there was a slightly higher percentage of empagliflozin-treated patients who shifted from WRR to above ULRR for serum phosphate (Table 135). There was also a slightly higher percentage of empagliflozin-treated patients who shifted from WRR to below LLRR for serum bicarbonate. A difference in serum phosphate was also seen in the percentage of empagliflozin-treated patients with potentially clinically significant abnormal results¹, specifically with high serum phosphate (Table 136). A difference was also seen between the empagliflozin-treated patients versus comparator-treated patients for serum bicarbonate, with a greater percentage of empagliflozin-treated patients with possibly clinically significant low serum bicarbonate. These findings appeared to have dose dependency, occurring in a higher percentage of patients in the Empa 25 group than the Empa 10 group.

¹Defined in 8.4.2 of the submitted Integrated Summary of Efficacy as:

Sodium < 130 or > 160 mEq/L

Potassium < 3.0 or > 6.0 mEq/L

Calcium < 7.2 or > 12.0 mg/dL

Chloride < 80 or > 120 mEq/L

Phosphate < 2.2 or > 5.3 mg/dL

Bicarbonate < 18 or > 32 mEq/L

Not defined for magnesium

Table 134 Median Change from Baseline – Electrolytes, Treated Set

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3
SAF-5										
Sodium (mEq/L)	N=3058		N=3974		N=7628		N=3233		N=4354	
- Baseline	141	140, 142	141	140, 142	141	140, 142	141	140, 142	141	140, 142
- LVOT	141	140, 142	141	140, 142	141	140, 142	141	140, 142	141	140, 142
- Change	0	-1, 1	0	-1, 1	0	-1, 1	0	-1, 1	0	-1, 1
Potassium (mEq/L)	N=3058		N=3972		N=7626		N=3232		N=4353	
- Baseline	4.2	4.0, 4.4	4.2	4.0, 4.4	4.2	4.0, 4.4	4.2	4.0, 4.4	4.2	4.0, 4.4
- LVOT	4.2	4.0, 4.4	4.2	4.0, 4.4	4.2	4.0, 4.4	4.2	4.0, 4.4	4.2	4.0, 4.4
- Change	0	-0.2, 0.2	0	-0.2, 0.2	0	-0.2, 0.2	0	-0.2, 0.2	0	-0.2, 0.2
Calcium (mg/dL)	N=3058		N=3975		N=7629		N=3233		N=4354	
- Baseline	9.7	9.5, 10.0	9.7	9.5, 10.0	9.7	9.5, 10.0	9.7	9.5, 10.0	9.7	9.5, 10.0
- LVOT	9.6	9.4, 9.9	9.6	9.4, 9.9	9.6	9.4, 9.9	9.6	9.4, 9.9	9.6	9.4, 9.9
- Change	-0.1	-0.3, 0.2	-0.1	-0.3, 0.2	-0.1	-0.3, 0.2	-0.1	-0.3, 0.2	-0.1	-0.3, 0.2
Magnesium (mEq/L)	N=3033		N=3950		N=7531		N=3206		N=4327	
- Baseline	1.8	1.7, 1.9	1.8	1.7, 1.9	1.8	1.7, 1.9	1.8	1.6, 1.9	1.8	1.7, 1.9
- LVOT	1.9	1.8, 2.0	1.9	1.8, 2.0	1.9	1.8, 2.0	1.8	1.6, 1.9	1.8	1.6, 1.9
- Change	0.1	0.0, 0.2	0.1	0.0, 0.2	0.1	0.0, 0.2	0.0	-0.1, 0.0	0.0	-0.1, 0.0
Chloride (mEq/L)	N=3033		N=3949		N=7530		N=3205		N=4326	
- Baseline	102	101, 103	102	101, 103	102	101, 103	102	101, 103	102	101, 103
- LVOT	102	101, 103	102	101, 103	102	101, 103	102	101, 103	102	101, 103
- Change	0	-1, 1	0	-1, 1	0	-1, 1	0	-1, 1	0	-1, 1
Phosphate (mg/dL)	N=3033		N=3950		N=7531		N=3204		N=4325	
- Baseline	3.7	3.5, 3.8	3.7	3.5, 3.8	3.7	3.5, 3.8	3.7	3.5, 3.8	3.7	3.5, 3.8
- LVOT	3.8	3.6, 3.9	3.8	3.6, 4.0	3.8	3.6, 3.9	3.8	3.6, 3.9	3.7	3.5, 3.8
- Change	0.1	-0.1, 0.2	0.1	-0.1, 0.3	0.1	-0.1, 0.2	0.0	-0.1, 0.2	0.0	-0.1, 0.2
Bicarbonate (mEq/L)	N=3019		N=3939		N=7506		N=3192		N=4312	
- Baseline	25.0	23.0, 27.0	25.0	23.0, 26.7	25.0	23.0, 27.0	25.0	23.0, 27.0	25.0	23.0, 26.9
- LVOT	24.0	22.0, 26.0	24.0	22.0, 26.0	24.0	22.0, 26.0	25.0	23.0, 26.0	24.9	23.0, 26.0
- Change	-1.0	-2.1, 1.0	-1.0	-2.0, 1.0	-1.0	-2.0, 1.0	0.0	-2.0, 1.0	0.0	-2.0, 1.0

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3
SAF-3										
Sodium (mEq/L)	N=802		N=785		N=1587		N=776		N=214	
- Baseline	141	140, 142	141	140, 142	141	140, 142	141	10, 142	141	140, 143
- LVOT	141	140, 142	141	140, 142	141	140, 142	142	140, 142	141	140, 143
- Change	0	-1, 1	0	-1, 1	1	-1, 1	0	-1, 1	0	-1, 1
Potassium (mEq/L)	N=802		N=785		N=1587		N=776		N=214	
- Baseline	4.1	4.0, 4.3	4.1	4.0, 4.3	4.3	4.0, 4.3	4.1	4.0, 4.3	4.1	3.9, 4.2
- LVOT	4.1	4.0, 4.3	4.1	3.9, 4.3	4.3	3.9, 4.3	4.1	4.0, 4.3	4.1	3.9, 4.3
- Change	0.0	-0.2, 0.2	-0.1	-0.2, 0.2	0.2	-0.2, 0.2	0.0	-0.2, 0.2	0.0	-0.2, 0.2
Calcium (mg/dL)	N=802		N=785		N=1587		N=776		N=214	
- Baseline	2.4	2.4, 2.5	2.4	2.4, 2.5	2.4	2.4, 2.5	2.5	2.4, 2.5	2.4	2.4, 2.5
- LVOT	2.4	2.4, 2.5	2.4	2.4, 2.5	2.4	2.4, 2.5	2.4	2.4, 2.5	2.4	2.3, 2.5
- Change	-0.0	-0.1, 0.0	-0.0	-0.0, 0.0	-0.0	-0.1, 0.0	-0.0	-0.1, 0.0	-0.0	-0.1, 0.0
Magnesium (mEq/L)	N=802		N=785		N=1587		N=776		N=214	
- Baseline	1.0	0.9, 1.0	1.0	0.9, 1.0	1.0	0.9, 1.0	1.0	0.9, 1.0	1.0	0.9, 1.1
- LVOT	1.0	0.9, 1.0	1.0	1.0, 1.1	1.0	0.9, 1.0	1.0	0.9, 1.0	1.0	0.9, 1.0
- Change	0.1	0.0, 0.1	0.1	0.0, 0.1	0.0	0.0, 0.1	0.1	0.0, 0.1	0.0	-0.1, 0.0
Chloride (mEq/L)	N=802		N=785		N=1587		N=776		N=214	
- Baseline	102	101, 103	102	101, 104	102	101, 013	102	101, 103	102	101, 103
- LVOT	103	102,104	103	102, 104	103	102, 104	103	102, 104	103	101, 104
- Change	0	-0, 1	0	-0, 1	0	-0, 1	0	-0,1	0	-0, 1
Phosphate (mg/dL)	N=802		N=785		N=1587		N=776		N=214	
- Baseline	1.2	1.1, 1.2	1.2	1.1, 1.2	1.2	1.1, 1.2	1.2	1.1, 1.2	1.2	1.1, 1.2
- LVOT	1.2	1.2, 1.3	1.2	1.1, 1.2	1.2	1.2, 1.3	1.2	1.2, 1.3	1.2	1.1, 1.2
- Change	0.0	-0.0, 0.0	0.0	-0.1, 0.0	0.0	-0.0, 0.1	0.0	-0.0, 0.1	-0.0	-0.1, 0.0
Bicarbonate (mEq/L)	N=802		N=786		N=1588		N=773		N=214	
- Baseline	25.0	23.0, 26.0	25.0	23.0, 26.0	25.0	23.0, 26.0	25.0	23.0, 26.0	25.0	23.0, 26.0
- LVOT	25.0	22.0, 26.0	25.0	23.0, 27.0	25.0	22.0, 26.0	25.0	22.0, 26.0	25.0	23.0, 27.0
- Change	0.0	-2.0, 2.0	0.5	-2.0, 2.0	0.0	-2.0, 2.0	0.0	-2.0, 2.0	0.5	-2.0, 2.0

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = All randomized comparators; SAF-5 = Safety Grouping 5; Q1 = first quartile; Q3 = third quartile; SAF-3 = Safety Grouping 3; Mdn = median; Q1 = first quartile; Q3 = third quartile; LVOT = last value on treatment
Source: Tables 8.1.5.1 and 6.2.3.1 (Integrated Summary of Safety)

Table 135 Incidence of Selected Categorical Shifts – Electrolytes, Treated Set

	Empa 10	Empa 25	All Empa	Placebo	All Comp
	%	%	%	%	%
SAF-5					
From WRR at baseline to above ULRR at last observation on treatment					
Sodium	1.1	1.0	1.0	0.9	0.9
Potassium	1.6	1.1	1.3	1.5	1.3
Calcium	1.7	1.5	1.6	2.1	2.0
Magnesium	0.5	0.5	0.5	0.3	0.2
Chloride	0.7	0.7	0.7	0.8	0.7
Phosphate	1.9	2.4	2.0	1.4	1.3
Bicarbonate	3.6	3.8	3.5	4.7	4.6
From WRR at baseline to below LLRR at last observation on treatment					
Sodium	0.4	0.2	0.3	0.5	0.4
Potassium	0.8	1.1	1.0	0.8	0.7
Calcium	1.6	1.4	1.5	1.5	1.3
Magnesium	1.5	1.4	1.3	7.9	7.1
Chloride	0.4	0.4	0.5	0.6	0.6
Phosphate	0.2	0.3	0.2	0.9	0.8
Bicarbonate	8.7	8.9	8.3	6.8	6.7
SAF-3					
From WRR at baseline to above ULRR at last observation on treatment					
Sodium	0.5	0.8	0.6	0.7	0.9
Potassium	0.4	0.1	0.3	0.8	0.0
Calcium	2.7	1.6	2.2	1.3	1.0
Magnesium	0.3	0.1	0.2	0.0	0.5
Chloride	1.0	0.5	0.8	0.7	2.8
Phosphate	1.5	1.9	1.7	0.4	0.0
Bicarbonate	5.0	5.9	5.4	6.5	9.4
From WRR at baseline to below LLRR at last observation on treatment					
Sodium	0.3	0.0	0.1	0.5	0.0
Potassium	0.5	1.2	0.8	0.5	0.5
Calcium	1.0	1.1	1.1	0.4	1.0
Magnesium	0.9	0.8	0.9	4.3	1.9
Chloride	0.6	0.4	0.5	0.4	0.0
Phosphate	0.0	0.1	0.1	0.4	0.0
Bicarbonate	10.5	8.4	9.5	7.1	3.3

