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RESEARCH**

APPLICATION NUMBER:

204629Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	July 31, 2014
From	William H. Chong
Subject	Cross-Discipline Team Leader Review
NDA/BLA #	NDA-204629; SD-35
Applicant	Boehringer Ingelheim
Date of Submission	June 3, 2014
PDUFA Goal Date	August 3, 2014
Proprietary Name / Established (USAN) names	JARDIANCE (empagliflozin)
Dosage forms / Strength	10 mg and 25 mg oral tablet
Proposed Indication(s)	Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Recommended:	<i>Approval</i>

Cross Discipline Team Leader Review

1. Introduction

Empagliflozin is a sodium glucose cotransporter 2 (SGLT2) inhibitor developed as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. The initial new drug application (NDA) was submitted on March 3, 2013. Due to concerns from the Office of Compliance with regard to Good Manufacturing Practices, a Complete Response letter was issued on March 4, 2014.

Subsequent to this, the Food and Drug Administration's (FDA's) Division of International Drug Quality notified the Applicant on May 28, 2013 that the facility of concern has been classified as acceptable. The Applicant has now submitted a Class 1 Resubmission for empagliflozin. The only new information included in this resubmission is a safety update.

The focus of this Cross-Discipline Team Leader (CDTL) review will be on the updated safety information and comparison with the safety findings from the initial NDA submission. Information reviewed and discussed during the initial NDA submission will not be discussed in this review. This information has been reviewed by Dr. Karen Mahoney in her CDTL review (dated February 27, 2014).

2. Background

Type 2 diabetes mellitus (T2DM) is a disease of abnormal glucose homeostasis which results in hyperglycemia. It is one of the most prevalent diseases in the United States and is associated with serious complications including cardiovascular disease, renal impairment, and blindness. Glycemic control has been the accepted target for therapies as studies have shown that improved glycemic control can improve clinical outcomes^{1,2}.

Many agents have been approved for use in improving glycemic control for patients with T2DM, and treatment with multiple agents is common. Despite the availability of many different drug classes, achievement of adequate glycemic control continues to elude many patients. There is a need for additional agents to treat T2DM.

¹ UK Prospective Study Group. "Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*, 1998; 352(9131): 837-853.

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

The SGLT2 inhibitors are the newest class of drugs to be approved for the treatment of T2DM. The mechanism of action for these drugs is to block renal glucose reabsorption. This in turn leads to renal glucose wasting and improved blood glucose levels. Two SGLT2 inhibitors (canagliflozin and dapagliflozin) have been approved for use in the United States. Empagliflozin would be the third member of this drug class. At the time of the data cut-off for the safety update (March 4, 2014), empagliflozin was not approved in any country. Since that time, The European Commission has adopted a decision to grant marketing authorization on May 22, 2014, and the Therapeutic Good Administration of Australia approved the registration of empagliflozin on April 7, 2014.

3. CMC/Device

No new Chemistry, Manufacturing and Controls (CMC) information is included in the NDA resubmission. For detailed discussion of the CMC reviewer's findings and recommendations see Dr. Joseph Leginus' reviews (dated September 13, 2013 and November 6, 2013). This information has been reviewed by Dr. Karen Mahoney in her CDTL review (dated February 27, 2014). No approval issues were identified in the CMC review, but there were concerns regarding GMP at a manufacturing facility. This led to the issuance of a Complete Response letter. These concerns have been addressed by the Applicant, and a letter classifying the facility as acceptable was issued on May 28, 2014 (see Appendix).

No CMC issues that would preclude approval have been identified.

4. Nonclinical Pharmacology/Toxicology

No new Pharmacology/Toxicology information is included in the NDA resubmission. For detailed discussion of the Pharmacology/Toxicology reviewer's findings and recommendations see Dr. Mukesh Summan's primary review (dated November 5, 2013) and Dr. Todd Bourcier's secondary review (dated November 7, 2013). This information has been reviewed by Dr. Karen Mahoney in her CDTL review (dated February 27, 2014).

No Pharmacology/Toxicology issues that would preclude approval have been identified.

5. Clinical Pharmacology/Biopharmaceutics

No new Clinical Pharmacology information is included in the NDA resubmission. For detailed discussion of the Clinical Pharmacology reviewer's findings and recommendations see Dr. Manoj Khurana's review (dated November 8, 2013). This information has been reviewed by Dr. Karen Mahoney in her CDTL review (dated February 27, 2014).

No Clinical Pharmacology issues that would preclude approval have been identified.

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

No new efficacy information is included in the NDA resubmission. For detailed discussion of the efficacy of empagliflozin see Dr. Dongmei Liu's review (dated October 30, 2013). This information has been reviewed by Dr. Karen Mahoney in her CDTL review (dated February 27, 2014).

To briefly summarize the efficacy findings, two doses of empagliflozin were studied in the phase 3 studies: 10 mg and 25 mg. The primary endpoint in all of the phase 3 studies was change in hemoglobin A1c (HbA1c). In all of the trials, both doses of empagliflozin demonstrated superiority to placebo in reducing HbA1c (Table 1).

Table 1: Summary of primary efficacy results for the pivotal phase 3 trials

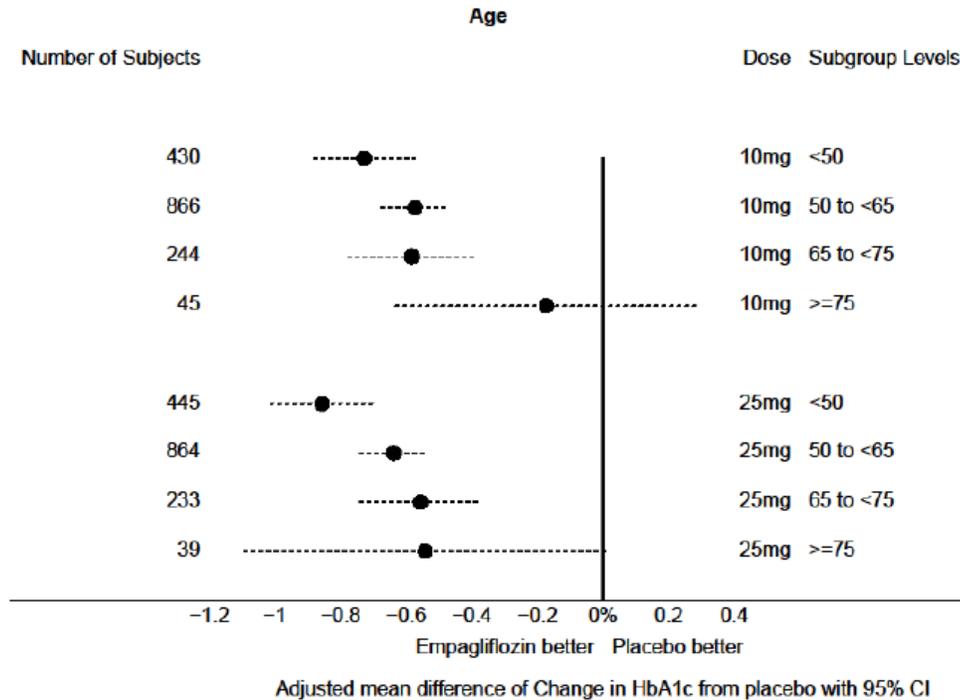
Trial /Treatment Group	Number of subjects	Baseline HbA1c Mean (SE)	Change from Baseline at Week 24 Mean (SE)	Difference from Placebo		
				Adjusted Mean Difference	97.5% CI	P value
1245.20 (monotherapy)						
Placebo	228	7.91 (0.05)	0.06 (0.05)	---	---	---
Empagliflozin 10 mg	224	7.87 (0.06)	-0.66 (0.05)	-0.72	(-0.89, -0.56)	<0.0001
Empagliflozin 25 mg	224	7.86 (-.06)	-0.77 (0.06)	-0.83	(-0.99, -0.68)	<0.0001
Sitagliptin	223	7.85 (0.05)	-0.65 (0.05)	-0.70	(-0.86, -0.54)	<0.0001
1245.23_(met) (metformin background)						
Placebo	207	7.90 (0.06)	-0.13 (0.05)	---	---	---
Empagliflozin 10 mg	217	7.94 (0.05)	-0.72 (0.05)	-0.57	(-0.72, -0.42)	<0.0001
Empagliflozin 25 mg	213	7.86 (0.06)	-0.75 (0.06)	-0.64	(-0.79, -0.48)	<0.0001
1245.23_(met+SU) (metformin + sulphonylurea background)						
Placebo	225	8.15 (0.06)	-0.18 (0.05)	---	---	---
Empagliflozin 10 mg	225	8.07 (0.05)	-0.80 (0.05)	-0.64	(-0.79, -0.49)	<0.0001
Empagliflozin 25 mg	216	8.10 (0.06)	-0.77 (0.05)	-0.60	(-0.76, -0.44)	<0.0001
1245.19 (pioglitazone ± metformin background)						
Placebo	165	8.16 (0.07)	-0.14 (0.08)	---	---	---
Empagliflozin 10 mg	165	8.07 (0.07)	-0.57 (0.07)	-0.48	(-0.70, -0.26)	<0.0001
Empagliflozin 25 mg	168	8.06 (0.06)	-0.70 (0.07)	-0.63	(-0.85, -0.41)	<0.0001

Source: Table 3 from Dr. Dongmei Liu's primary Statistical review (dated October 30, 2013)

The Applicant used the Last Observation Carried Forward method for imputing data, which is not currently recommended by the FDA. Sensitivity analyses using other methods produced similar results. Subgroup analyses were performed based on specific demographic features. These included age, gender, race, ethnicity, baseline HbA1c, and renal function. There was a suggestion of an interaction for age (Figure 1) and gender (Figure 2). The reduction in HbA1c

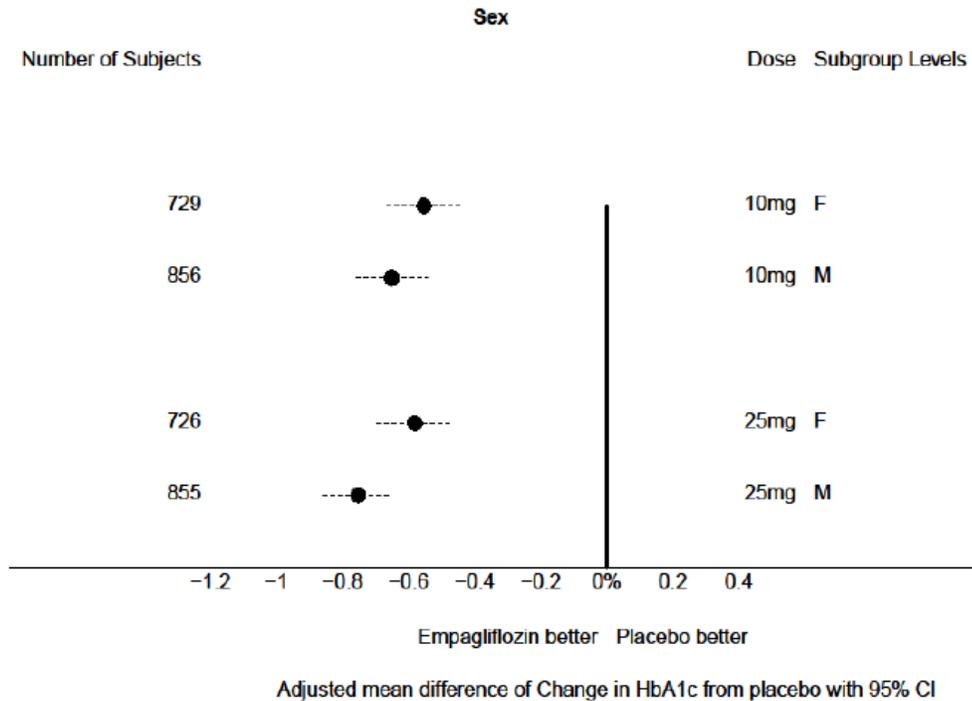
was smaller for older patients compared to younger patients, and for women compared to men. There was a clear interaction between renal function and efficacy with empagliflozin being less efficacious in patients with worse renal function (Figure 3). This may be an expected finding based on the mechanism of action. Additionally, this observation is consistent with other members of the drug class. Whether the effect of renal function on efficacy plays a role on the observed interaction with age and gender is not clear.

Figure 1: Change in hemoglobin A1c by baseline age



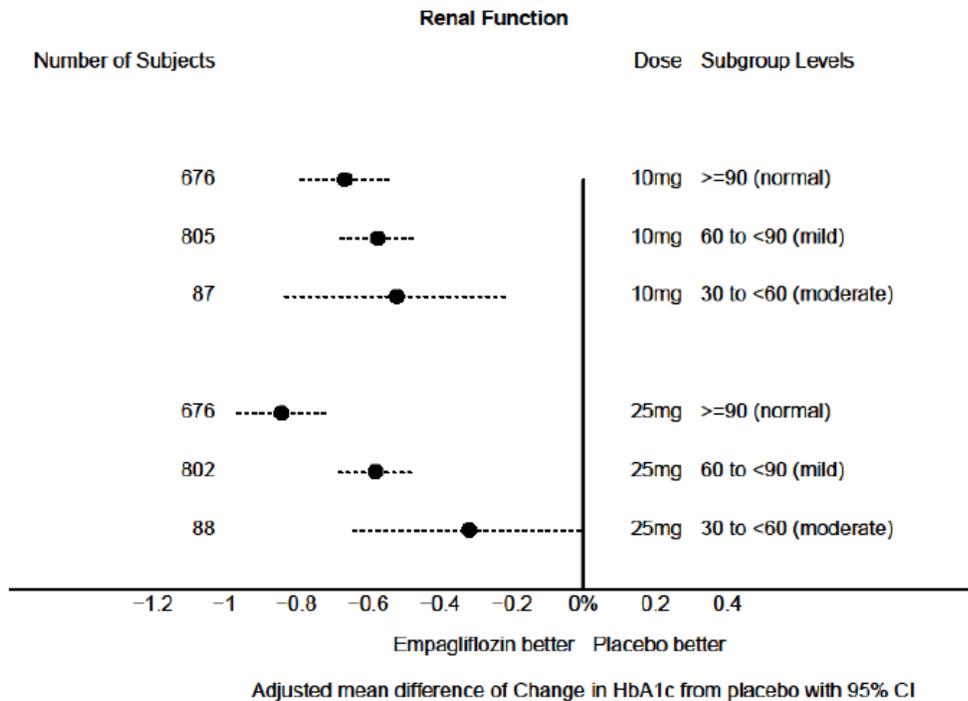
Source: Figure 6 from Dr. Dongmei Liu's primary Statistical review (dated October 30, 2013)

Figure 2: Change in hemoglobin A1c by gender



Source: Figure 7 from Dr. Dongmei Liu's primary Statistical review (dated October 30, 2013)

Figure 3: Change in hemoglobin A1c by baseline renal function



Source: Figure 14 from Dr. Dongmei Liu's primary Statistical review (dated October 30, 2013)

Secondary endpoints analyzed during the initial NDA review included changes in body weight, changes in fasting plasma glucose, ability to achieve target HbA1c, and changes in blood pressure. See Dr. Dongmei Liu’s primary statistical review (dated October 30, 2013), my primary clinical review (dated November 5, 2013), and Dr. Karen Mahoney’s CDTL review (dated February 27, 2014) for discussion of these secondary endpoints.

In the initial NDA submission, the Applicant proposed approval and marketing of the 25 mg dose only. The efficacy data supports approval and marketing of both the 10 mg and 25 mg dose. While the difference in HbA1c reduction between the two doses was small (~0.1%) and the evidence of additional benefit on this endpoint did not consistently favor the 25 mg dose (see HbA1c change from baseline in study 1245.23_{met+SU}), the 25 mg dose was consistently better in the percentage of patients achieving a target HbA1c < 7.0% (Table 2). Other secondary endpoints also suggested that the 25 mg dose offered some additional benefit over the 10 mg dose (see my primary clinical review, dated November 5, 2013). During the initial review cycle, it was discussed with the Applicant that both doses demonstrated efficacy and that the FDA would favor approval of both doses. An updated label with both doses was submitted for review during the initial review cycle. In this resubmission, both doses are included in the proposed label.

Table 2: Percentage of Patients Achieving Hemoglobin A1c < 7.0% - 24 Weeks, Full Analysis Set, Noncompleters Considered Failure

– For patients with baseline Hemoglobin A1c ≥ 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				

	N	n	%	OR	95% CI		p-value
					LL	UL	
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: Adapted from Table 3.2.1.1.1: 2 of the Summary of Clinical Efficacy

No efficacy issues which would preclude approval have been identified.

8. Safety

The safety database included in the initial NDA submission was adequate for an assessment of safety. Safety issues identified during the initial NDA review included:

- Genitourinary infections
- Volume depletion
- Changes in renal function
- Hypoglycemia
- Changes in serum cholesterol
- Changes in hematocrit

Other safety issues considered during the initial NDA review included:

- Malignancy (specifically lung cancer and melanoma)
- Hepatotoxicity
- Cardiovascular risk

For the safety update submitted with the NDA resubmission, a safety set identified as SAF-5+ by the Applicant was used for the primary updated safety analyses. Unblinded data from a completed study (study 1245.49 [add-on to multiple daily injections of insulin]), and final analyses from study 1245.31 (extension of the pivotal phase 3 studies) and study 1245.28 (empagliflozin vs. glimepiride) have been incorporated into the data from the initial NDA submission and the 4 month safety update. No additional data from the ongoing cardiovascular outcomes study (study 1245.25) is included. This is acceptable.

Compared to the original safety pool (SAF-5), there are an additional 529 patients randomized and treated for SAF-5+ (Table 3). Exposure to study drug also increased (Table 4). The

majority of this data comes from study 1245.49. It should be noted that there were 34 patients removed from the original SAF-5 and not included in the safety update as the study sites where these patient were enrolled were discontinued due to serious non-compliance. These patients are not included in the tabulations for SAF-5+, and the Applicant states that none of these patients died, experienced a malignancy event, or had elevated liver transaminases.

Table 3: Number of patients in the original safety pool compared to the safety update

	Placebo	Empa 10	Empa 25	All Empa	Active Comparator
SAF-5	3522	3630	4602	8400	1154
SAF-5+	3695	3806	4782	8756	1154
All studies in update ¹	3802	4928	5905	11001	1484

¹ includes studies not included in SAF-5+ (i.e. study 1245.52, study 1275.1, and study 1276.10)

Empa = empagliflozin; SAF-5 = original safety pool; SAF-5+ = updated safety pool

Source: Adapted from Table 1.2: 2, Table 1.2: 3, Table 1.2: 4, and Table 1.2:5 of the Summary of Clinical Safety Update

Since there were no additional patients treated with an active comparator in SAF-5+, I will focus my discussion of safety in comparison to placebo.

Table 4: Exposure to study drug in the original safety pool compared to the safety update
- expressed in patient-years

	Placebo	Empa 10	Empa 25	All Empa
SAF-5	2758.1	3258.2	4448.1	7827.8
SAF-5+	3253.5	3840.1	5648.5	9610.2

Empa = empagliflozin; SAF-5 = original safety pool; SAF-5+ = updated safety pool

Source: Adapted from Table 1.2:2 of the Summary of Clinical Safety Update

The Applicant reports that there were other studies where patients were exposed to empagliflozin that are not incorporated into SAF-5+ (Table 5). The rationale for not including these studies is that they are conducted with different products, for different indications, in different patient populations, or were of a different design. Safety data for these studies are separately presented by the Applicant. This approach seems acceptable.

Table 5: Studies not incorporated into SAF-5+

Study	Description	Rationale
1245.52	Uncontrolled, 52-week safety study only in Japanese patients	Uncontrolled, different patient population
1245.53	PK/PD study only in Japanese patients	Phase 1 study, different patient population
1245.35	4 week study of postprandial glucose only in Japanese patients	Different patient population
1245.46	Open-label, 8-week, adjunct to insulin study in patients with type 1 diabetes	Different patient population
1275.1	52 week, factorial study of the empagliflozin/linagliptin FDC	Different drug product, different design
1275.9	24 week study of the empagliflozin/linagliptin FDC compared to linagliptin	Different drug product
1275.10	24 week study of the empagliflozin/linagliptin FDC compared to empagliflozin	Different drug product
1276.6, 1276.7, 1276.8	Single dose, open-label, bioequivalence studies for the empagliflozin/metformin FDC	Phase 1 study, different drug product
1276.10	16 week study of empagliflozin once daily versus twice daily as add-on to metformin	Different dose regimen, different drug product
1276.13	Single-dose, open-label, bioequivalence study for the empagliflozin/metformin XR FDC	Phase 1 study, different drug product

PK = pharmacokinetics; PD = pharmacodynamics; FDC = fixed dose combination; XR = extended release
Source: Adapted from pages 12 and 13 of the Summary of Clinical Safety Update

Adverse events (AEs) have been coded using an updated version of the Medical Dictionary for Regulatory Activities (MedDRA). In the original NDA submission, version 15.0 was used while version 16.1 is used for the safety update. This change resulted in some changes to the customized MedDRA queries (CMQs) used for the adverse events of special interest (AESIs). Otherwise adverse events were evaluated using the same approach that was used in the initial NDA submission. See my primary clinical review (dated November 5, 2013) for details.

8.1 Disposition

There was no evident difference in the discontinuation rate between SAF-5 and SAF-5+ (Table 6). Reasons for discontinuation were similar between SAF-5 and SAF-5+.

Table 6: Summary of discontinuation for the original safety pool and the updated safety pool

	SAF-5		SAF-5+	
	N	%	N	%
Treated	12873	100.0	13402	100.0
Discontinued study drug	2184	17.0	2712	20.2
- due to AE	506	3.9	595	4.4
- worsening of study disease	35	0.3	33	0.2
- worsening of other disease	61	0.5	77	0.6
- other AE	412	3.2	485	3.6
- lack of efficacy	33	0.3	36	0.3

SAF-5 = original safety pool; SAF-5+ = updated safety pool; AE = adverse event

Source: Adapted from Table 1.2: 1 of Summary of Clinical Safety Update

8.2 Adverse Events

Comparison of deaths, nonfatal serious adverse events, and AESIs will be separated and discussed further in this section. While there was a small increase in the incidence of adverse events in the updated safety pool, these increases were seen equally across all treatment groups. Additionally, the event rate (reported as per 100 patient-years) did not change with SAF-5+ compared to SAF-5 (Table 7).

Table 7: Overall adverse events

	Placebo			Empa 10			Empa 25			All Empa		
	N	pt-yrs		N	pt-yrs		N	pt-yrs		N	pt-yrs	
SAF-5	3522	2758.1		3630	3258.2		4602	4448.1		8400	7827.8	
SAF-5+	3695	3253.5		3487	3840.1		4465	5648.5		8553	9610.2	
	N	%	per 100	N	%	per 100	N	%	per 100	N	%	per 100
SAF-5												
Any AE	2415	68.6	87.6	2472	68.1	75.9	3199	69.5	71.9	5785	68.9	73.9
SAE	446	12.7	16.2	347	9.6	10.7	474	10.3	10.7	830	9.9	10.6
AESI												
- Decreased renal function	36	1.0	1.3	41	1.1	1.3	58	1.3	1.3	99	1.2	1.3
- Hepatic injury	54	1.5	2.0	43	1.2	1.3	65	1.4	1.5	111	1.3	1.4
- Urinary tract infection	284	8.1	10.3	324	8.9	9.9	406	8.8	9.1	737	8.8	9.4
- Genital infection	35	1.0	1.3	160	4.4	4.9	218	4.7	4.9	386	4.6	4.9
- Confirmed hypoglycemia	443	12.6	16.1	457	12.6	14.0	501	10.9	11.3	963	11.5	12.3
- Bone fracture	55	1.6	2.0	59	1.6	1.8	51	1.1	1.1	110	1.3	1.4
- Volume depletion	49	1.4	1.8	52	1.4	1.6	67	1.5	1.5	119	1.4	1.5
- Malignancy	32	0.9	1.2	37	1.0	1.1	51	1.1	1.1	89	1.1	1.1
SAF-5+												
Any AE	2621	70.9	80.6	2686	77.0	69.9	3499	78.4	61.9	6299	73.6	65.5
SAE	494	13.4	15.2	393	11.3	10.2	573	12.8	10.1	975	11.4	10.1
AESI												
- Decreased renal function	36	1.0	1.1	46	1.3	1.2	64	1.4	1.1	110	1.3	1.1
- Hepatic injury	66	1.8	2.0	52	1.5	1.4	82	1.8	1.5	137	1.6	1.4
- Urinary tract infection	344	9.3	10.6	374	10.7	9.7	497	11.1	8.8	878	10.3	9.1
- Genital infection	41	1.1	1.3	177	5.1	4.6	268	6.0	4.7	453	5.3	4.7
- Confirmed hypoglycemia	567	15.3	17.4	562	16.1	14.6	627	14.0	11.1	1194	14.0	12.4
- Bone fracture	67	1.8	2.1	66	1.9	1.7	63	1.4	1.1	129	1.5	1.3
- Volume depletion	51	1.4	1.6	57	1.6	1.5	74	1.7	1.3	131	1.5	1.4
- Malignancy	36	1.0	1.1	46	1.3	1.2	67	1.5	1.2	114	1.3	1.2

Empa = empagliflozin; SAF-5 = original safety pool; SAF-5+ = updated safety pool; pt-yrs = patient years; per 100 = estimate of event rate per 100 patient-years (calculated using number of patients / exposure x 100); AE = adverse event; SAE = serious adverse event; AESI = adverse event of special interest

Source: Adapted from Table 2: 1 of the Summary of Clinical Safety Update and Table 4 of this review

8.2.1 Deaths

For the updated safety pool (SAF-5+), there were an additional eight deaths. Four of the deaths came from empagliflozin treated patients (1 from Empa 10, 3 from Empa 25), and four came from active comparators (3 from glimepiride, 1 from sitagliptin). This small number of additional deaths did not noticeably change the incidence of death or the rate of death events compared to SAF-5 (Table 8).

Table 8: Comparison of on-treatment deaths between original safety pool and updated safety pool

- does not include deaths from active comparators

	Placebo	Empa 10	Empa 25	All Empa
SAF-5				
N	3522	3630	4602	8400
Exposure (years)	2758.1	3258.2	4448.1	7827.8
Deaths (N, %)	29 (0.8%)	18 (0.5)	23 (0.5)	41 (0.5)
Per 100	1.04	0.55	0.51	0.52
SAF-5+				
N	3695	3806	4782	8756
Exposure (years)	3253.5	3840.1	5648.5	9610.2
Deaths (N, %)	29 (0.8)	19 (0.5)	26 (0.5)	45 (0.5)
Per 100	0.88	0.49	0.46	0.46

Empa = empagliflozin; SAF-5 = original safety pool; SAF-5+ = updated safety pool; per 100 = events per 100 patient-years

Source: Adapted from Table 2.1.2: 1 of the Summary of Clinical Safety Update

Narratives for the additional deaths from the empagliflozin treated patients are summarized below:

Patient 1245.0019.010846 (Empa 10): Death

This 52 year old male died 480 days after randomization. Over the course of his participation in the study, he reported anginal symptoms and was advised to seek evaluation with a cardiologist. Following consultation, he was advised to start medication and to schedule an angiography. The angiography was never performed. In the submitted narrative, it is reported that he reported feeling “uneasy” while at work. After returning home, he had the same “uneasy” feeling but did not seek medical attention. Early the following morning, he had a bout of vomiting and collapsed. He was pronounced dead, no autopsy was performed.

Reviewer Comment: This is an apparent case of cardiovascular death. The history suggests undiagnosed cardiovascular disease with a fatal myocardial infarction.

Patient 1245.0028.080812 (Empa 25): Adenocarcinoma pancreas

This 59 year old male died from pancreatic cancer. Symptoms of the pancreatic cancer began prior to randomization. After 45 days of study drug treatment, he presented to the emergency room with worsening abdominal pain. Gastroscopy was performed leading to the identification of a neoplasm, initially thought to be gastric cancer. Study drug was discontinued on day 47. He had some form of surgical resection followed by radiation and chemotherapy. A second resection performed on day 143 led to a correction of the diagnosis to pancreatic adenocarcinoma. He died 484 days after randomization.

Reviewer Comment: The short duration of exposure prior to the diagnosis of cancer is unlikely to have contributed to tumorigenesis.

Patient 1245.0049.078251 (Empa 25): Lung cancer metastatic

This 57 year old male died from lung cancer. In addition to the diagnosis of T2DM, he had a history of chronic obstructive pulmonary disease and tobacco use. After 219 days of exposure to study drug, he presented with a complaint of back pain for which a CY scan was performed. A mass was identified in the right upper lobe of the lung with metastases to the rib and spine. Study drug was discontinued on day 260. The patient was treated with palliative measures and died on day 297.

Reviewer Comment: While an imbalance in lung cancers was seen in the original submission, there were many confounders. This case is confounded by the concurrent diagnosis of chronic obstructive pulmonary disease and tobacco use. No further clarity on the risk of lung cancer with empagliflozin is provided with this additional information.

Patient 1245.0019.011480 (Empa 25): Cerebrovascular accident

This 60 year old female died from a stroke. After 782 days of exposure to study drug, she had a stroke which led to hospitalization. No treatment is described in the narrative, and she died on day 785.

Reviewer Comment: Patients with diabetes mellitus are at increased risk of cardiovascular death.

(b) (4)

The Applicant has excluded the 1.8 pre-market risk margin from the upper limit of the 95% confidence interval in their cardiovascular risk meta-analysis (see Dr. Janelle Charles' Statistical Review [dated November 1, 2013]).

Deaths from the other ongoing trials are also reported in the Safety Update (Table 9). There were six deaths from study 1275.1, and one death from study 1245.52. All of these patients were treated with empagliflozin, though patients in study 1275.1 may have been treated with

the empagliflozin/linagliptin fixed dose combination product. There was no placebo controlled arm in either of these studies. These additional events do not result in meaningful changes in the evaluation of the incidence of death with empagliflozin treatment.

Table 9: Deaths from studies not included in the updated safety pool

Patient ID number	Treatment	Age (years)	Gender	Preferred term
1275.0001.098439	Empa/Lina 10/5	63	M	Hemorrhagic stroke
1275.0001.097041	Empa/Lina 10/5	53	M	Hypertensive cardiovascular disease
1275.0001.090242	Empa 10	61	M	Non-small cell lung cancer metastatic
1275.0001.099111	Empa 10	75	M	Road traffic accident
1275.0001.091001	Empa 25	77	M	Meningitis
1275.0001.095051	Empa 25	61	M	Hepatic mass
1245.0052.244008	Empa 25	72	M	Lung cancer; Colorectal cancer

ID = identification; Empa/Lina = empagliflozin/linagliptin fixed dose combination; M = male; Empa = empagliflozin

Source: Adapted from Table 2.1.2: 3 of the Summary of Clinical Safety Update and review of the included narratives

8.2.2 Serious adverse events

Comparison of the incidence of serious adverse events between SAF-5 and SAF-5+ did not demonstrate any meaningful difference (Table 7). The “Cardiac disorders” system organ class (SOC) was the most commonly reported SOC for both safety pools (Table 10). Placebo patients had a higher incidence of serious adverse events compared to either empagliflozin dose in both safety pools. Overall, the incidence in SAF-5+ was similar to SAF-5 when looking at SOC and preferred term (PT). (b) (4)



Overall, there is no evidence of increased cardiovascular risk, and as discussed in Dr. Janelle Charles’ Statistical Review (dated November 1, 2013) the 1.8 pre-market risk margin was excluded from the 95% confidence interval in the cardiovascular safety meta-analysis.

Table 10: Serious adverse events (including fatal events) for the original safety pool versus the updated safety pool

- only includes events occurring in > 0.2% by preferred term for either SAF-5 or SAF-5+

System Organ Class - Preferred Term	Placebo	Empa 10	Empa 25	All Empa
SAF-5 (N)	3522	3630	4602	8400
Cardiac disorders	(b) (4)			

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System Organ Class - Preferred Term	Placebo		Empa 10		Empa 25		All Empa	
- Unstable angina	(b) (4)							
- Acute myocardial infarction								
- Coronary artery disease								
- Cardiac failure								
- Angina pectoris								
- Myocardial infarction								
Infections and infestations	75	2.1	54	1.5	75	1.6	131	1.6
- Pneumonia	14	0.4	7	0.2	14	0.3	22	0.3
Nervous system disorders	55	1.6	43	1.2	67	1.5	110	1.3
- Cerebrovascular accident	(b) (4)							
- Transient ischemic attack	9	0.3	4	0.1	14	0.3	8	0.2
- Ischemic stroke	(b) (4)							
General disorders and administration site conditions	31	0.9	24	0.7	39	0.8	64	0.8
- Chest pain	13	0.4	5	0.1	15	0.3	21	0.3
Injury, poisoning and procedural complications	28	0.8	26	0.7	37	0.8	64	0.8
- Fall	6	0.2	5	0.1	10	0.2	15	0.2
SAF-5+ (N)	3695		3806		4782		8756	
Cardiac disorders	(b) (4)							
- Unstable angina	(b) (4)							
- Acute myocardial infarction								
- Coronary artery disease								
- Cardiac failure								
- Angina pectoris								
- Myocardial infarction								
Infections and infestations	79	2.1	65	1.7	88	1.8	155	1.8
- Pneumonia	15	0.4	11	0.3	16	0.3	28	0.3
Nervous system disorders	63	1.7	50	1.3	83	1.7	133	1.5
- Cerebrovascular accident	(b) (4)							
- Transient ischemic attack	10	0.3	3	0.1	15	0.3	18	0.2
- Ischemic stroke	(b) (4)							
General disorders and administration site conditions	31	0.8	26	0.7	39	0.8	66	0.8
- Chest pain	13	0.4	5	0.1	16	0.3	22	0.3
Injury, poisoning and procedural complications	31	0.8	31	0.8	47	1.0	79	0.9
- Fall	6	0.2	5	0.1	14	0.3	19	0.2

Empa = empagliflozin; SAF-5 = original safety pool; SAF-5+ = updated safety pool

Source: Adapted from Table 2.1.3: 1 of the Summary of Clinical Safety Update, Table 5.6.5.1 of the Integrated Summary of Safety from the Initial NDA submission, and Table 5.6.1 of the Tables for Resubmission Summary Clinical Safety Update

8.2.3 Adverse events of special interest

The adverse events discussed in more detail in this section are either concerns identified during review of the initial NDA submission or are drug class related concerns. The general concern of cardiovascular risk related to anti-diabetic medications was addressed in the initial NDA submission, and no additional analysis is included in the resubmission.

8.2.3.1 Decreased renal function

Changes in renal function are a drug class concern due to the mechanism of action. As was done with the initial NDA submission, changes in renal function were assessed by reported adverse events using the narrow standard MedDRA query (SMQ) for “acute renal failure” (SMQ 20000003), and by change in estimated glomerular filtration rate (eGFR). Decreased renal function AEs were slightly more common in the empagliflozin treated patients, but the difference was small (Table 11). In looking at sub-populations, there was an increased incidence of AEs in the patients with renal impairment at baseline and the imbalance between treatment arms became more apparent (Table 12). This is consistent with what was seen in the initial NDA submission where patients with underlying renal impairment were at increased risk of experiencing a decreased renal function AE.

Table 11: Incidence of decreased renal function in the original safety pool versus the updated safety pool

- based on “Acute renal failure” SMQ

	Placebo		Empa 10		Empa 25		All Empa	
	N	%	N	%	N	%	N	%
SAF-5 (N)	3522		3630		4602		8400	
SMQ	36	1.0	41	1.1	58	1.3	99	1.2
Preferred term								
- Renal impairment	17	0.5	24	0.7	34	0.7	58	0.7
- Acute renal failure	11	0.3	7	0.2	12	0.3	19	0.2
- Renal failure	8	0.2	9	0.2	10	0.2	19	0.2
- Azotemia	0	0.0	0	0.0	3	< 0.1	3	< 0.1
- Oliguria	0	0.0	1	< 0.1	0	0.0	1	< 0.1
- Acute prerenal failure	0	0.0	0	0.0	0	0.0	0	0.0
SAF-5+ (N)	3695		3806		4782		8756	
SMQ	36	1.0	46	1.2	64	1.3	110	1.3
Preferred term								
- Renal impairment	17	0.5	29	0.8	37	0.8	66	0.8
- Acute renal failure	11	0.3	7	0.2	13	0.3	20	0.2
- Renal failure	8	0.2	9	0.2	12	0.3	21	0.2
- Azotemia	0	0.0	0	0.0	3	0.1	3	< 0.1
- Oliguria	0	0.0	0	< 0.1	0	0.0	1	< 0.1
- Acute prerenal failure	0	0.0	0	0.0	1	< 0.1	1	< 0.1

Empa = empagliflozin; SAF-5 = original safety pool; SMQ = standardized MedDRA query; SAF-5+ = updated safety pool

Source: Adapted from Table 2.1.5.1: 2 of the Summary of Clinical Safety Update

Table 12: Incidence of decreased renal function adverse event in the original safety pool versus the updated safety pool by baseline estimated glomerular filtration rate

- estimated glomerular filtration rate expressed in ml/min/1.73 m²

	Placebo		Empa 10		Empa 25		All Empa	
	n/N	%	n/N	%	n/N	%	n/N	%
SAF-5								
≥ 90	3/956	0.3	2/1079	0.2	3/1406	0.2	5/2592	0.2
60 to < 90	8/1798	0.4	15/1991	0.8	15/2391	0.6	30/4439	0.7
45 to < 60	11/475	2.3	13/410	3.2	14/516	2.7	27/930	2.9
30 to < 45	8/239	3.3	9/138	6.5	19/227	8.4	28/365	7.7
< 30	6/52	11.5	2/7	28.6	7/56	12.5	9/63	14.3
SAF-5+								
≥ 90	3/1015	0.3	2/1143	0.2	4/1474	0.3	6/2724	0.2
60 to < 90	8/1908	0.4	18/2094	0.9	19/2500	0.8	37/4651	0.8
45 to < 60	11/479	2.3	15/419	3.6	15/521	2.9	30/944	3.2
30 to < 45	8/239	3.3	9/138	6.5	19/225 ¹	8.4	28/363 ¹	7.7
< 30	6/52	11.5	2/7	28.6	7/56	12.5	9/63	14.3

¹ the number of patients at baseline is < that in the original safety pool due to exclusion of patients due to clinical site non-compliance

Empa = empagliflozin; n = number with event; N = number at baseline; SAF-5 = original safety pool; SAF-5+ = updated safety pool

Source: Adapted from Table 2.1.5.1: 2 of the Summary of Clinical Safety Update

8.2.3.2 Hepatic injury

In the review of the initial NDA submission, no imbalance in reported liver adverse events was seen. An imbalance in liver enzyme elevations, however, was seen. Cases of concern were identified based on alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (T. Bili), and alkaline phosphatase (Alk Phos) fold-increases above the upper limit of the reference range (ULRR) and patterns of elevations³.

As was seen with the original safety pool, there was no notable imbalance in hepatic adverse events (Table 7). Consistent with SAF-5, there was a small numerical imbalance in liver enzyme elevations in the safety update (Table 13). The numerical imbalance does not favor empagliflozin, but the number and percentage of subjects is small which limits the ability to make conclusions from this observation.

³ Patterns of interest in the original NDA submission were (1) ALT/AST ≥ 3x with T. Bili ≥ 2x ULRR, and (2) ALT/AST ≥ 10x ULRR

Table 13: Patients from the original safety pool and the updated safety pool with elevated liver enzymes during treatment

	Placebo		Empa 10		Empa 25		All Empa	
	N	%	N	%	N	%	N	%
SAF-5 (N)	3522		3630		4602		8400	
ALT and/or AST \geq 3x ULRR	28	0.8	16	0.4	25	0.5	42	0.5
ALT and/or AST \geq 5x ULRR	3	0.1	6	0.2	10	0.2	16	0.2
ALT and/or AST \geq 10x ULRR	0	0.0	2	0.1	4	0.1	6	0.1
ALT and/or AST \geq 20x ULRR	0	0.0	0	0.0	1	< 0.1	1	< 0.1
ALT and/or AST \geq 3x ULRR with T. Bili \geq 2x ULRR	0	0.0	2	0.1	2	< 0.1	4	< 0.1
- Alk Phos < 2x ULRR	0	0.0	1	< 0.1	2	< 0.1	3	< 0.1
- Alk Phos \geq 2x ULRR	0	0.0	1	< 0.1	0	0.0	1	< 0.1
SAF-5+ (N)	3522		3630		4602		8400	
ALT and/or AST \geq 3x ULRR	37	1.0	21	0.6	31	0.6	53	0.6
ALT and/or AST \geq 5x ULRR	3	0.1	7	0.2	12	0.3	19	0.2
ALT and/or AST \geq 10x ULRR	0	0.0	2	0.1	5	0.1	7	0.1
ALT and/or AST \geq 20x ULRR	0	0.0	0	0.0	2	< 0.1	2	< 0.1
ALT and/or AST \geq 3x ULRR with T. Bili \geq 2x ULRR	0	0.0	1	< 0.1	2	< 0.1	3	< 0.1
- Alk Phos < 2x ULRR	0	0.0	1	< 0.1	2	< 0.1	3	< 0.1
- Alk Phos \geq 2x ULRR	0	0.0	1	< 0.1	1	< 0.1	2	< 0.1

Empa = empagliflozin; SAF-5 = original safety pool; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULRR = upper limit of reference range; T. Bili = total bilirubin; Alk Phos = alkaline phosphatase; SAF-5+ = updated safety pool

Source: Adapted from Table 2.1.5.2: 1 of the Summary of Clinical Safety Update

To identify potential cases of concern in the updated safety pool, the Applicant used the following liver enzyme patterns: (1) ALT/AST \geq 3x ULL with T. Bili \geq 2x ULRR, and (2) ALT/AST \geq 5x ULRR. It is notable that this second pattern is different from that used in the initial NDA submission (which was ALT/AST \geq 10x ULRR). The change would not be expected to obscure cases, but would increase the number of cases identified.

For SAF-5+, there were an additional six cases identified since the initial NDA submission. Of these six, two were on treatment (one from Empa 10, one from Empa 25), and four were post-treatment⁴ (three from Empa 25, one from placebo). Review of the narratives included for these cases was performed and alternatives to empagliflozin are present for all cases (Table 14). Cases reported for the other clinical studies not included in SAF-5+ were also reviewed.

⁴ Post-treatment defined in the initial NDA submission as period starting seven days after last dose of study medication.

Table 14: Patients with liver enzyme elevations of concern since the original NDA submission

Patient ID	Treatment	ALT/AST ≥ 3x ULRR, T. Bili ≥2x ULRR, Alk Phos < 2x ULRR	ALT/AST ≥ 3x ULRR, T. Bili ≥2x ULRR, Alk Phos ≥ 2x ULRR	ALT/AST ≥ 5x ULRR	Proposed alternative etiology
SAF-5+					
1245.0020.021703	E10	N	N	Y	Hepatitis B
1245.0019.010819	E25	Y	N	Y	Hepatitis E
1245.0028.086221	E25P	Y	N	N	Hepatitis E
1245.0020.023834	E25P	Y	N	Y	Other medication
1245.0049.075161	E25P	N	N	Y	Autoimmune
1245.0049.075406	PP	N	N	Y	Pancreatic cancer
Study 1245.52					
1245.0052.281002	E10	N	N	Y	Gallstone
1245.0052.213017	E10P	N	N	Y	Gallstone ¹
1245.0052.227016	E25 P	Y	N	Y	Alcohol; occurred 40 days after discontinuation of study drug
Study 1275.1					
1275.0001.099749	E10	N	N	Y	Gallbladder disease
1275.0001.095576	E/L 10/5	N	N	Y	Statin
1275.0001.095816	E10P	N	N	Y	Unknown; has history of hepatitis B, occurred one day after completing study
1275.0001.093525	E/L 10/5P	N	N	Y	Other medication; occurred one month after completion of study
Study 1276.10					
1276.0001.082471	E10	N	N	Y	Statin
1276.0001.082214	E10 ²	N	N	Y	Gallstone

¹ No narrative submitted for this case; ² administered as 5 mg twice daily

ID = identification; ALT = alanine aminotransferase; AST = aspartate aminotransferase; ULRR = upper limit of reference range; T. Bili = total bilirubin; Alk Phos = alkaline phosphatase; SAF-5+ = updated safety pool; E10 = empagliflozin 10 mg; E25 = empagliflozin 25 mg; E25P – post = empagliflozin 25 mg, post-treatment; PP = placebo, post-treatment; E10P = empagliflozin 10 mg, post-treatment; E/L 10/5 = empagliflozin/linagliptin fixed dose combination 10 mg/5 mg; E/L 10/5P = empagliflozin/linagliptin fixed dose combination 10 mg/5 mg – post-treatment

Source: Adapted from Table 2.1.5.2: 2, Table 2.1.5.2: 3, Table 2.1.5.2: 4, and Table 2.1.5.2: 5 of the Summary of Clinical Safety Update

Combining these new cases with the cases reported in the original safety pool does not substantially change the observed imbalance. The original conclusion that there do not appear to be any cases of serious hepatotoxicity with clear attribution to empagliflozin remains. The potential for hepatotoxicity should be further evaluated as an adverse event of interest in the ongoing cardiovascular safety study.

8.2.3.3 Urinary tract infection

Given the mechanism of action for SGLT2 inhibitors, genitourinary infections are a class concern. In my original review (dated November 5, 2013), there was no apparent imbalance for SAF-5 when using the Applicant defined custom MedDRA query (CMQ). In SAF-5+, there is similarly no apparent imbalance based on an Applicant defined CMQ (Table 7). A higher incidence was seen in older patients in SAF-5, and this is again seen with SAF-5+ (Table 15). Other demographic features did not appear to clearly demonstrate an increased risk with treatment.

Serious urinary tract infections (i.e. pyelonephritis and sepsis) were separately analyzed. There was no evident imbalance for these infections in SAF-5. There were no new cases in SAF-5+, thus there is no difference from the original safety pool.

Table 15: Incidence of urinary tract infections in the original safety pool and the updated safety pool based on a customized MedDRA query subdivided by age in years

	Placebo		Empa 10		Empa 25		All Empa	
	n/N	%	n/N	%	n/N	%	n/N	%
SAF-5								
< 50	44/446	9.9	35/522	6.7	66/736	9.0	102/1301	7.8
50 to < 65	142/1860	7.6	168/1908	8.8	169/2381	7.1	341/4378	7.8
65 to < 75	73/979	7.5	87/983	8.9	130/1213	10.7	218/2230	9.8
≥ 75	25/237	10.5	34/217	15.7	41/272	15.1	76/791	15.5
SAF-5+								
< 50	59/495	11.9	47/560	8.4	83/769	10.8	131/1372	9.5
50 to < 65	171/1953	8.8	195/2014	9.7	217/2483	8.7	416/4586	9.1
65 to < 75	87/1011	8.6	96/1012	9.5	151/1251	12.1	248/2297	10.8
≥ 75	27/236	11.4	36/220	16.4	46/279	16.5	83/501	16.6

Empa = empagliflozin; n = number with event; N = number at baseline; SAF-5 = original safety pool; SAF-5+ = updated safety pool

Source: Adapted from Table 2.1.5.3: 1 of the Summary of Clinical Safety Update

8.2.3.4 Genital infection

Given the mechanism of action for SGLT2 inhibitors, genitourinary infections are a class concern. From my original clinical review (dated November 5, 2013), an imbalance not favoring empagliflozin for genital infections was seen. This was seen in the analysis of genital

infections by CMQ in SAF-5+ (Table 7). This increased incidence was seen for both male and female patients, though the events were more common in female patients.

Table 16: Incidence of genital infections in the original safety pool and the updated safety pool based on a customized MedDRA query subdivided by gender

	Placebo		Empa 10		Empa 25		All Empa	
	n/N	%	n/N	%	n/N	%	n/N	%
SAF-5								
Male	17/2237	0.8	79/2327	3.4	90/2911	3.1	175/5354	3.3
Female	18/1285	1.4	81/1303	6.2	128/1691	7.6	211/3046	6.9
SAF-5+								
Male	18/2301	0.8	83/2417	3.4	112/2987	3.7	201/5520	3.6
Female	23/1394	1.6	94/1389	6.8	156/1795	8.7	252/3236	7.8

Empa = empagliflozin; n = number with event; N = number at baseline; SAF-5 = original safety pool; SAF-5+ = updated safety pool

Source: Adapted from Table 2.1.5.4: 1 of the Summary of Clinical Safety Update

8.2.3.5 Bone fracture

Due to concerns regarding an imbalance in fractures seen in the canagliflozin development program, fractures were analyzed as part of the initial empagliflozin review. A CMQ was utilized to evaluate the events. In SAF-5, there were no evident imbalances, and this remains true with SAF-5+ (Table 7). This was also the case when examining the individual PTs that comprise the CMQ.

In addition to the assessment of clinical events, changes in laboratory markers of bone health (i.e. serum calcium, phosphate, 25-hydroxy vitamin D, intact parathyroid hormone, urine N-terminal telopeptide) were examined. No marked changes from baseline to end of treatment were observed in SAF-5 and the results from SAF-5+ are similar.

