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Empagliflozin (heart failure with preserved ejection fraction) –

Addendum to Commission A22-39[1]

Addendum

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Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KCCQ	Kansas City Cardiomyopathy Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
OSS	overall summary score
PT	Preferred Term
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
TSS	total symptom score

1 Background

On 9 August 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A22-39 (Empagliflozin – benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the responder analyses subsequently submitted in the commenting procedure by the pharmaceutical company (hereinafter referred to as "the company") on the individual domains of the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score (OSS) and of the composite outcome on renal morbidity and of the outcome of acute kidney injury (Preferred Term [PT]) from the EMPEROR-Preserved study, taking into account the information in the dossier [2].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The dossier assessment used the randomized controlled trial (RCT) EMPEROR-Preserved for the benefit assessment of empagliflozin. In this study, empagliflozin was compared with placebo, each in combination with optimized standard therapy.

In accordance with the commission, the following sections provide an assessment of the responder analyses subsequently submitted in the commenting procedure by the company on the individual KCCQ OSS domains, as well as of the analyses for the composite outcome on renal morbidity and the outcome of acute kidney injury (PT) available in the company's dossier.

2.1 Health-related quality of life

In the EMPEROR-Preserved study, the outcomes of health-related quality of life were recorded via the KCCQ. For the KCCQ, Module 4 A of the dossier provided responder analyses for the OSS as well as for the total symptom score (KCCQ TSS) contained therein. The KCCQ OSS also includes 3 domain scores on physical, mental and social limitations, for which no results were available in Module 4 A of the dossier. With its comments [3], the company now presented analyses on these 3 domain scores. These are presented in Table 1 together with the analyses of KCCQ OSS and KCCQ TSS already presented in the dossier assessment.

Table 1: Results (health-related quality of life, dichotomous) – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study Outcome category Outcome	Empagliflozin + optimized standard therapy		Placebo + optimized standard therapy		Empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value[b]
EMPEROR-Preserved					
Health-related quality of life					
KCCQ OSS[c]	2884	642 (22.3)	2867	576 (20.1)	1.05 [0.96; 1.15]; 0.296
Domains (supplementary information)					
Physical limitation	*2829*	*669 (23.6)*	*2823*	*652 (23.1)*	*1.01 [0.92;1.10]; 0.840*
Psychological quality of life	*2884*	*964 (33.4)*	*2867*	*896 (31.3)*	*1.03 [0.96;1.11]; 0.360*
Social limitation	*2686*	*765 (28.5)*	*2700*	*726 (26.9)*	*1.02 [0.94; 1.11]; 0.584*
Symptoms (KCCQ TSS)[c]	*2884*	*754 (26.1)*	*2867*	*648 (22.6)*	*1.08 [0.99; 1.18]; 0.066*

a. Number of patients considered in the analysis (patients without value at baseline and at least one post-baseline value, as well as patients with missing values for model covariates were excluded from the analysis); missing values were imputed using LOCF (KCCQ OSS and KCCQ TSS: 14.3% each in the treatment arms; domains: ND).
b. Log-link Poisson model with "robust estimators of variance"; adjusted for region, sex, age, diabetes status, LVEF, eGFR value and respective baseline value.
c. Percentage of patients with score increase by ≥ 15 points from baseline at week 52, given a scale range of 0 to 100. Higher (increasing) values indicate an improvement of health status/symptoms/health-related quality of life.

CI: confidence interval; eGFR: estimated glomerular filtration rate; KCCQ: Kansas City Cardiomyopathy Questionnaire; LOCF: last observation carried forward; LVEF: left ventricular ejection fraction; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; OSS: overall summary score; RCT: randomized controlled trial; RR: relative risk; TSS: total symptom score

Since the domain scores including the KCCQ TSS are included in the KCCQ OSS and were therefore already taken into account in the benefit assessment, these results are only presented as supplementary information and are not used for the assessment. Regardless of this, no significant effects were shown in the individual domains (as already in the summary score).

2.2 Outcomes on renal morbidity

Composite outcome on renal morbidity

The composite outcome on renal morbidity is not used for the benefit assessment in the operationalization presented by the company, as it is not ensured that all events of the composite outcome represent a deterioration of the disease noticeable for the patients. Detailed reasons can be found in dossier assessment A22-39 [1].

The results of the composite outcome and of its components on renal morbidity are presented as supplementary information in Appendix A.