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = All randomized comparators; SAF-5 = Safety Grouping 5; SAF-3 = Safety Grouping 3; WRR = within reference range; ULRR = upper limit of reference range; LLRR = lower limit of reference range

Source: Table 3.2: 2 (Summary of Clinical Safety) and Table 6.1.3.1 (Integrated Summary of Safety)

Table 136 Percent of Patients with Possibly Clinically Significant Abnormalities – Selected Electrolytes, SAF-5

	Empa 10	Empa 25	All Empa	Placebo	All Comp
	%	%	%	%	%
Serum Phosphate					
High (above 1.7 mmol/L)	1.9	2.5	2.1	1.0	1.0
Low (below 0.7 mmol/L)	0.2	0.2	0.2	0.4	0.5
Serum Bicarbonate					
High (above 32 mmol/L)	1.5	1.5	1.4	1.7	1.7
Low (below 18 mmol/L)	2.4	3.1	3.0	2.5	2.3

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = all randomized comparators

Source: Table 3.2: 3 (Summary of Clinical Safety)

The changes in serum electrolytes are of uncertain clinical significance. Similar increases in serum phosphate were seen in the dapagliflozin and canagliflozin development programs. Changes in serum bicarbonate do not appear to have been seen in the dapagliflozin or canagliflozin development programs, though in the canagliflozin development program an increase in serum bicarbonate with placebo was seen compared to no change in serum bicarbonate with canagliflozin treatment. With empagliflozin, no change in median values for serum bicarbonate were seen, but there was a greater percentage of patients treated with empagliflozin who shifted from normal to low, or had a possibly clinically significant low serum bicarbonate. Whether this is predictive of a risk for developing acidosis is not known. There was no apparent imbalance in the rates of acid-base disorders in SAF-5 (Table 137). No clear underlying mechanism for these changes is known, but altered renal excretion is a possibility.

Table 137 Incidence of Treatment-Emergent Acid-Base Adverse Events – Safety Grouping 5

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
N	3630			4602			8400			3522			4676		
Exposure (years)	3258.2			4448.1			7827.8			2758.1			4184.4		
System Organ Class - Preferred Term	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
Possible alkalotic events															
Investigations	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	2	0.06	0.07	2	0.04	0.05
- Blood bicarbonate increased	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	2	0.06	0.07	2	0.04	0.05
Possible acidotic events															
Investigations	1	0.03	0.03	1	0.02	0.02	2	0.02	0.03	1	0.03	0.04	1	0.02	0.02
- Blood bicarbonate decreased	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
- Blood lactic acid increased	1	0.03	0.03	1	0.02	0.02	2	0.02	0.03	0	0.00	0.00	0	0.00	0.00
Metabolism and nutrition disorders	3	0.08	0.09	3	0.07	0.07	6	0.07	0.08	5	0.14	0.18	5	0.11	0.12
- Acidosis	2	0.06	0.06	1	0.02	0.02	3	0.04	0.04	0	0.00	0.00	0	0.00	0.00
- Diabetic ketoacidosis	0	0.00	0.00	1	0.02	0.02	1	0.01	0.01	2	0.06	0.07	2	0.04	0.05
- Ketoacidosis	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	1	0.03	0.04	1	0.02	0.02
- Lactic acidosis	1	0.03	0.03	1	0.02	0.02	2	0.02	0.03	0	0.00	0.00	0	0.00	0.00
- Metabolic acidosis	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	2	0.06	0.07	2	0.04	0.05

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = All randomized comparators; per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files

7.4.2.3 Enzymes

There were no marked differences in median values at baseline and at last value on treatment between groups for the measured enzymes (Table 138). There was a suggestion of more frequent increases in serum amylase with treatment (Table 139). A similar finding was seen with serum lipase to a lesser degree. Based on predefined possibly clinically significant abnormalities¹, there was a slightly numerically higher frequency for elevations in serum lipase with empagliflozin treatment than in the comparator groups (Table 140). Though serum lipase and amylase appeared to be more commonly increased in the empagliflozin-treated patients, there was no increase in the incidence of pancreatitis with empagliflozin treatment (Table 141). These observations are of unclear clinical significance. Additional discussion on changes in liver enzymes can be found in Section 7.3.5.2.

¹Defined in 8.4.2 of the submitted Integrated Summary of Efficacy as:

Amylase > 2x ULRR

Lipase > 2x ULRR

Table 138 Median Change from Baseline – Enzymes, Safety Grouping 5

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3
SAF-5										
AST (U/L)	N=3172		N=4097		N=7865		N=3351		N=4472	
- Baseline	12	8, 18	12	8, 19	12	8, 19	12	8, 18	12	8, 19
- LVOT	11	7, 16	11	7, 16	11	7, 16	11	7, 18	12	8, 19
- Change	-1	-5, 2	-1	-5, 2	-1	-5, 2	-1	-4, 3	0	-4, 3
ALT (U/L)	N=3173		N=4097		N=7866		N=3353		N=4474	
- Baseline	17	11, 25	17	11, 26	17	11, 26	16	11, 25	17	11, 27
- LVOT	14	9, 21	13	9, 20	14	9, 21	15	10, 23	16	10, 25
- Change	-3	-8, 2	-3	-8, 1	-3	-8, 1	-1	-5, 3	-1	-6, 3
Alkaline Phosphatase (U/L)	N=3173		N=4097		N=7866		N=3354		N=4475	
- Baseline	60	45, 80	60	45, 80	61	46, 80	60	45, 80	60	45, 81
- LVOT	60	45, 80	60	45, 81	60	46, 80	60	45, 81	60	45, 82
- Change	0	-7, 6	0	-7, 7	0	-7, 6	0	-6, 6	0	-7, 6
GGT (U/L)	N=317		N=374		N=1080		N=339		N=549	
- Baseline	51	28, 92	50	29, 89	49	28, 86	48	27, 88	48	27, 82
- LVOT	42	24, 73	39	24, 75	40	24, 68	48	27, 92	44	26, 86
- Change	-6	-21, 2	-6	-19, 2	-6	-19, 2	0	-6, 12	0	-10, 9
LDH (U/L)	N=3037		N=3951		N=7584		N=3205		N=4323	
- Baseline	184	170, 200	182	169, 198	183	170, 199	184	170, 201	184	169, 200
- LVOT	181	167, 197	180	167, 195	180	167, 196	183	170, 200	182	170, 200
- Change	-3	-12, 6	-3	-12, 6	-3	-12, 6	-1	-9, 8	0	-9, 9
Creatine Kinase (U/L)	N=3057		N=3975		N=7628		N=3233		N=4354	
- Baseline	198	139, 294	196	138, 293	195	137, 291	196	135, 289	194	134, 284
- LVOT	189	134, 284	190	131, 280	188	131, 278	205	140, 308	204	141, 308
- Change	-5	-52, 39	-5	-49, 35	-6	-51, 36	5	-37, 53	8	-34, 57
Lipase (U/L)	N=3049		N=3966		N=7610		N=3226		N=4347	
- Baseline	93	69, 131	99	72, 133	93	69, 131	96	72, 136	96	72, 133
- LVOT	99	72, 136	101	72, 139	96	69, 136	96	71, 136	96	72, 133
- Change	0	-13, 19	3	-13, 19	2	-13, 19	0	-16, 13	0	-14, 15

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3
Amylase (U/L)	N=367		N=352		N=1094		N=360		N=510	
- Baseline	91	75, 115	94	73, 110	93	75, 113	93	76, 111	91	74, 108
- LVOT	94	77, 119	96	76, 113	95	77, 115	91	75, 111	90	75, 110
- Change	3	-4, 11	3	-4, 11	3	-4, 10	-1	-8, 4	0	-7, 7
SAF-3										
AST (U/L)	N=802		N=787		N=1589		N=776		N=214	
- Baseline	12	8, 18	12	8, 19	12	8, 18	12	8, 18	14	9, 20
- LVOT	9	7, 15	10	7, 15	10	7, 15	11	7, 17	13	9, 19
- Change	-2	-6, 1	-2	-6, 1	-2	-6, 1	-1	-5, 3	-1	-5, 4
ALT (U/L)	N=802		N=787		N=1589		N=776		N=214	
- Baseline	17	11, 27	17	11, 26	17	11, 26	17	10, 27	20	14, 29
- LVOT	13	8, 19	13	9, 18	13	8, 18	15	9, 23	18	11, 28
- Change	-4	-10, 1	-3	-9, 0	-3	-9, 1	-2	-7, 3	-3	-9, 2
Alkaline Phosphatase (U/L)	N=802		N=787		N=1589		N=776		N=214	
- Baseline	63	48, 84	60	45, 81	62	47, 83	62	47, 84	66	51, 89
- LVOT	62	47, 84	60	47, 80	62	47, 83	63	45, 85	57	44, 80
- Change	0	-9, 7	0	-8, 6	0	-8, 7	0	-8, 8	-6	-14, 0
GGT (U/L)	N=35		N=38		N=73		N=34		N=10	
- Baseline	58	24, 102	49	31, 98	52	26, 98	42	27, 88	46	22, 121
- LVOT	48	22, 77	38	24, 67	39	24, 67	46	31, 98	79	28, 155
- Change	-6	-34, 0	-7	-7, 10	-6	-23, 0	4	-4, 17	4	-10, 27
LDH (U/L)	N=797		N=780		N=1577		N=769		N=213	
- Baseline	181	167, 194	181	167, 196	181	167, 195	180	167, 197	186	172, 202
- LVOT	176	163, 191	177	165, 194	176	164, 192	179	165, 195	182	169, 197
- Change	-4	-13, 5	-3	-13, 6	-3	-13, 6	-2	-10, 8	-3	-11, 7
Creatine Kinase (U/L)	N=802		N=785		N=1587		N=776		N=214	
- Baseline	181	128, 274	181	133, 263	181	131, 269	180	126, 256	191	133, 255
- LVOT	177	126, 261	185	129, 259	181	127, 259	189	139, 275	200	144, 304
- Change	-2	-46, 39	0	-41, 39	-2	-42, 39	6	-32, 55	13	-25, 63