In study 1245.28 (empagliflozin vs. glimepiride) bone mineral density measurements were obtained as part of a body composition sub-study. No meaningful changes in T-score were noted at 52 weeks (interim analysis submitted in initial NDA submission), and the Applicant states that the additional data at 104 weeks (updated) is similar. The study report for study 1245.28 which describes this data has not yet been submitted for review.

8.2.3.6 Volume depletion

Since empagliflozin acts as a diuretic, volume depletion was a concern considered during the initial NDA review. While volume depletion did not seem to be a concern in SAF-5 overall, there were certain sub-populations (e.g. elderly patients, patients taking diuretics) where this appeared to be a concern. In SAF-5+, there did not appear to be an increased incidence with

empagliflozin in the overall population (Table 7). The sub-populations identified as at risk in SAF-5 were separately examined for SAF-5+ (Table 17). Observations similar to that seen in the initial review were seen. Older patients had a higher incidence of volume depletion events with the 25 mg dose, and patients on loop diuretics appeared to be at greater risk for volume depletion events. Interestingly, the incidence of volume depletion events was greatest in the patients treated with the 10 mg dose. Review of the updated safety information does not demonstrate any substantially different findings compared to the original safety pool.

Table 17: Incidence of volume depletion in the original safety pool and the updated safety pool based on a customized MedDRA query subdivided by age and by diuretic use

	Placebo		Empa 10		Empa 25		All Empa	
	n/N	%	n/N	%	n/N	%	n/N	%
SAF-5								
Age								
- < 50	4/446	0.9	2/522	0.4	5/736	0.7	7/1301	0.5
- 50 to < 65	19/1860	1.0	20/1908	1.0	24/2381	1.0	44/4378	1.0
- 65 to < 75	21/979	2.1	25/986	2.5	26/1213	2.1	51/2230	2.3
- ≥ 75	5/237	2.1	5/217	2.3	12/272	4.4	17/491	3.5
Diuretic at baseline								
- No	24/2400	1.0	24/2528	0.9	30/3228	0.9	54/5910	0.9
- Yes	25/1122	2.2	28/1102	2.5	37/1374	2.7	65/2490	2.6
Loop diuretic at baseline								
- No	39/3181	1.2	39/3363	1.2	56/4236	1.3	95/7766	1.2
- Yes	10/341	2.9	13/267	4.9	11/366	3.0	24/634	3.8
SAF-5+								
Age								
- < 50	4/495	0.8	2/560	0.4	9/769	1.2	11/1372	0.8
- 50 to < 65	21/1953	1.1	22/2014	1.1	25/2483	1.0	47/4586	1.0
- 65 to < 75	21/1011	2.1	28/1012	2.8	28/1251	2.2	56/2297	2.4
- ≥ 75	5/236	2.1	5/220	2.3	12/279	4.3	17/501	3.4
Diuretic at baseline								
- No	24/2505	1.0	27/2639	1.0	33/3343	1.0	60/6136	1.0
- Yes	27/1190	2.3	30/1167	2.6	41/1439	2.8	71/2620	2.7
Loop diuretic at baseline								
- No	41/3343	1.2	43/3527	1.2	62/4406	1.4	105/8100	1.3
- Yes	10/352	2.8	14/279	5.0	12/376	3.2	26/656	4.0

Empa = empagliflozin; n = number with event; N = number at baseline; SAF-5 = original safety pool; SAF-5+ = updated safety pool

Source: Adapted from Table 2.1.5.7: 2 of the Summary of Clinical Safety Update

8.2.3.7 Malignancy

Review of the initial NDA submission showed an imbalance in lung cancer and melanoma that did not favor empagliflozin. Taking the entirety of the safety data (SAF-5+ plus study 1245.52, study 1275.1, and study 1276.10), there were an additional nine cases of lung cancer and an additional two cases of melanoma (Table 18). Some of these events occurred prior to 180 days of study drug exposure.

Table 18: Number of patients with lung cancer or melanoma in the original safety pool and the combined studies submitted in the safety update

	Placebo	Empa 10	Empa 25	Active comparator
Original¹ (N)	3522	3630	4602	1154
Update² (N)	3802	4928	5905	1484
Lung cancer, any exposure				
Original (n, %)	2 (0.06)	4 (0.11)	8 (0.17)	1 (0.09)
Update (n, %)	3 (0.08)	7 (0.14)	12 (0.20)	2 (0.13)
Lung cancer, > 180 day exposure				
Original (n, %)	0 (0.00)	3 (0.08)	3 (0.07)	1 (0.09) ³
Update (n, %)	1 (0.03)	5 (0.10)	6 (0.10)	2 (0.13)
Melanoma, any exposure				
Original (n, %)	0 (0.00)	2 (0.06)	4 (0.09)	0 (0.00)
Update (n, %)	1 (0.03)	2 (0.04)	4 (0.07)	1 (0.07)
Melanoma, > 180 day exposure				
Original (n, %)	0 (0.00)	2 (0.06)	4 (0.09)	0 (0.00)
Update (n, %)	1 (0.03)	2 (0.04)	4 (0.07)	1 (0.07)

¹ Original = SAF-5; ² Update = SAF-5+ plus study 1245.52, study 1275.1, and study 1276.10; ³ not included in analysis of lung cancer events from initial submission, included here as a result of update to MedDRA version used for analysis

Empa = empagliflozin

Source: Adapted from Table 3 of this review, and Table 2.1.5.8: 5 and Table 2.1.5.8: 6 of the Summary of Clinical Safety Update

An imbalance for lung cancer that does not favor empagliflozin remains but, the difference is narrowed. The imbalance for melanoma that does not favor empagliflozin remains, but the difference is narrowed. Additionally, events in comparator patients are now present which allows for a crude estimate of risk. Previously, there were no cases in comparator. No increased concern for these malignancies results from the updated data.

The narratives of the additional cases were reviewed. Only one of the additional lung cancer cases did not have any reported risk factors. This patient was diagnosed after less than 180 days of exposure to empagliflozin. One of the two additional cases of melanoma did not have any reported risk factors. This patient was treated with placebo.

As a result of safety findings from review of other SGLT2 inhibitors, other malignancies of interest include breast cancer, bladder cancer, and renal cancer. No clear imbalance of these malignancies is seen in the updated safety data (Table 19).

Table 19: Number of patients with selected malignancy events in the original safety pool and the updated safety pool

- limited to patients with an event occurring after more than 6 months of study drug exposure

	Placebo	Empa 10	Empa 25	All Empa	All Comp
SAF-5 (N)	2281	2696	3581	6287	3295
Breast cancer (n, %)	1 (0.04)	1 (0.04)	0 (0.00)	1 (0.02)	2 (0.06)
Bladder cancer (n, %)	0 (0.00)	2 (0.07)	0 (0.00)	3 (0.05)	1 (0.03)
Renal cancer (n, %)	2 (0.09)	0 (0.00)	0 (0.00)	0 (0.00)	2 (0.06)
SAF-5+	2446	2860	3751	6621	3459
Breast cancer (n, %)	2 (0.08)	1 (0.04)	1 (0.03)	2 (0.03)	3 (0.09)
Bladder cancer (n, %)	0 (0.00)	2 (0.07)	0 (0.00)	3 (0.05)	2 (0.06)
Renal cancer (n, %)	2 (0.08)	0 (0.00)	1 (0.03)	1 (0.02)	2 (0.06)

Empa = empagliflozin; Comp = comparator; SAF-5 = original safety pool; SAF-5+ = updated safety pool

Source: Adapted from Table 2.1.5.8: 2 of the Summary of Clinical Safety Update

8.2.3.8 Hypoglycemia

With all anti-diabetic agents, there is concern that treatment may lead to hypoglycemia. In the initial NDA submission, the Applicant evaluated hypoglycemic events based on information recorded in the case report forms. Events did not need to be coded to the “Hypoglycemia” PT to be considered a hypoglycemic event. A confirmed hypoglycemic event was defined as an event with typical hypoglycemic symptoms and an associated plasma glucose \leq 70 mg/dL, or requiring assistance of another person. Asymptomatic hypoglycemia was defined as plasma glucose between 54 mg/dL and 70 mg/dL without symptoms of hypoglycemia. These were not reported as adverse events.

In SAF-5, an increased incidence of hypoglycemia was noted for patients treated with empagliflozin who had a background of insulin or sulfonylurea therapy. For SAF-5+, the incidence of confirmed hypoglycemia was essentially unchanged (Table 7). Patients treated with insulin or sulfonylureas as background therapy were more likely to have hypoglycemic events (Table 20). Though no increased incidence of hypoglycemia was seen at 52 weeks for study 1245.9 (add-on to multiple daily dose insulin), at 18 weeks (fixed dose insulin period) the patients treated with empagliflozin did have a higher incidence of hypoglycemia. The updated information is consistent with what was observed in the initial submission.

Table 20: Incidence of hypoglycemia when added to patients with a background of insulin and/or sulfonylurea

Study	Time (weeks)	Hypoglycemia Criterion	Placebo		Empa 10		Empa 25	
			n/N	%	n/N	%	n/N	%
1245.23 _{met+SU}	24	≤ 70 mg/dL	19/225	8.4	36/224	16.0	25/217	12.0
		≤ 54 mg/dL	7/225	3.1	13/224	5.8	9/217	4.1
		Assistance	0/225	0.0	0/224	0.0	0/217	0.0
	76 ⁺¹	≤ 70 mg/dL	35/225	15.6	53/224	23.7	42/217	19.4
		≤ 54 mg/dL	14/225	6.2	22/224	9.8	16/217	7.4
		Assistance	1/225	0.4	1/224	0.4	0/217	0.0
1245.33	78	≤ 70 mg/dL	60/170	35.3	61/169	36.1	56/155	36.1
		≤ 54 mg/dL	39/170	22.9	37/169	21.9	36/155	23.2
		Assistance	0/170	0.0	0/169	0.0	2/155	1.3
1245.49	18 ²	≤ 70 mg/dL	70/188	37.2	74/186	39.8	78/189	41.3
		≤ 54 mg/dL	52/188	27.7	51/186	27.4	59/189	31.2
		Assistance	1/188	0.5	1/186	0.5	1/189	0.5
	52 ³	≤ 70 mg/dL	109/188	58.0	95/186	51.1	109/189	57.7
		≤ 54 mg/dL	90/188	47.9	73/186	39.2	90/189	47.6
		Assistance	3/188	1.6	3/186	1.6	1/189	0.5

¹ includes treatment to completion of extension study 1245.31 which was ongoing until the last patient enrolled had treatment for an additional 52 weeks after the original study; ² fixed insulin dose period; ³ titratable insulin period

Empa = empagliflozin; n = number with event; N = number treated

Source: Adapted from Table 2.1.5.5: 1 of the Summary of Clinical Safety Update and Table 15.3.2.5: 3 of the study report for Study 1245.49

8.2.3.9 Laboratory Test Changes

There was no substantial difference between SAF-5 and SAF-5+ for changes in laboratory tests. An increase in hematocrit was seen, as was an increase in cholesterol. As was seen with the initial submission, there was a slight dose-dependent increase in upward categorical shifts for serum phosphate, and for downward categorical shifts for serum bicarbonate. See my primary clinical review (dated November 5, 2013) for details. The clinical significance of this remains unclear. Changes in eGFR and liver enzymes are discussed in 8.2.3.1 and 8.2.3.2.

8.2.3.10 Vital Sign Changes

There was no substantial difference between SAF-5 and SAF-5+ for changes in vital signs. A small decrease in mean systolic and diastolic blood pressure was seen. This change was < 5 mmHg, and was consistent with what was seen in SAF-5. Mean heart rate was essentially unchanged from baseline in SAF-5 and SAF-5+. See my primary clinical review (dated November 5, 2013) for details.

9. Advisory Committee Meeting

Not applicable. No Advisory Committee was held either during the initial review or during review of the resubmission.

10. *Pediatrics*

No changes or updates to the pediatric study plan that was submitted with the initial NDA submission are included in the resubmission. The Applicant will be expected to perform a pharmacokinetics and pharmacodynamics study in pediatric patients with T2DM to inform dose selection. Following this, a safety and efficacy study will be performed. The age range of the population will be 10 to < 18 years of age. Study in patients < 10 years of age will be waived.

11. *Other Relevant Regulatory Issues*

As discussed above, the Complete Response that was issued during the initial review cycle was due to concerns regarding Good Manufacturing Practices. These concerns have been addressed, and the Applicant has been issued a letter (dated May 28, 2014) stating that the manufacturing facility has been classified as acceptable.

12. *Labeling*

During the initial review cycle, some labeling issues that were addressed included the inclusion of the 10 mg and 25 mg dose, the addition of increased cholesterol, increased hematocrit, risks of renal impairment, and contraindicating use below and eGFR of 45 ml/min/1.73 m².

During review of the resubmission, issues addressed include the time of dosing, whether a study of blood pressure changes with empagliflozin should be included, and interaction with assays for urinary glucose and 1,5-anhydroglucitol. Further labeling discussions are ongoing at the time this review was completed.

13. *Recommendations/Risk Benefit Assessment*

- Recommended Regulatory Action

I recommend approval of empagliflozin as an adjunct to diet and exercise for the improvement of glycemic control in adult patients with type 2 diabetes mellitus pending final agreement on labeling.

- Risk Benefit Assessment

Overall, the data submitted in support of empagliflozin favors approval. There is consistent evidence that the use of empagliflozin improves glycemic control. Given the generally accepted belief that improving glycemic control is associated with improved clinical outcomes, this is a meaningful endpoint. Though there is some inconsistency in further HbA1c reduction

with the 25 mg dose compared to the 10 mg dose, approval of both doses is reasonable given the similarity in safety profile for the two doses. The safety concerns associated with empagliflozin and with the drug class are acceptable in light of the evident benefit. The risks appear to be addressable with labeling and proper clinical prescribing/monitoring. A summary of the benefits and risks identified follow:

Benefit:

- 1. Improved glycemic control***
- 2. Absence of negative weight effects (i.e. not associated with weight gain)***

Risks:

- 1. Volume depletion/hypotension***
- 2. Renal impairment***
- 3. Increased risk of genitourinary infections***
- 4. Hypoglycemia***
- 5. Unfavorable changes in serum lipids***
- 6. Increases in hematocrit***

Additional potential risks considered during the review include hepatotoxicity, lung cancer, melanoma, and bone fracture. The evidence is less compelling that empagliflozin is a causative factor for these, and thus they are not included in labelling. Additional data will be collected in the CVOT to further examine these events.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

No Risk Evaluation and Management Strategy is recommended for this NDA.

- Recommendation for other Postmarketing Requirements and Commitments

Recommended Postmarketing Requirements include:

1. Completion of the ongoing cardiovascular outcomes study to meet the requirements outlined in “FDA Guidance for Industry: Diabetes mellitus – evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes”. In addition to evaluating cardiovascular outcomes, data on other adverse events of interest (i.e. changes in renal function, occurrence of malignancies [lung, bladder, kidney, and melanoma], occurrence of hepatotoxicity, complicated genital infections, complicated urinary tract

infections, volume depletion events, fractures, and serious hypersensitivity events).

2. Performance of studies in pediatrics as required under PREA. This will include a pharmacokinetic/pharmacodynamic study, and a safety and efficacy study. As part of the safety and efficacy study, the effect on bone health and development will be evaluated.
3. Completion of a nonclinical juvenile toxicity study with a particular focus on renal development.

The possibility of using enhanced pharmacovigilance or other means to help assess the risk of some of these safety concerns was discussed. Ultimately it was decided that the signals were not sufficiently concerning to warrant requiring further study in a clinical study or epidemiological study. Enhanced pharmacovigilance was not felt to be a useful tool for the evaluation of lung cancer and melanoma due to the frequency in the general population of these malignancies and the absence of a control group for comparison. These events will be further assessed as part of the safety analysis of the cardiovascular safety study.

While enhanced pharmacovigilance for pregnancy outcomes was required for dapagliflozin and canagliflozin, the usefulness of this approach was questioned during the empagliflozin resubmission. Though there are concerns that exposure to SGLT2 inhibitors during pregnancy (particularly in the 2nd and 3rd trimesters), it is unclear how much useful information will be obtained through enhanced pharmacovigilance. Current prescribing practices would likely result in patients being switched to insulin therapy, thus exposure in the later part of pregnancy is unlikely. As such, it was decided that this would not be a post-marketing requirement for empagliflozin.

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/s/

WILLIAM H CHONG
07/31/2014

JEAN-MARC P GUETTIER
07/31/2014

I concur with Dr. Chong's recommendation.