Acute kidney injury

In the EMPEROR-Preserved study, the time to first occurrence of acute kidney injury (recorded as PT acute kidney injury according to the Medical Dictionary for Regulatory Activities [MedDRA]) was investigated as a secondary outcome (efficacy). This outcome is used for the benefit assessment, but it only represents a partial aspect of the patient-relevant events of renal morbidity. No suitable data are available for a comprehensive representation of renal morbidity (including chronic renal insufficiency and dialysis, for example).

Module 4 A provides results on different operationalizations of the outcome of acute kidney injury (PT), which are presented together in Table 2:

- acute kidney injury (PT) as secondary outcome on renal morbidity: operationalized as time to first event
- acute kidney injury (PT) as adverse event (AE) and serious AE (SAE): operationalized as number of patients with event (supplementary information)

The analyses of the event time analyses on the secondary outcome of acute kidney injury (PT) reported more patients with event than the analyses on side effects. The number of patients with event thus differs between the operationalizations. It is assumed that this is due to the fact that longer observation periods were taken into account for the analysis of the secondary outcome than for the analyses of side effects (side effects up to 7 days after treatment discontinuation versus secondary outcomes until the end of the study, see also dossier assessment A22-39) and therefore events after treatment discontinuation were also included in the analysis of the secondary outcome. The results of the secondary outcome are used for the benefit assessment.

2.3 Results

The results on renal morbidity/side effects are presented in Table 2.

Table 2: Results (time to event) – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study **Outcome category** **Outcome**	**Empagliflozin + optimized standard therapy**		**Placebo + optimized standard therapy**		**Empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
EMPEROR-Preserved					
Morbidity/side effects					
Renal morbidity (composite outcome)	No usable data				
Acute kidney injury					
PT (secondary outcome)[b]	2997	ND 97 (3.2)	2991	ND 131 (4.4)	0.73 [0.56; 0.95]; 0.019[c]
PT, AE (supplementary information)[d]	*2996*	*ND* *81 (2.7)*	*2989*	*ND* *107 (3.6)*	*RR: 0.76 [0.57; 1.00][e]; < 0.053[f]*
PT, SAE (supplementary information)[d]	*2996*	*ND* *81 (2.7)*	*2989*	*ND* *107 (3.6)*	*RR: 0.76 [0.57; 1.00][e]; < 0.053[f]*

a. Unless stated otherwise, HR, 95% CI and p-value: Cox proportional hazards model; adjusted for region, sex, age, diabetes status, LVEF, and baseline eGFR.
b. Recorded as secondary outcome via the PT acute kidney injury according to MedDRA; a follow-up observation of 30 days is assumed.
c. Result of the Institute's calculation of RR, 95% CI (asymptotic) and p-value (unconditional exact test [CSZ method according to [4]]): 0.74 [0.57; 0.96]; 0.021.
d. Recorded as AE or SAE via the PT acute kidney injury according to MedDRA; follow-up observation of 7 days.
e. Cochran-Mantel-Haenszel method.
f. Institute's calculation: unconditional exact test (CSZ method according to [4])

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; eGFR: estimated glomerular filtration rate; HR: hazard ratio; LVEF: left ventricular ejection fraction; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Morbidity/side effects

Acute kidney injury (PT)

A statistically significant difference between treatment arms in favour of empagliflozin + optimized standard therapy was shown for the outcome of acute kidney injury (PT). This results in a hint of an added benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Subgroups and effect modifiers

For the outcome of acute kidney injury (PT), there are no effect modifications due to the characteristics of age (< 70 years versus ≥ 70 years), sex and left ventricular ejection fraction (< 50% versus ≥ 50%).

2.4 Summary

Table 3 presents only the relevant results in the present addendum.

Table 3: Extent of added benefit at outcome level: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Intervention vs. comparator** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Morbidity/side effects		
Renal morbidity (composite outcome)	No usable data	Lesser benefit/added benefit not proven
Acute kidney injury	ND vs. ND HR: 0.73 [0.56; 0.95] p = 0.019 Probability: "hint"	Outcome category: serious/severe symptoms/late complications Added benefit, extent: "non-quantifiable"
Health-related quality of life		
KCCQ OSS; improvement by ≥ 15 points	22.3% vs. 20.1% RR: 1.05 [0.96; 1.15] p = 0.296	Lesser benefit/added benefit not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; HR: hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; ND: no data; OSS: overall summary score; RR: relative risk; SAE: serious adverse event

Table 4summarizes the results included in the overall conclusion on the extent of added benefit. The subsequent assessment of the outcome of acute kidney injury (PT) results in an additional positive effect in the category of side effects.