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3
Lipase (U/L)	N=802		N=785		N=1587		N=776		N=214	
- Baseline	99	77, 131	96	77, 125	99	77, 128	96	77, 128	91	75, 115
- LVOT	101	80, 133	96	77, 128	99	77, 131	96	75, 125	99	77, 128
- Change	0	-13, 16	0	-13, 16	0	-13, 16	-3	-16, 11	5	-8, 21

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = All randomized comparators; SAF-5 = Safety Grouping 5; Mdn = median; Q1 = first quartile; Q3 = third quartile; SAF-3 = Safety Grouping 3; LVOT = last value on treatment; AST = aspartate aminotransferase; ALT = alanine aminotransferase; GGT = gamma glutamyl transpeptidase; LDH = lactate dehydrogenase
Source: Tables 6.2.5.1 and 6.2.3.1 (Integrated Summary of Safety)

Table 139 Incidence of Selected Categorical Shifts - Enzymes, Treated Set

	Empa 10	Empa 25	All Empa	Placebo	All Comp
	%	%	%	%	%
SAF-5					
From WRR at baseline to above ULRR at last observation on treatment					
AST	2.1	1.9	2.0	2.8	3.3
ALT	2.7	2.1	2.3	3.6	4.6
Alkaline phosphatase	2.4	2.7	2.4	2.5	2.6
GGT	4.6	5.5	4.0	6.0	5.6
LDH	1.4	1.8	1.5	2.3	2.0
Creatine kinase	6.0	5.3	5.5	6.9	7.3
Lipase	9.7	9.6	9.0	8.8	8.8
Amylase	1.5	2.9	2.2	0.6	0.4
From WRR at baseline to below LLRR at last observation on treatment					
AST	0.4	0.3	0.3	0.5	0.5
ALT	0.1	0.1	0.1	0.1	0.1
Alkaline phosphatase	1.6	1.5	1.4	1.6	1.8
GGT	1.3	0.3	0.6	0.4	0.2
LDH	0.1	0.1	0.2	0.1	0.1
Creatine kinase	0.6	0.3	0.5	0.2	0.3
Lipase	0.0	0.0	0.0	0.1	0.1
Amylase	2.7	0.6	1.6	2.5	2.4
SAF-3					
From WRR at baseline to above ULRR at last observation on treatment					
AST	1.6	2.6	2.1	1.9	3.0
ALT	3.5	2.3	2.9	2.7	5.6
Alkaline phosphatase	2.2	2.4	2.3	3.2	0.5
GGT	4.0	0.0	1.9	11.1	14.3
LDH	1.0	1.4	1.2	1.6	0.9
Creatine kinase	5.4	6.1	5.8	4.8	10.3
Lipase	10.3	6.7	8.5	6.6	7.8

	Empa 10	Empa 25	All Empa	Placebo	All Comp
	%	%	%	%	%
From WRR at baseline to below LLRR at last observation on treatment					
AST	0.1	0.4	0.3	0.4	0.5
ALT	0.4	0.1	0.3	0.0	0.0
Alkaline phosphatase	1.4	1.9	1.6	2.0	3.6
GGT	0.0	3.6	1.9	0.0	0.0
LDH	0.0	0.0	0.0	0.1	0.0
Creatine kinase	0.3	0.3	0.3	0.0	0.0
Lipase	0.0	0.0	0.0	0.0	0.0

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = All randomized comparators; SAF-5 = Safety Grouping 5; SAF-3 = Safety Grouping 3; WRR = within reference range; ULRR = upper limit of reference range; LLRR = lower limit of reference range; AST = aspartate aminotransferase; ALT = alanine aminotransferase. GGT = gamma glutamyl transpeptidase; LDH = lactate dehydrogenase

Source: Tables 6.1.5.1 and 6.1.3.1 (Integrated Summary of Safety)

Table 140 Percentage of Patients with Possibly Clinically Significant Abnormalities – Enzymes, Safety Grouping 5

	Empa 10	Empa 24	All Empa	Placebo	All Comp
	%	%	%	%	%
AST					
High (> 3x ULRR)	0.2	0.4	0.3	0.3	0.2
ALT					
High (> 3x ULRR)	0.4	0.4	0.4	0.6	0.6
Alkaline phosphatase					
High (> 2x ULRR)	0.2	0.3	0.2	0.3	0.3
GGT					
High (> 3x ULRR)	3.9	3.1	2.8	4.3	3.7
LDH					
High (> 3x ULRR)	0.0	0.0	0.0	0.0	0.0
Creatine kinase					
High (> 3x ULRR)	1.3	1.2	1.2	1.6	1.6
Lipase					
High (> 2x ULRR)	6.1	6.3	5.9	4.9	5.1
Amylase					
High (> 2x ULRR)	0.5	0.3	0.5	0.3	0.2

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = All randomized comparators; ULRR = upper limit of reference range; AST = aspartate aminotransferase; ALT = alanine; GGT = gamma glutamyl transpeptidase; LDH = lactate dehydrogenase

Source: Table 6.3.5.1 (Integrated Summary of Safety)

Table 141 Incidence of Pancreatitis Events – SAF-5

	Empa 10			Empa 25			All Empa			Placebo			All Comp		
N	3630			4602			8400			3522			4676		
Estimated exposure	3258.2			4448.1			7827.8			2758.1			4184.4		
	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
Pancreatitis acute	1	0.00	0.03	2	0.00	0.04	3	0.00	0.04	1	0.00	0.04	2	0.00	0.05
Pancreatitis	2	0.10	0.06	1	0.00	0.02	3	0.00	0.04	4	0.10	0.15	4	0.10	0.10
Pancreatitis chronic	1	0.00	0.06	0	0.00	0.00	1	0.00	0.03	2	0.10	0.07	2	0.00	0.05
Pancreatic enzymes increased	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	0	0.00	0.00	2	0.00	0.05
Total	4	0.11	0.15	3	0.07	0.07	7	0.08	0.10	7	0.20	0.25	10	0.21	0.24

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = All randomized comparators; per 100 = events per 100 patient-years

Source: Submitted AE xpt and DM xpt files

7.4.2.4 Serum Uric Acid

Serum uric acid values decreased from baseline in all empagliflozin-treated groups. This may indicate uricosuria due to treatment with empagliflozin, signaling a potential for causing renal insufficiency/impairment (Table 142). Though the percentage of patients shifting from WRR to below LLRR was only slightly higher in the empagliflozin-treated patients, there was a more marked difference in the percentage of patients with serum uric acid above ULRR at baseline that shifted to WRR (Table 143). These findings are supportive of each other, but the clinical significance of these changes is unclear. Notably, a propensity for empagliflozin-treated patients to develop decreases in eGFR was seen. These changes in eGFR were reversible with discontinuation of empagliflozin treatment. See 7.3.5.6 for discussion of renal insufficiency/impairment.

Table 142 Median Change from Baseline – Serum Uric Acid, Safety Grouping 5

	Empa 10	Empa 25	All Empa	Placebo	All Comp
# of patients with uric acid data	3058	3975	7629	3232	4353
Baseline					
– Median	303	312	307	317	312
– Q1,Q3	228, 391	231, 400	231, 396	232, 412	236, 404
Last value on treatment					
– Median	267	269	267	324	324
– Q1, Q3	195, 350	197, 356	197, 350	237, 412	240, 410
Difference					
– Median	-34	-35	-35	0	8
– Q1, Q3	-89, 22	-91, 17	-89, 17	-46, 51	-41, 54

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = All randomized comparators; Q1 = first quartile; Q3 = third quartile

Source: Table 3.4: 1 (Summary of Clinical Safety)

Table 143 Incidence of Categorical Shifts – Serum Uric Acid, Safety Grouping 5

	Last value on treatment		
	Below LLRR	WRR	Above ULRR
Baseline value	%	%	%
Empa 10			
– Below LLRR	50.0	50.0	0.0
– WRR	2.1	94.7	3.2
– Above ULRR	0.0	61.6	38.4
Empa 25			
– Below LLRR	61.5	38.5	0.0
– WRR	1.9	94.8	3.3
– Above ULRR	0.0	58.9	41.1
All Empa			
– Below LLRR	57.3	42.7	0.0
– WRR	2.0	95.0	3.1
– Above ULRR	0.0	60.8	39.2
Placebo			
– Below LLRR	61.2	38.8	0.0
– WRR	1.4	92.7	6.0
– Above ULRR	0.0	36.5	63.5
All Comp			
– Below LLRR	57.6	42.4	
– WRR	1.1	93.0	5.9
– Above ULRR	0.0	37.4	62.6

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = All randomized comparators; lower limit of reference range; WRR = within reference range; ULRR = upper limit of reference range

Source: 6.1.5.1 (Integrated Summary of Safety)

7.4.2.5 Lipids

Analysis of changes in lipid parameters is limited to Studies 1245.19, 1245.20, 1245.23, 1245.25, 1245.31, and 1245.36 as they were not systematically measured in the other clinical studies. Several dose-dependent changes in lipid parameters were noted (Table 144). Notably, there appeared to be a dose-dependent increase from baseline in total cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), and non-HDL cholesterol with empagliflozin treatment compared to placebo at 24 and 52 weeks. Additional changes observed include increases in TG with placebo compared to empagliflozin treatment at week 24. By week 52 no noticeable difference between groups was seen. Values for TGs increased from baseline for all groups. These findings are supported by the increased incidence of empagliflozin-treated patients who shifted from WRR to above ULRR for total cholesterol, HDL cholesterol and LDL cholesterol (Table 145).

The significance of these findings is unclear. Whether these changes translate into changes in risk of developing cardiovascular disease is not known. Additional discussion of the cardiovascular risk associated with empagliflozin treatment can be found in 7.3.5.1.

Table 144 Mean Change from Baseline – Lipids, Treated Set (Observed Cases Including Values After Rescue Medication)

- Restricted to Studies 1245.19, 1245.20, 1245.23, 1245.25, 1245.31, 1245.36

	Week 24			Week 52		
	Placebo	Empa 10	Empa 25	Placebo	Empa 10	Empa 25
Total cholesterol (mg/dL)						
Baseline						
- Mean	168.99	168.99	170.5	168.99	168.99	170.5
- SE	0.93	0.98	0.91	0.93	0.98	0.91
Change from baseline						
- Mean	3.29	5.53	7.97	4.04	7.78	9.36
- SE	0.67	0.69	0.66	0.86	0.9	0.83
% change (mean)	1.95	3.27	4.67	2.39	4.60	5.49
Difference from placebo						
- Mean	--	2.25	4.68	--	3.74	5.33
- 95% CI (LL, UL)	--	0.34, 4.14	2.84, 6.52	--	1.30, 6.19	2.98, 7.67
HDL cholesterol (mg/dL)						
Baseline						
- Mean	46.21	46.57	46.84	46.21	46.57	46.84
- SE	0.26	0.27	0.27	0.26	0.27	0.27
Change from baseline						
- Mean	-0.26	1.51	1.77	-0.62	1.28	1.55
- SE	0.16	0.16	0.15	0.2	0.21	0.19

	Week 24			Week 52		
	Placebo	Empa 10	Empa 25	Placebo	Empa 10	Empa 25
% change (mean)	-0.56	3.24	3.78	-1.34	2.75	3.31
Difference from placebo						
– Mean	--	1.77	2.03	--	1.9	2.18
– 95% CI (LL, UL)	--	1.33, 2.21	1.61, 2.46	--	1.34, 2.47	1.63, 2.72
LDL cholesterol (mg/dL)						
Baseline						
– Mean	90.56	90.33	90.55	90.56	90.33	90.55
– SE	0.78	0.83	0.74	0.78	0.83	0.74
Change from baseline						
– Mean	2.12	4.17	5.91	3.57	5.84	6.37
– SE	0.56	0.58	0.55	0.72	0.75	0.70
% change (mean)	2.34	4.62	6.53	3.94	6.47	7.03
Difference from placebo						
– Mean	--	2.05	3.79	--	2.27	2.81
– 95% CI (LL, UL)	--	0.47, 3.63	2.25, 5.33	--	0.22, 4.32	0.84, 4.77
Non-HDL cholesterol (mg/dL)						
Baseline						
– Mean	122.78	122.42	123.66	122.78	122.42	123.66
– SE	0.91	0.96	0.89	0.91	0.96	0.89
Change from baseline						
– Mean	3.62	4.02	6.16	4.72	6.46	7.75
– SE	0.65	0.68	0.65	0.85	0.88	0.82
% change (mean)	2.95	3.28	4.98	3.84	5.28	6.27
Difference from placebo						
– Mean	--	0.4	2.54	--	1.74	3.03
– 95% CI (LL, UL)	--	-1.44, 2.24	0.74, 4.34	--	-0.66, 4.14	0.73, 5.34
TG (mg/dL)						
Baseline						
– Mean	167.03	167.15	167.18	167.03	167.15	167.18
– SE	2.58	2.86	2.92	2.58	2.86	2.92
Change from baseline						
– Mean	9.04	-0.71	1.45	6.13	4.18	9.22
– SE	2.14	2.23	2.12	2.72	2.84	2.64
% change (mean)	5.41	-0.42	0.87	3.67	2.50	5.52
Difference from placebo						
– Mean	--	-9.75	-7.59	--	-1.95	3.09
– 95% CI (LL, UL)	--	-15.82, -3.69	-13.50, -1.68	--	-9.68, 5.79	-4.34, 10.52

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; CI = confidence interval; LL = lower limit; UL = upper limit;
SE = standard error; LDL= low density lipoprotein; HDL = high density lipoprotein; TG = triglycerides
Source: Tables 8.3.5.1.1, 8.3.5.2.1, 8.3.5.3.1, 8.3.5.4.1, and 8.3.5.5.1 (Integrated Summary of Safety))

Table 145 Incidence in shifts from Values Within the Reference Range to Values Above the Upper Limit of the Reference Range - Lipids

	Empa 10	Empa 25	All Empa	Placebo	All Comp
	%	%	%	%	%
Total cholesterol	15.5	18.9	16.7	12.4	12.9
HDL cholesterol	2.1	2.2	2.3	1.1	1.3
LDL cholesterol	9.1	10.4	9.8	7.9	8.2
Triglycerides	6.9	7.7	7.3	9.2	8.7

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = All randomized comparators; HDL = high density lipoprotein; LDL = low density lipoprotein

Source: Table 3.5: 2 (Summary of Clinical Safety)

7.4.3 Vital Signs

Baseline blood pressure (systolic and diastolic) and heart rate were similar between the empagliflozin-treated patients and the comparator groups (Table 146, Table 147). Following treatment, there was a decrease in systolic and diastolic blood pressure seen with empagliflozin treatment that was not seen with the comparator groups. Despite evidence of decreases in blood pressure, there was no increase in volume depletion events as discussed in 0, except in patients > 75 years of age with the 25 mg dose (Table 149). There was no evidence of compensatory increases in heart rate to signal significant volume depletion. Additional discussion of blood pressure changes can be found in 6.1.5.3 and 6.1.6.2.

Table 146 Median Change from Baseline – Blood Pressure, Safety Grouping 5

	Empa 10	Empa 25	All Empa	Placebo	All Comp
Systolic Blood Pressure					
Baseline					
– Median	132.0	132.7	132.0	133.0	133.0
– Q1, Q3	122.0, 143.3	122.3, 143.7	122.3, 143.3	122.3, 144.3	122.3, 143.7
LVOT					
– Median	128.3	128.0	128.0	132.0	132.0
– Q1, Q3	119.0, 138.3	118.3, 138.0	118.7, 138.0	122.0, 143.3	122.0, 142.7
Change from baseline					
– Median	-4	-4.7	-4.3	-0.7	-0.7
– Q1, Q3	-13.0, 5.0	-14.0, 3.7	-13.3, 4.0	-10.0, 7.7	-9.7, 7.7
Diastolic Blood Pressure					
Baseline					
– Median	78.3	78.3	78.3	78.3	79.0
– Q1, Q3	70.7, 84.0	71.5, 84.3	71.3, 84.3	71.0, 84.3	71.7, 84.7
LVOT					
– Median	76.0	75.7	76.0	77.5	78.0
– Q1, Q3	69.7, 81.7	69.3, 81.7	69.7, 81.7	70.7, 84.0	71.0, 84.0

	Empa 10	Empa 25	All Empa	Placebo	All Comp
Change from baseline					
- Median	-2.0	-2.3	-2.0	-0.7	-0.7
- Q1, Q3	-7.7, 2.7	-8.0, 2.7	-7.7, 2.7	-6.3, 4.3	-6.0, 4.3

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = All randomized comparators; Q1 = first quartile; Q3 = third quartile; LVOT = last value on treatment

Source: Tables 4.1.1: 1 and 4.1.1: 2 (Summary of Clinical Safety)

Table 147 Median Change from Baseline – Heart Rate, Safety Grouping 5

	Empa 10	Empa 25	All Empa	Placebo	All Comp
Heart Rate					
Baseline					
- Median	72.0	72.0	72.0	72.0	72.0
- Q1, Q3	65.0, 80.0	65.0, 80.0	65.0, 79.0	65.0, 79.0	65.0, 80.0
LVOT					
- Median	71.81	71.99	71.86	72.23	72.87
- Q1, Q3	64.0, 78.0	64.0, 78.0	64.0, 78.0	64.0, 79.0	65.0, 80.0
Change from baseline					
- Median	0.00	0.00	0.00	0.00	0.00
- Q1, Q3	-6.0, 5.0	-6.0, 5.0	-6.0, 5.0	-5.0, 5.0	-5.0, 6.0

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = All randomized comparators; Q1 = first quartile; Q3 = third quartile; LVOT = last value on treatment

Source: Table 7.1.5.3 (Integrated Summary of Safety)

7.4.4 Electrocardiograms (ECGs)

Study 1245.16 was a randomized, placebo-controlled, double-blind, single-dose cross-over study to assess the effect of empagliflozin on QT interval in healthy patients. Moxifloxacin 400 mg was used as an open-label positive control. Two doses of empagliflozin were explored in this study: the expected therapeutic dose of 25 mg and a suprathreshold dose of 200 mg. The 200 mg dose was expected to result in a 7-fold higher C_{max} compared to the 25 mg dose. This 7-fold increase in concentration was considered to cover potential increase plasma levels due to drug-drug interactions, or drug-disease interactions. Placebo-corrected adjusted mean changes from baseline in QTc were 0.59 ms following empagliflozin 25 mg and -0.22 ms for empagliflozin 200 mg. Use of different formulae for calculating QTc (i.e. Friederica, Bazett's) produced similar results. No patients experienced changes in QTc > 30 ms, no patients had QTc > 480 ms or QT > 500 ms.

The study report for this study was submitted to IND-102145 (SD-90, July 26, 2011) and the Interdisciplinary Review Team for QT Studies was consulted. No significant QTc prolongation was detected in Study 1245.16. The upper limit of the 90% confidence interval for change in

QTc was < 10 ms, which is the threshold of regulatory concern (Figure 25).

Figure 25 Summary of Corrected QT Interval Findings from Study 1245.16

Table 1: The Point Estimates and the 90% CIs Corresponding to the Largest Upper Bounds for BI10773 (25 mg and 200 mg) and the Largest Lower Bound for Moxifloxacin (FDA Analysis)

Treatment	Time (hour)	$\Delta\Delta\text{QTcF}$ (ms)	90% CI (ms)
BI10773 25 mg	12	1.6	(-0.7, 3.9)
BI10773 200 mg	2.5	2.0	(-0.1, 4.2)
Moxifloxacin 400 mg*	2.5	14.4	(11.6, 17.1)

* Multiple endpoint adjustment of 3 time points was not applied. The largest lower bound without Bonferroni adjustment is 12.2 ms.

CI = confidence interval; FDA = Food and Drug Administration; QTcF = Corrected QT interval using Fridericia formula
Source: Table 1 of Dr. Qianyu Dang's Consult Review submitted to DARRTS (IND-102145, September 13, 2011)

7.4.5 Special Safety Studies/Clinical Studies

There is an ongoing cardiovascular outcomes study (Study 1245.25). Discussion of cardiovascular safety can be found in 7.3.5.1 and in the review by Janelle Charles.

7.4.6 Immunogenicity

Not applicable.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Discussion of dose dependency for CV events can be found in 7.3.5.1. From the overall SAF-5 population, there were only a few adverse events with a suggestion of dose dependency. Adverse events with suggestion of dose dependency included the PTs "Vulvovaginal mycotic infection", "Vulvitis", "Vulvovaginitis", "Dry mouth", and for the development of phimosis (Table 102, Table 105, and Table 130). These occurred more frequently in empagliflozin-treated patients than placebo and are discussed in more detail in 7.3.5.5.

Looking at subpopulations, there was suggestion of dose dependency for the "Urinary tract

infection” CMQ in male patients and in patients 65 to ≤ 75 years of age (Table 149, Table 150). In female patients the “Genital infection” CMQ showed a suggestion of dose dependency. This was also suggested for patients 50 to ≤ 65 years of age. Volume depletion events, as defined by the “Volume depletion” CMQ, and decreased renal function, as defined by the “Acute Renal Failure” SMQ, appeared to occur in a dose-dependent fashion for patients > 75 years of age (Table 106, Table 149). Data from patients with moderate renal impairment at baseline suggested dose dependency for the “Genital infection” CMQ and for decreased renal function events, as defined by the “Acute renal failure” SMQ (Table 106, Table 153).

There was suggestion of dose dependency for some laboratory and vital sign parameters (i.e. increases in hematocrit (Table 132), increases in serum phosphate and decreases in serum bicarbonate (Table 135, Table 136), increases in lipid parameters (Table 144), and systolic and diastolic blood pressure (Table 146)). Suggestion of dose dependency was also seen with changes in eGFR for patients with moderate renal impairment at baseline (Table 154). As noted above, the clinical significance of these changes is unknown.

Reviewer Comment on Dose Dependency for Safety:

There is a plausible mechanism for some of the observed differences with the 10 mg vs. the 25 mg dose. This leads me to believe that some of these findings of dose dependency are real. As such, availability of the 10 mg dose is desirable, particularly for older patients and for patients with moderate renal impairment. Tolerability may also be improved with the lower dose, as some adverse events that could affect tolerability and compliance (e.g. dry mouth) were more frequent with the higher dose.

7.5.2 Time Dependency for Adverse Events

Discussion of time dependency for CV events can be found in 7.3.5.1. Examination of the adverse events of special interest at 30 days, 60 days, 120 days, and 180 days after initiation of therapy for SAF-5 demonstrated findings similar to the overall findings for adverse events for SAF-5 (Table 148). At all of these time points, urinary tract infections occurred slightly more frequently in the empagliflozin-treated patients than in placebo, and genital infections were more frequent in the empagliflozin-treated patients than in placebo. While in the overall safety population there was no increased incidence of decreased renal function with empagliflozin treatment (either by adverse event reports or serum creatinine changes), an imbalance not favoring empagliflozin is seen at each of these time points. This suggests that there are early changes in renal function with empagliflozin therapy that converge with placebo over time (see 0).

Examination of the incidence of these events over the 180 day time frame suggests that these events accumulate continuously over time at a relatively steady rate, as demonstrated by the near linear trend line (Figure 26). Of note, the incidence of genital infections appears to accumulate at a faster rate for the empagliflozin-treated patients compared to placebo, as evidenced by the steeper slopes. This suggests that the imbalance in genital infections would widen further with more time. This observation was not seen for any of the other AESIs.

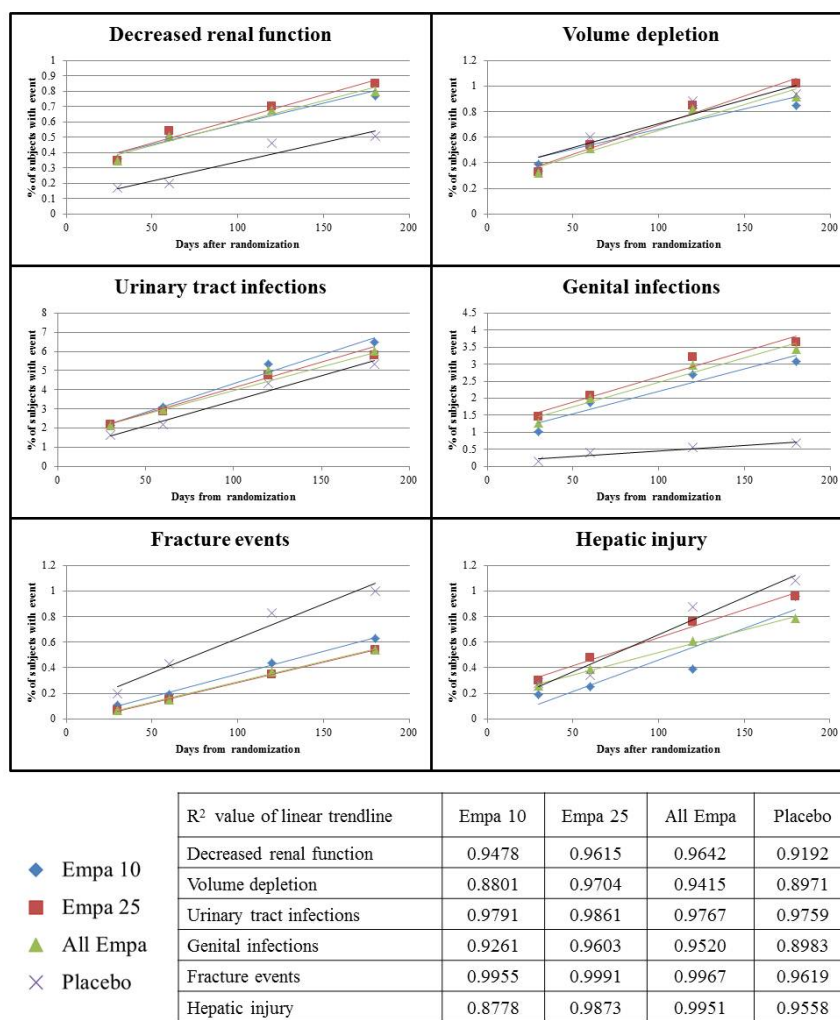
Table 148 Incidence of Adverse Events of Special Interest Over Time – Safety Grouping 5, Treated Set

	Empa 10		Empa 25		All Empa		Placebo	
	3627		4598		8393		3514	
	N	%	N	%	N	%	N	%
30 days from initiation of randomized therapy								
Decreased renal function	13	0.36	16	0.35	29	0.35	6	0.17
Hepatic injury	7	0.19	14	0.30	22	0.26	10	0.28
Urinary Tract Infection	77	2.12	101	2.20	179	2.13	57	1.62
Genital infection	37	1.02	67	1.46	107	1.27	5	0.14
Bone fracture	4	0.11	3	0.07	6	0.07	7	0.20
Volume depletion	14	0.39	15	0.33	27	0.32	13	0.37
60 days from initiation of randomized therapy								
Decreased renal function	18	0.50	25	0.54	43	0.51	7	0.20
Hepatic injury	9	0.25	22	0.48	33	0.39	12	0.34
Urinary tract infection	112	3.09	132	2.87	247	2.94	77	2.19
Genital infection	68	1.87	96	2.09	169	2.01	14	0.40
Bone fracture	7	0.19	7	0.15	13	0.15	15	0.43
Volume depletion	20	0.55	25	0.54	43	0.51	21	0.60
120 days from initiation of randomized therapy								
Decreased renal function	25	0.69	32	0.70	57	0.68	16	0.46
Hepatic injury	14	0.39	35	0.76	51	0.61	31	0.88
Urinary tract infection	194	5.35	218	4.74	422	5.03	153	4.35
Genital infection	98	2.70	147	3.20	251	2.99	20	0.57
Bone fracture	16	0.44	16	0.35	31	0.37	29	0.83
Volume depletion	30	0.83	39	0.85	69	0.82	31	0.88
180 days from initiation of randomized therapy								
Decreased renal function	28	0.77	39	0.85	67	0.80	18	0.51
Hepatic injury	21	0.58	44	0.96	66	0.79	38	1.08
Urinary tract infection	235	6.48	266	5.79	504	6.01	188	5.35
Genital infection	112	3.09	168	3.65	289	3.44	24	0.68
Bone fracture	23	0.63	25	0.54	45	0.54	35	1.00
Volume depletion	31	0.85	47	1.02	77	0.92	33	0.94

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin

Source: August 14, 2013 Response to Information Request (NDA-204629, SD-16, eCTD-0015)

Figure 26 Adverse Events of Special Interest Over the First 180 Days – Safety Grouping 5



Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin
Source: Table 143

7.5.3 Drug-Demographic Interactions

7.5.3.1 Age

Discussion of the impact of age on CV events can be found in 7.3.5.1. For the assessment of the impact of age on other safety events, patients in SAF-5 were grouped into the following age categories: < 50, 50 to < 65, 65 to < 75, and ≥ 75 years.

As was seen with the entire SAF-5 population, there was an increased frequency of genitourinary infections with empagliflozin treatment across all age groups (Table 149). While volume depletion events were not seen with an increased frequency with empagliflozin treatment in the aggregate SAF-5 population, stratifying by age suggests that there is an age-dependent and dose-dependent increase in these events. Events of decreased renal function appeared to become more frequent with increasing age, particularly with the empagliflozin 25 mg dose. Increasing age also showed a higher incidence of AEs leading to discontinuation and SAEs, but the empagliflozin-treated patients did not appear to have an increased incidence compared to placebo.

Table 149 Incidence of Adverse Events by Age – Safety Grouping 5

	< 50 years		50 to < 65 years		65 to < 75 years		≥ 75 years	
	N	%	N	%	N	%	N	%
Placebo	446		1860		979		237	
Empa 10	522		1908		983		217	
Empa 25	736		2381		1213		272	
Any adverse event								
– Placebo	303	67.9	1251	67.3	691	70.6	170	71.1
– Empa 10	346	66.3	1289	67.6	676	68.8	161	74.2
– Empa 25	497	67.5	1629	68.4	869	71.6	204	75.0
AE leading to discontinuation								
– Placebo	11	2.5	84	4.5	67	6.8	26	11.0
– Empa 10	10	1.9	97	5.1	52	5.3	15	6.9
– Empa 25	15	2.0	100	4.2	85	7.0	26	9.6
Serious adverse events								
– Placebo	34	7.6	197	10.6	161	16.4	54	22.8
– Empa 10	27	5.2	174	9.1	111	11.3	35	16.1
– Empa 25	48	6.5	215	9.0	165	13.6	46	16.9
Decreased renal function								
– Placebo	2	0.4	16	0.9	14	1.4	4	1.7
– Empa 10	0	0.0	22	1.2	17	1.7	2	0.9
– Empa 25	7	1.0	25	1.0	20	1.6	6	2.2
Hepatic injury								
– Placebo	12	2.7	30	1.6	9	0.9	3	1.3
– Empa 10	10	1.9	21	1.1	12	1.2	0	0.0
– Empa 25	13	1.8	34	1.4	16	1.3	2	0.7
Urinary tract infection								
– Placebo	44	9.9	142	7.6	73	7.5	25	10.5
– Empa 10	35	6.7	168	8.8	87	8.9	34	15.7
– Empa 25	66	9.0	169	7.1	130	10.7	41	15.1

	< 50 years		50 to < 65 years		65 to < 75 years		≥ 75 years	
	N	%	N	%	N	%	N	%
Genital infection								
- Placebo	10	2.2	10	0.5	12	1.2	3	1.3
- Empa 10	34	6.5	77	4.0	40	4.1	9	4.1
- Empa 25	44	6.0	115	4.8	48	4.0	11	4.0
Confirmed hypoglycemia								
- Placebo	43	9.6	216	11.6	154	15.7	30	12.7
- Empa 10	51	9.8	233	12.2	145	14.8	28	12.9
- Empa 25	51	6.9	250	10.5	169	13.9	31	11.4
Fracture events								
- Placebo	7	1.6	25	1.3	19	1.9	4	1.7
- Empa 10	5	1.0	31	1.6	19	1.9	4	1.8
- Empa 25	9	1.2	27	1.1	11	0.9	4	1.5
Volume depletion								
- Placebo	4	0.9	19	1.0	21	2.1	5	2.1
- Empa 10	2	0.4	20	1.0	25	2.5	5	2.3
- Empa 25	5	0.7	24	1.0	26	2.1	12	4.4

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg

Source: Table 5.1.1: 1 (Summary of Clinical Safety)

7.5.3.2 Gender

Discussion of the impact of gender on CV events can be found in 7.3.5.1. Examination of differences by gender showed a greater frequency of adverse events in female patients than in male patients (Table 150). In particular, urinary tract infections and genital infections were more common in female patients. This was true regardless of treatment. Urinary tract infections and genital infections were increased with empagliflozin treatment for both male and female patients. There was a suggestion of dose-dependency for genital infections in the female patients, while there was a suggestion of dose dependency for urinary tract infections in the male patients. The incidence of decreased renal function events was numerically greater in the female patients.

Table 150 Incidence of Adverse Events by Gender – Safety Grouping 5

	Male		Female	
	N	%	N	%
Placebo	2237		1285	
Empa 10	2327		1303	
Empa 25	2911		1691	
Any adverse event				
- Placebo	1487	66.5	928	72.2
- Empa 10	1508	64.8	964	74.0
- Empa 25	1954	67.1	1245	73.6

	Male		Female	
	N	%	N	%
AE leading to discontinuation				
- Placebo	118	5.3	70	5.4
- Empa 10	105	4.5	69	5.3
- Empa 25	150	5.2	76	4.5
Serious adverse events				
- Placebo	295	13.2	151	11.8
- Empa 10	223	9.6	124	9.5
- Empa 25	323	11.1	151	8.9
Decreased renal function				
- Placebo	29	1.3	7	0.5
- Empa 10	21	0.9	20	1.5
- Empa 25	31	1.3	21	1.2
Hepatic injury				
- Placebo	29	1.3	25	1.9
- Empa 10	27	1.2	16	1.2
- Empa 25	45	1.5	20	1.2
Urinary tract infection				
- Placebo	71	3.2	213	16.6
- Empa 10	84	3.6	240	18.4
- Empa 25	118	4.1	288	17.0
Genital infection				
- Placebo	17	0.8	18	1.4
- Empa 10	79	3.4	81	6.2
- Empa 25	90	3.1	128	7.6
Confirmed hypoglycemia				
- Placebo	282	12.6	161	12.5
- Empa 10	298	12.8	159	12.2
- Empa 25	329	11.3	172	10.2
Fracture events				
- Placebo	30	1.3	25	1.9
- Empa 10	26	1.1	33	2.5
- Empa 25	30	1.0	21	1.2
Volume depletion				
- Placebo	30	1.3	19	1.5
- Empa 10	32	1.4	20	1.5
- Empa 25	45	1.5	22	1.3

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg

Source: Tables 5.1.5.3, 5.10.5.3, 5.11.5.3, 5.12.5.4, 5.13.5.4, 5.14.5.8, 5.15.5.3, and 5.16.5.3 (Integrated Summary of Safety)

7.5.3.3 Race/Ethnicity

Discussion of the impact of race and ethnicity on CV events can be found in 7.3.5.1.

Examination of racial subgroups revealed some baseline differences. Asian patients had a lower baseline BMI. Asian patients also had a lower proportion of patients with a history of hypertension compared to White and Black patients. The duration of diabetes was also shorter

for Asian patients. Black patients made up a small percentage of the overall population, and had a shorter mean exposure compared to White or Asian patients. This raises a question about the generalizability of the overall observations for this group of patients.

In terms of safety outcomes, some minor differences based on race were seen (Table 151). Black patients treated with empagliflozin had a higher incidence of discontinuation due to adverse event, but a lower incidence of serious adverse events. There was a higher incidence of decreased renal function events in the Black patients compared to White or Asian patients, regardless of treatment. Empagliflozin treatment appeared to result in a slight increase in the incidence of decreased renal function events regardless of race. Consistent with what was observed in the entire SAF-5 population, genital infections were more common in empagliflozin-treated patients, regardless of race. While the incidence of urinary tract infections was increased in White and Black patients treated with empagliflozin, it did not appear to be increased in Asian patients.

Baseline demographics were balanced between non-Hispanic/Latino patients and Hispanic/Latino patients. Genital infections remained more common in the empagliflozin-treated patients, regardless of ethnicity (Table 152). This was consistent with what was observed for the entire SAF-5 population.

Table 151 Incidence of Adverse Events by Race – Safety Grouping 5

	White		Black		Asian	
	N	%	N	%	N	%
Placebo	2184		151		1163	
Empa 10	2235		134		1236	
Empa 25	2843		161		1570	
Any adverse event						
– Placebo	1468	67.2	105	69.5	825	70.9
– Empa 10	1489	66.6	99	73.9	866	70.1
– Empa 25	1981	69.7	112	69.6	1087	69.2
AE leading to discontinuation						
– Placebo	136	6.2	6	4.0	44	3.8
– Empa 10	126	5.6	5	3.7	42	3.4
– Empa 25	155	5.5	12	7.5	58	3.7
Serious adverse events						
– Placebo	299	13.7	29	19.2	113	9.7
– Empa 10	233	10.4	13	9.7	100	8.1
– Empa 25	318	11.2	22	13.7	133	8.5

	White		Black		Asian	
	N	%	N	%	N	%
Decreased renal function						
- Placebo	20	0.9	4	2.6	11	0.9
- Empa 10	25	1.1	5	3.7	11	0.9
- Empa 25	32	1.1	6	3.7	20	1.3
Hepatic injury						
- Placebo	27	1.2	2	1.3	25	2.1
- Empa 10	24	1.1	2	1.5	17	1.4
- Empa 25	32	1.1	2	1.2	30	1.9
Urinary tract infection						
- Placebo	168	7.7	12	7.9	101	8.4
- Empa 10	208	9.3	14	10.4	99	8.0
- Empa 25	267	9.4	9	5.6	128	8.2
Genital infection						
- Placebo	23	1.1	4	2.6	8	0.7
- Empa 10	113	5.1	6	4.5	36	2.9
- Empa 25	176	6.2	6	3.7	35	2.2
Confirmed hypoglycemia						
- Placebo	286	13.1	27	17.9	127	10.9
- Empa 10	307	13.7	29	21.6	118	9.5
- Empa 25	332	11.7	29	18.0	136	8.7
Fracture events						
- Placebo	35	1.6	3	2.0	17	1.5
- Empa 10	30	1.3	3	2.2	25	2.0
- Empa 25	38	1.3	0	0.0	13	0.8
Volume depletion						
- Placebo	33	1.5	4	2.6	12	1.0
- Empa 10	36	1.6	3	2.2	13	1.1
- Empa 25	41	1.4	4	2.5	21	1.3

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; AE = adverse event

Source: Tables 5.1.5.4, 5.10.5.4, 5.11.5.4, 5.12.5.5, 5.13.5.5, 5.14.5.10, 5.15.5.4, and 5.16.5.4 (Integrated Summary of Safety)

Table 152 Incidence of Adverse Events by Ethnicity – Safety Grouping 5

	Non-Hispanic		Hispanic	
	N	%	N	%
Placebo	3046		417	
Empa 10	3118		452	
Empa 25	3973		572	
Any adverse event				
- Placebo	2125	69.8	269	64.5
- Empa 10	2154	69.1	293	64.8
- Empa 25	2810	70.7	367	64.2

	Non-Hispanic		Hispanic	
	N	%	N	%
AE leading to discontinuation				
- Placebo	161	5.3	25	6.0
- Empa 10	147	4.7	26	5.8
- Empa 25	205	5.2	21	3.7
Serious adverse events				
- Placebo	395	13.0	51	12.2
- Empa 10	305	9.8	42	9.3
- Empa 25	435	10.9	39	6.8
Decreased renal function				
- Placebo	33	1.1	3	0.7
- Empa 10	35	1.1	6	1.3
- Empa 25	50	1.3	8	1.4
Hepatic injury				
- Placebo	45	1.5	8	1.9
- Empa 10	38	1.2	5	1.1
- Empa 25	61	1.5	4	0.7
Urinary tract infection				
- Placebo	248	8.1	36	8.6
- Empa 10	268	8.6	55	12.2
- Empa 25	355	8.9	50	8.7
Genital infection				
- Placebo	30	1.0	5	1.2
- Empa 10	144	4.6	15	3.3
- Empa 25	192	4.8	25	4.4
Confirmed hypoglycemia				
- Placebo	386	12.7	57	13.7
- Empa 10	395	12.7	62	13.7
- Empa 25	444	11.2	57	10.0
Fracture events				
- Placebo	47	1.5	8	1.9
- Empa 10	54	1.7	5	1.1
- Empa 25	42	1.1	9	1.6
Volume depletion				
- Placebo	44	1.4	5	1.2
- Empa 10	43	1.4	9	2.0
- Empa 25	63	1.6	4	0.7

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; AE = adverse event

Source: Tables 5.1.5.5, 5.10.5.5, 5.11.5.5, 5.12.5.6, 5.13.5.6, 5.14.5.12, 5.15.5.5, and 5.16.5.5 (Integrated Summary of Safety)

Reviewer Comment on Safety by Race/Ethnicity:

Black patients made up a small percentage of the patients in empagliflozin development program. This raises question about the generalizability of the findings (both safety and efficacy) from the overall development program for this racial group. Additional study in this racial group may be warranted.

7.5.3.4 Renal function

Discussion of the impact of renal function on CV events can be found in 7.3.5.1. Renal function categories were based on eGFR calculated by MDRD as follow:

eGFR (ml/min/1.73 m ²)	Renal function
≥ 90	Normal
60 to < 90	Mild impairment
30 to < 60	Moderate impairment
45 to < 60	Moderate impairment A
30 to < 45	Moderate impairment B
< 30	Severe impairment

eGFR = estimated glomerular filtration rate

Only minor differences were seen between Moderate impairment A and Moderate impairment B, thus these patients are presented collectively as Moderate impairment. At baseline, the age, percentage of patients with a history of hypertension, and percentage of patients with a duration of diabetes greater than five years increased as renal function worsened. The incidence of adverse events increased as renal function worsened (Table 153). The proportion of patients who discontinued due to an adverse event also increased as renal function decreased. There was no increased incidence with empagliflozin treatment vs. placebo/comparator-treated patients.

In patients with normal renal function at baseline, adverse events were reported more frequently in the empagliflozin-treated patients. In patients with mild renal impairment, the frequency of adverse events was similar between groups. For patients with moderate renal impairment, adverse events were reported less frequently in the empagliflozin-treated patients, but there was a greater incidence of decreased renal function events in the empagliflozin-treated patients. The increased frequency of decreased renal function was due to a higher frequency of the PT “renal impairment” in the empagliflozin-treated patients. Other PTs in this SMQ were balanced between the groups.

Genital and urinary tract infections were more common in empagliflozin-treated patients regardless of baseline renal function. This is consistent with what was observed for the entire SAF-5 grouping. For the AESI of “hepatic injury”, there appeared to be an increased incidence with the 25 mg dose in patients with moderate renal impairment at baseline. This finding was not seen in other renal impairment groupings, or in the overall SAF-5 population. Its significance is unclear.

Table 153 Incidence of Adverse Events by Baseline Renal Function – Safety Grouping 5

	Normal		Mild		Moderate		Severe	
	N	%	N	%	N	%	N	%
Placebo	956		1798		714		52	
Empa 10	1079		1991		548		7	
Empa 25	1406		2391		743		56	
Any adverse event								
– Placebo	596	62.3	1222	68.0	552	77.3	45	86.5
– Empa 10	710	65.8	1357	68.2	395	72.1	7	100.0
– Empa 25	956	68.0	1645	68.8	551	74.2	45	80.4
AE leading to discontinuation								
– Placebo	37	3.9	87	4.8	55	7.7	9	17.3
– Empa 10	43	4.0	86	4.3	44	8.0	1	14.3
– Empa 25	61	4.3	101	4.2	56	7.5	8	14.3
Serious adverse events								
– Placebo	90	9.4	208	11.6	136	19.0	12	23.1
– Empa 10	86	8.0	180	9.0	80	14.6	1	14.3
– Empa 25	109	7.8	239	10.0	111	14.9	15	26.8
Decreased renal function								
– Placebo	3	0.3	8	0.4	19	2.7	6	11.5
– Empa 10	2	0.2	15	0.8	22	4.0	2	28.6
– Empa 25	3	0.2	15	0.6	33	4.4	7	12.5
Hepatic injury								
– Placebo	19	2.0	32	1.8	3	0.4	0	0.0
– Empa 10	13	1.2	28	1.4	2	0.4	0	0.0
– Empa 25	27	1.9	27	1.1	10	1.3	1	1.8
Urinary tract infection								
– Placebo	65	6.8	144	8.0	69	9.7	6	11.5
– Empa 10	82	7.6	164	8.2	75	13.7	2	28.6
– Empa 25	116	8.3	194	8.1	87	11.7	9	16.1
Genital infection								
– Placebo	9	0.9	21	1.2	5	0.7	0	0.0
– Empa 10	52	4.8	95	4.8	12	2.2	0	0.0
– Empa 25	71	5.0	117	4.9	30	4.0	0	0.0
Confirmed hypoglycemia								
– Placebo	62	6.5	206	11.5	155	21.7	20	38.5
– Empa 10	104	9.6	252	12.7	97	17.7	3	42.9
– Empa 25	103	7.3	238	10.0	145	19.5	15	26.8
Fracture events								
– Placebo	4	0.4	28	1.6	23	3.2	0	0.0
– Empa 10	17	1.6	28	1.4	14	2.6	0	0.0
– Empa 25	19	1.4	19	0.8	13	1.7	0	0.0

	Normal		Mild		Moderate		Severe	
	N	%	N	%	N	%	N	%
Volume depletion								
- Placebo	8	0.8	18	1.0	18	2.5	5	9.6
- Empa 10	10	0.9	27	1.4	14	2.6	1	14.3
- Empa 25	9	0.6	37	1.5	17	2.3	4	7.1

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; AE = adverse event

Source: Table 5.1.6: 1 (Summary of Clinical Safety)

In addition to the analysis of decreased renal function event by reported adverse events, analysis of change in eGFR by baseline renal function category was performed (Table 154). For the patients with normal renal function or mild renal impairment, the change in eGFR was similar between all treatment groups. For patients with moderate renal impairment, empagliflozin treatment resulted in a decrease in eGFR which was not seen in the placebo-treated patients. There is suggestion of dose dependence for these changes in the moderate renal impairment patients, as the Empa 10 group showed smaller median decreases than the Empa 25 group. Subjects in the severe renal impairment group showed a greater decrease compared to placebo for patients treated with empagliflozin 25 mg. The number of patients with severe renal impairment treated with Empa 10 was quite small (n=7), limiting the ability to draw conclusions from these data.

The decrease in eGFR seen with empagliflozin treatment was reversible after cessation of treatment (see 7.3.5.6).

Table 154 Changes in Estimated Glomerular Filtration Rate by Baseline Estimated Glomerular Filtration Rate – Safety Grouping 5

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3
≥ 90	955		1294		2521		956		1428	
- Baseline	102.5	95.3, 111.5	101.4	95.2, 109.9	101.9	95.3, 110.7	101.5	95.3, 110.5	101.5	95.3, 110.4
- LVOT	100.7	90.6, 111.9	98.3	88.6, 109.9	99.2	89.9, 110.6	99.3	90.9, 110.9	98.4	90.2, 110.3
- Change	-3.0	-11.0, 5.55	-4.1	-12.9, 4.1	-3.7	-12.0, 4.4	-3.6	-11.7, 4.26	-4.1	-12.1, 4.0
- % change	-2.9		-4.0		-3.6		-3.5		-4.0	

	Empa 10		Empa 25		All Empa		Placebo		All Comp	
	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3	Mdn	Q1, Q3
60 to < 90	1799		2201		4314		1798		2442	
- Baseline	75.6	68.5, 82.3	76.1	69.1, 82.6	76.0	69.0, 82.6	75.5	68.8, 82.5	76.1	69.4, 82.8
- LVOT	74.7	66.2, 83.3	75.1	67.2, 83.8	75.2	67.0, 83.7	75.8	67.5, 83.7	76	68.0, 84.1
- Change	-0.5	-6.6, 5.5	-0.3	-6.4, 6.4	-0.3	-6.4, 6.0	-0.1	-6.0, 6.1	-0.2	-6.1, 6.1
- % change	-0.7		-0.4		-0.4		-0.1		-0.3	
30 to < 60	545		729		1288		714		750	
- Baseline	51.3	44.9, 56.3	49.9	42.8, 55.4	50.6	43.8, 55.9	49.8	42.0, 55.4	50.3	42.6, 55.8
- LVOT	49.5	42.6, 56.9	48.3	39.9, 55.3	48.9	41.1, 56.0	49.4	41.4, 56.7	49.7	42.0, 57.2
- Change	-0.5	-5.7, 4.0	-1.2	-5.8, 3.7	-0.9	-5.8, 3.9	0.9	-4.1, 5.7	0.9	-4.1, 5.9
- % change	-1.0		-2.4		-1.8		1.8		1.8	
< 30	7		56		63		51			
- Baseline	28.4	27.9, 29.0	25.6	22.2, 28.6	26.7	22.4, 28.7	23.1	20.8, 26.5		
- LVOT	31.8	26.5, 46.7	22.2	17.7, 27.5	24.5	19.1, 30.7	23	18.5, 26.9		
- Change	2.5	-1.4, 18.4	-1.9	-5.1, 2.3	-1.5	-4.3, 2.8	-0.2	-3.9, 2.4		
- % change	8.8		-7.4		-5.6		-0.9			

Empa 10 = empagliflozin 10 mg; Empa 25 = empagliflozin 25 mg; All Empa = all randomized empagliflozin; All Comp = All randomized comparators; Mdn = median; Q1 = first quartile; Q3 – third quartile; LVOT = last value on treatment
Source: Table 2.1.5.1.2: 4 (SCS)

In addition to the overall evaluation of safety across studies in the development program, Study 1245.36 was a phase 3 study designed to examine the safety and efficacy of empagliflozin in patients with type 2 diabetes mellitus and renal impairment. Subjects were stratified by renal function as above, and were treated with empagliflozin as add-on to baseline therapy. The 10 mg dose of empagliflozin was studied only in mild renal impairment, while the 25 mg dose was studied in mild, moderate, and severe renal impairment.

In terms of incidence of any adverse events, there was similarity between all treatment groups in this study for patients with mild renal impairment (Table 155). Serious adverse events were more frequent with placebo than with empagliflozin, though the 25 mg dose resulted in a higher percentage of patients reporting an SAE compared to the 10 mg dose. Nothing can be said about the 10 mg dose in moderate or severe renal impairment.

Table 155 Incidence of Adverse Events by Degree of Baseline Renal Impairment – Study 1245.36

	Empa 10		Empa 25		Placebo	
Mild						
– N	98		97		95	
– Any AE (N, %)	78	79.6	71	73.2	71	74.7
– SAE (N, %)	2	2.0	7	7.2	9	9.5
Moderate						
– N	0		187		187	
– Any AE (N, %)	0	0.0	138	73.8	130	69.5
– SAE (N, %)	0	0.0	12	6.4	9	4.8
Severe						
– N	0		37		37	
– Any AE (N, %)	0	0.0	33	89.2	31	83.8
– SAE (N, %)	0	0.0	7	18.9	5	13.5

Source: Table 15.3.2.9.2.1: 1 (Study 1245.36 study report)

*spell out abbreviations

The most frequently reported SOC in this study was “Infections and infestations”, followed by “Metabolism and nutrition disorders”. The most frequently report PTs were “Hypoglycaemia” and “Urinary tract infection”. This is consistent with what was seen for the overall SAF-5 population.

7.5.4 Drug-Disease Interactions

For detailed discussion of drug-disease interactions, see the Clinical Pharmacology review by Manoj Khurana.

Exposure to empagliflozin increased with renal impairment. Discussion of the efficacy and safety of empagliflozin in renal impairment can be found in Sections 6.1.7.1 and 7.5.3.4, respectively, of this review. Subjects with liver disease were excluded from the phase 3 studies, limiting the information that can be stated with regards the interaction of liver disease on empagliflozin. A phase 1 clinical study (1245.13) was performed in patients with varying degrees of hepatic impairment (as defined by Childs-Pugh score). A single dose of empagliflozin 50 mg was administered to patients. Though increases in exposure were seen with hepatic impairment, the Applicant did not feel these differences were clinically meaningful. Few adverse events were reported, and no increased incidence of adverse events was seen in the patients with hepatic impairment vs. the healthy volunteers. As this was a single dose trial, no conclusions should be drawn on the safety and efficacy of empagliflozin in hepatic impairment.

7.5.5 Drug-Drug Interactions

For detailed discussion of drug-drug interactions, see the Clinical Pharmacology review by Manoj Khurana. All drug-drug interaction studies were performed in healthy volunteers. No clinically relevant pharmacokinetic interaction was reported by the Applicant.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Please refer to 7.3.5.7.1. There was a small imbalance in lung cancers and melanomas between the empagliflozin-treated patients and the comparator-treated patients. The absence of a plausible mechanism and the small number of cases without known risk factors limits the confidence with which conclusions can be made, but there is no convincing evidence of carcinogenicity with empagliflozin.

7.6.2 Human Reproduction and Pregnancy Data

Based on the nonclinical data, empagliflozin is not expected to impact fertility, implantation, or fetal development. Inhibition of rat pup weight gain was observed when doses ≥ 10 mg/kg/day of empagliflozin were administered to the mothers. This was reversible, and suspected to be due to exposure through milk.

No randomized data on use in pregnant or nursing women were collected as they were excluded from any study in the development program. Women of child-bearing potential had pregnancy testing and were counseled to use an acceptable form of contraception. Nevertheless, 8 patients became pregnant while being treated with study medication. Study medication was stopped in all cases, and the patients were followed to birth or termination. Four of the 8 patients were taking empagliflozin at the time of discovery of the pregnancy.

Table 156 Subjects with Pregnancy While on Study Medication

Subject ID	Treatment	Exposure before pregnancy (days) ¹	Exposure during pregnancy (days) ²	Outcome
1245-0009-008916	Empa 10	523	22	Induced abortion
1245-0019-011631	Placebo	67	46	Healthy baby girl
1245-0020-020348	Empa 25	4	33	Miscarriage
1245-0025 (b) (4)	Placebo	207	37	Healthy baby girl
1245-0028-082578	Glimepiride	113	36	Healthy baby girl
1245-0028-086509	Glimepiride	320	46	Miscarriage
1245-0031-034570	Empa 25	60	217	Healthy baby girl
1245-0038-806010	Empa 25	43	2	Healthy baby boy

¹(day of last menstrual period or day of first positive pregnancy test) – (day of first dose of randomized study medication) + 1

²(day of last dose of randomized study medication) – (day of last menstrual period or day of first positive pregnancy test) + 1

Source: Table 5.4: 1 (Summary of Clinical Safety)

No safety conclusions can be drawn from this limited clinical data.

7.6.3 Pediatrics and Assessment of Effects on Growth

No clinical data are available on the use of empagliflozin in pediatric patients or effects on growth.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

There is little concern for overdose with empagliflozin. The proposed dosage strength (b) (4) once daily. Higher doses (single doses up to 800 mg, repeated doses of 100 mg for eight days) have been used in the development program in healthy volunteers and patients with T2DM, and no specific safety concerns became apparent. Theoretical risks with overdose would be further increases in and/or prolonged urinary glucose excretion, with possible hypoglycemia and hypovolemia. Both of these theoretical concerns could be readily monitored and managed if overdose occurs.

There is no concern for drug abuse with empagliflozin. There is no indication that there is an impact on the central nervous system, and there was no evidence of drug-seeking behavior or drug abuse in the clinical studies.

Subjects were followed for a minimum of one week after discontinuation of study drug. There were no reported adverse events of withdrawal syndrome or rebound. For the examined efficacy

and safety parameters¹, discontinuation of empagliflozin typically resulted in a return to baseline.

7.7 Additional Submissions / Safety Issues

None.

8. Postmarket Experience

Not applicable. Empagliflozin is not currently approved for marketing in the United States or in any other country.

9. Appendices

9.1 Literature Review/References

None.

9.2 Labeling Recommendations

General recommendations for labeling include:

1. Addition of the 10 mg dosage with the recommended starting dose being 10 mg once daily. The label will need to be modified throughout to include data for the 10 mg dose.
2. Dosage can be increased to 25 mg
3. Cautious use in elderly patients and in patients with moderate renal impairment. The 25 mg dose not recommended in these patients.
4. Addition of language discussing increased risk of volume depletion when used concomitantly with other diuretics, particularly loop diuretics
5. Removal of (b) (4) data
6. Removal of data (b) (4) patients
7. Removal of (b) (4)
8. Removal of (b) (4)
9. Edits to language to harmonize the label with the canagliflozin label

Detailed labeling recommendations will be discussed in dedicated labeling meetings.

¹Fasting plasma glucose, body weight, blood pressure, basal insulin dose, serum creatinine, hemoglobin/hematocrit, and uric acid

9.3 Advisory Committee Meeting

Not applicable.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H CHONG
11/05/2013

KAREN M MAHONEY
11/05/2013

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 204629

**Applicant: Boehringer
Ingelheim Pharmaceuticals
Inc**

Stamp Date: March 5, 2013

Drug Name: Empagliflozin

NDA/BLA Type: NME

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.				The application has been submitted in eCTD format
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			Submitted as Summary of Clinical Safety (SCS)
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			Submitted as Summary of Clinical Efficacy (SCE)
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			Submitted in the clinical overview
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?				This is a 505(b)(1) Application
DOSE					
13.	<p>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)?</p> <p>1. <u>Study Number:</u> 1245.9 <u>Study Title:</u> A phase IIb, randomized, parallel group safety, efficacy, and pharmacokinetics study of BI 10773 (5 mg, 10 mg, and 25 mg) administered orally once daily over 12 weeks compared double blind to placebo, as</p>	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>monotherapy, with an additional open-label metformin arm in type 2 diabetic patients with insufficient glycemic control <u>Location in submission:</u> 5.3.5.1</p> <p>2. <u>Study Number:</u> 1245.10 <u>Study Title:</u> A phase IIb, randomized, parallel group safety, efficacy, and pharmacokinetics study of BI 10773 (1 mg, 5 mg, 10 mg, 25 mg, and 50 mg) administered orally once daily over 12 weeks compared double blind to placebo with an additional open-label sitagliptin arm in type 2 diabetic patients with insufficient glycemic control despite metformin therapy <u>Location in submission:</u> 5.3.5.1</p> <p>3. <u>Study Number:</u> 1245.19 <u>Study Title:</u> A randomised, double-blind, placebo-controlled parallel group efficacy and safety trial of BI 10773 (10 and 25 mg administered orally once daily) over 24 weeks in patients with type 2 diabetes mellitus with insufficient glycaemic control despite a background therapy of pioglitazone alone or in combination with metformin <u>Location in submission:</u> 5.3.5.1</p> <p>4. <u>Study Number:</u> 1245.20 <u>Study Title:</u> A phase III randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 10773 and sitagliptin administered orally over 24 weeks, in drug naïve patients with type 2 diabetes mellitus and insufficient glycaemic control despite diet and exercise <u>Location in submission:</u> 5.3.5.1</p> <p>5. <u>Study Number:</u> 1245.23 <u>Study Title:</u> A phase III randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 10773 (10 mg, 25 mg) administered orally, once daily over 24 weeks in patients with type 2 diabetes mellitus with insufficient glycaemic control despite treatment with metformin alone or metformin in combination with a sulphonylurea <u>Location in submission:</u> 5.3.5.1</p>				
EFFICACY					
14.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>Pivotal Clinical Trials</p> <p>1. 1245.19: A randomised, double-blind, placebo-controlled parallel group efficacy and safety trial</p>	X			

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	<p>of BI 10773 (10 and 25 mg administered orally once daily) over 24 weeks in patients with type 2 diabetes mellitus with insufficient glycaemic control despite a background therapy of pioglitazone alone or in combination with metformin</p> <p>2. 1245.20: A phase III randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 10773 and sitagliptin administered orally over 24 weeks, in drug naïve patients with type 2 diabetes mellitus and insufficient glycaemic control despite diet and exercise</p> <p>3. 1245.23: A phase III randomised, double-blind, placebo-controlled, parallel group, efficacy and safety study of BI 10773 (10 mg, 25 mg) administered orally, once daily over 24 weeks in patients with type 2 diabetes mellitus with insufficient glycaemic control despite treatment with metformin alone or metformin in combination with a sulphonylurea</p>				
15.	Do all pivotal efficacy studies appear to be adequate and 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?	X			
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	Submitted studies are multi-national studies, including the United States
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.	<p>Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product (<i>e.g.</i>, QT interval studies, if needed)?</p> <p>Study 1245.16: Assessment of 25 mg and 200 mg of BI 10772 as a single dose on the QT interval in healthy female and male subjects.</p> <ul style="list-style-type: none"> - A randomised, placebo controlled, double blind, five period crossover Phase-I-study with moxifloxacin as a positive control 	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
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			6594 subjects exposed for ≥ 24 weeks - 2856 empa 10 mg - 3738 empa 25 mg 4261 subjects exposed for ≥ 52 weeks - 1720 empa 10 mg - 2541 empa 25 mg 1482 subjects exposed for ≥ 76 weeks - 601 empa 10 mg - 881 empa 25 mg
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 v15.0
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 (<i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			Waiver requested for ages 0-9, Deferral requested for ages 10-18
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	Submitted studies are multi-national studies, including the United States

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).

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
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

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

William H. Chong

Reviewing Medical Officer

Date

Karen Mahoney

Clinical Team Leader

Date

File name: 5_Clinical Filing Checklist for NDA_BLA or Supplement 010908

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

WILLIAM H CHONG
05/02/2013

KAREN M MAHONEY
05/03/2013