Table 4: Positive and negative effects from the assessment of empagliflozin + optimized standard therapy in comparison with optimized standard therapy

Positive effects	**Negative effects**
Serious/severe secondary diseases and side effects ▪ Hospitalization for heart failure: hint of an added benefit – extent: "non-quantifiable" ▪ Acute kidney injury: hint of an added benefit – extent: "non-quantifiable" ▪ SAEs: hint of lesser harm – extent: "non-quantifiable" ▫ Metabolism and nutrition disorders (SAEs); musculoskeletal and connective tissue disorders (SAEs); blood and lymphatic system disorders (SAEs); hypertensive crisis (SAEs); basal cell carcinoma (SAEs): hint of lesser harm – extent: "non-quantifiable" ▫ Respiratory, thoracic and mediastinal disorders (SAEs): - Age (≥ 70 years): hint of an added benefit – extent: "non-quantifiable"	Serious/severe secondary diseases ▪ Myocardial infarction ▫ Sex (women): hint of lesser benefit – extent: "non-quantifiable"
SAE: serious adverse event	

The subsequent assessment of the outcome of acute kidney injury (PT) results in an additional positive effect.

The data subsequently submitted by the company in the commenting procedure and the outcome of acute kidney injury subsequently assessed in the addendum do not change the conclusion on added benefit of empagliflozin drawn in dossier assessment A22-39. The following Table 5 shows the result of the benefit assessment of empagliflozin, taking into account dossier assessment A22-39 and the present addendum.

Table 5: Empagliflozin – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with symptomatic chronic heart failure with preserved ejection fraction (HFpEF)[b, c]		
▪ without T2DM and without CKD or ▪ with/without T2DM and with CKD	Optimized standard therapy for the treatment of the underlying conditions, such as hypertension, cardiac arrhythmias, coronary heart disease, diabetes mellitus, hypercholesterolaemia as well as of the concomitant symptoms	Hint of non-quantifiable added benefit
▪ with T2DM and without CKD		Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. In the context of the present assessment, HFpEF is defined as heart failure with LVEF > 40%.
c. The conclusion on added benefit is based on the results of the EMPEROR-Preserved study. To qualify for this study, patients had to exceed certain NT-proBNP thresholds. It remains unclear whether the observed effects can be transferred to other patients in the target population.

CKD: chronic kidney disease; G-BA: Federal Joint Committee; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide; T2DM: type 2 diabetes mellitus

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Empagliflozin (Herzinsuffizienz mit erhaltener Ejektionsfraktion) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2022 [Accessed: 04.07.2022]. URL: https://www.iqwig.de/download/a22-39_empagliflozin_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Boehringer Ingelheim Pharma. Empagliflozin (Jardiance); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2022 [Accessed: 08.07.2022]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/810/#dossier.

3. Boehringer Ingelheim Pharma. Stellungnahme zum IQWiG-Bericht Nr. 1382: Empagliflozin(Herzinsuffizienz mit erhaltener Ejektionsfraktion) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. 2022: [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/810/#beschluesse in the document "Zusammenfassende Dokumentation"].

4. Andrés AM, Mato AS. Choosing the optimal unconditioned test for comparing two independent proportions. Comput Stat Data Anal 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

Appendix A – Supplementary presentation of the results on the composite outcome of renal morbidity

Table 6: Results (time to event) – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study Outcome category Outcome	Empagliflozin + optimized standard therapy		Placebo + optimized standard therapy		Empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
EMPEROR-Preserved					
Renal morbidity (composite outcome)	2997	ND 108 (3.6)	2991	ND 112 (3.7)	0.95 [0.73; 1.24]; 0.724
Chronic dialysis	2997	ND 11 (0.4)	2991	ND 11 (0.4)	0.92 [0.40; 2.13]; 0.849
Kidney transplant	2997	ND 0 (0)	2991	ND 0 (0)	1.00 [NC; NC]; NC
Sustained eGFR < 15/< 10 mL/min/1.73 m²[b]	2997	ND 10 (0.3)	2991	ND 8 (0.3)	1.01 [0.39; 2.61]; 0.990
Sustained eGFR reduction by ≥ 40%	2997	ND 99 (3.3)	2991	ND 107 (3.6)	0.92 [0.70; 1.21]; 0.547

a. Unless stated otherwise, HR, 95% CI and p-value: Cox proportional hazards model; adjusted for region, sex, age, diabetes status, LVEF, and baseline eGFR.
b. Sustained eGFR < 15 mL/min/1.73 m^2 for patients with a baseline eGFR ≥ 30 mL/min/1.73 m^2 or sustained eGFR < 10 mL/min/1.73 m^2 for patients with a baseline eGFR < 30 mL/min/1.73 m^2.

CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; LVEF: left ventricular ejection fraction; n: number of patients with event; N: number of analysed patients; ND: no data;
RCT: randomized controlled trial; RR: relative risk

Appendix B – Cumulative incidence curves

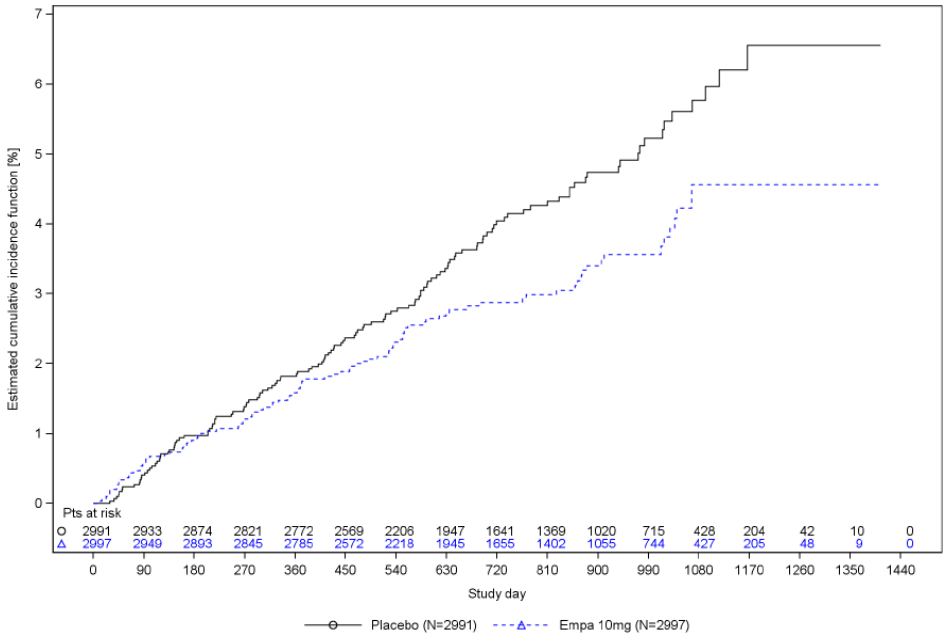

Figure 1: Cumulative incidence curves for the outcome of acute kidney injury (death from any cause as a competing event) of the EMPEROR-Preserved study – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

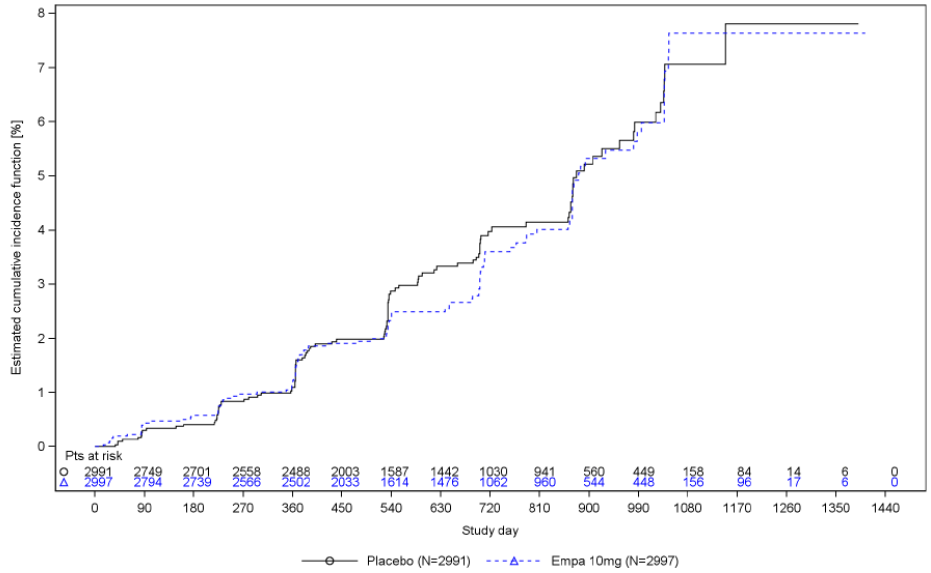

Figure 2: Cumulative incidence curves for the composite outcome on renal morbidity (death from any cause as a competing event) of the EMPEROR-Preserved study presented as supplementary information – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy