Dapagliflozin (heart failure with LVEF > 40 %)

Addendum to Project A23-11 (dossier assessment)[1]

ADDENDUM

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[1] Translation of addendum A23-71 *Dapagliflozin (Herzinsuffizienz mit LVEF > 40 %) – Addendum zum Projekt A23-11 (Dossierbewertung)*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Abbreviation	Meaning
ACT	appropriate comparator therapy
eGFR	estimated glomerular filtration rate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LVEF	left ventricular ejection fraction

1 Background

On 11 July 2023, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A23-11 (Dapagliflozin – Benefit assessment according to § 35a Social Code Book V) [1].

In its dossier, the pharmaceutical company (hereinafter referred to as the "company") presented the DELIVER study for the assessment of the added benefit of dapagliflozin in comparison with optimized standard therapy as appropriate comparator therapy (ACT) in adults with symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) > 40% [2]. No usable data on the outcome of renal morbidity were available for the benefit assessment. The G-BA commissioned IQWiG with the assessment of the outcome of renal morbidity from the DELIVER study under consideration of the information provided in the dossier.

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

In Module 4 A of the dossier, the company presented analyses on the following operationalizations for the outcome of renal morbidity [2]:

- confirmed ≥ 50% sustained decline in estimated glomerular filtration rate (eGFR)
- doubling of serum creatinine level accompanied by an eGFR ≤ 45 mL/min/1.73 m^2

Neither operationalization was used for the assessment in dossier assessment A23-11 [1]. For the first operationalization chosen, the company did not specify how "confirmed sustained decline" was defined. In addition, baseline eGFR was ≥ 60 mL/min/1.73 m^2 in about half of the patients in the DELIVER study. Due to these high baseline values, a relative decline in eGFR of ≥ 50% compared with baseline is not necessarily patient-relevant. Taking into account serum creatinine levels at baseline, the second operationalization was also assessed as not suitable to show a tangible deterioration of renal function for all affected patients in the DELIVER study with sufficient certainty.

The results and Kaplan-Meier curves for both operationalizations of the renal morbidity outcome are presented in Appendix A. Subgroup analyses are not considered in this addendum, as the results presented by the company in the dossier using the methods described in dossier assessment A23-11 [1] did not show any effect modification by sex (male versus female) and LVEF at baseline (< 50% versus ≥ 50%).

2.1 Summary

The present addendum does not change the conclusions on the added benefit of dapagliflozin from dossier assessment A23-11.

The following Table 1 shows the result of the benefit assessment of dapagliflozin under consideration of dossier assessment A23-11 and the present addendum.

Table 1: Dapagliflozin – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adults with symptomatic chronic heart failure with LVEF > 40%[b, c]		
▪ Without T2DM and without CKD or ▪ with/without T2DM and with CKD	Optimized standard therapy for the treatment of symptomatic chronic heart failure with LVEF > 40% and underlying medical conditions, e.g. hypertension, cardiac arrhythmias, coronary heart disease, diabetes mellitus, chronic kidney disease, dyslipoproteinaemias, and concomitant symptoms	Hint of non-quantifiable added benefit
▪ With T2DM and without CKD		Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. This includes HFpEF, defined as heart failure with LVEF > 50%, and HFmrEF, defined as heart failure with LVEF > 40 to 49%.
c. The conclusion on added benefit is based on the results of the DELIVER study. For study inclusion, patients had to exceed certain NT-proBNP thresholds: ≥ 300 pg/mL for patients without ongoing atrial fibrillation/flutter or ≥ 600 pg/mL for patients with ongoing atrial fibrillation/flutter. 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; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal prohormone B-type 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. Dapagliflozin (Herzinsuffizienz mit erhaltener Ejektionsfraktion); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2023 [Accessed: 13.07.2023]. URL: https://www.iqwig.de/download/a23-11_dapagliflozin_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. AstraZeneca. Dapagliflozin (Forxiga); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2023 [Accessed: 13.07.2023]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/930/#dossier.

Appendix A Results on the outcome of renal morbidity

Table 2: Results (morbidity) – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study Outcome category Outcome	Dapagliflozin + optimized standard therapy		Placebo + optimized standard therapy		Dapagliflozin + 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]
DELIVER					
Mortality					
Renal morbidity					
Confirmed ≥ 50% sustained decline in eGFR	3131	ND 44 (1.4)	3132	ND 46 (1.5)	0.96 [0.63; 1.45]; 0.830
Doubling of serum creatinine level accompanied by an eGFR ≤ 45 mL/min/1.73 m^2	3131	ND 35 (1.1)	3132	ND 36 (1.1)	0.98 [0.62; 1.56]; 0.932

a. Effect, CI and p-value: Cox proportional hazards model stratified by T2DM status at randomization.

CI: confidence interval; eGFR: estimated glomerular filtration rate; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; T2DM: type 2 diabetes mellitus

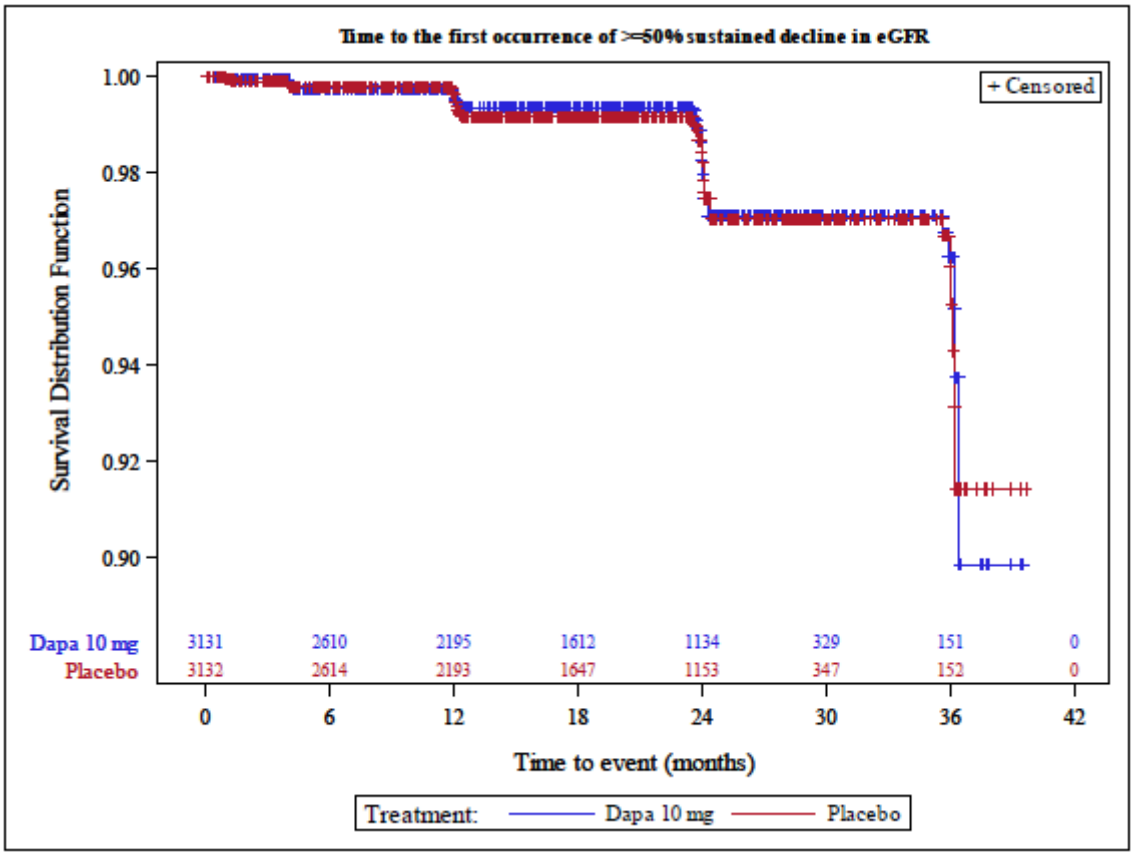

Figure 1: Kaplan-Meier curves for time to first occurrence of confirmed ≥ 50% sustained decline in eGFR

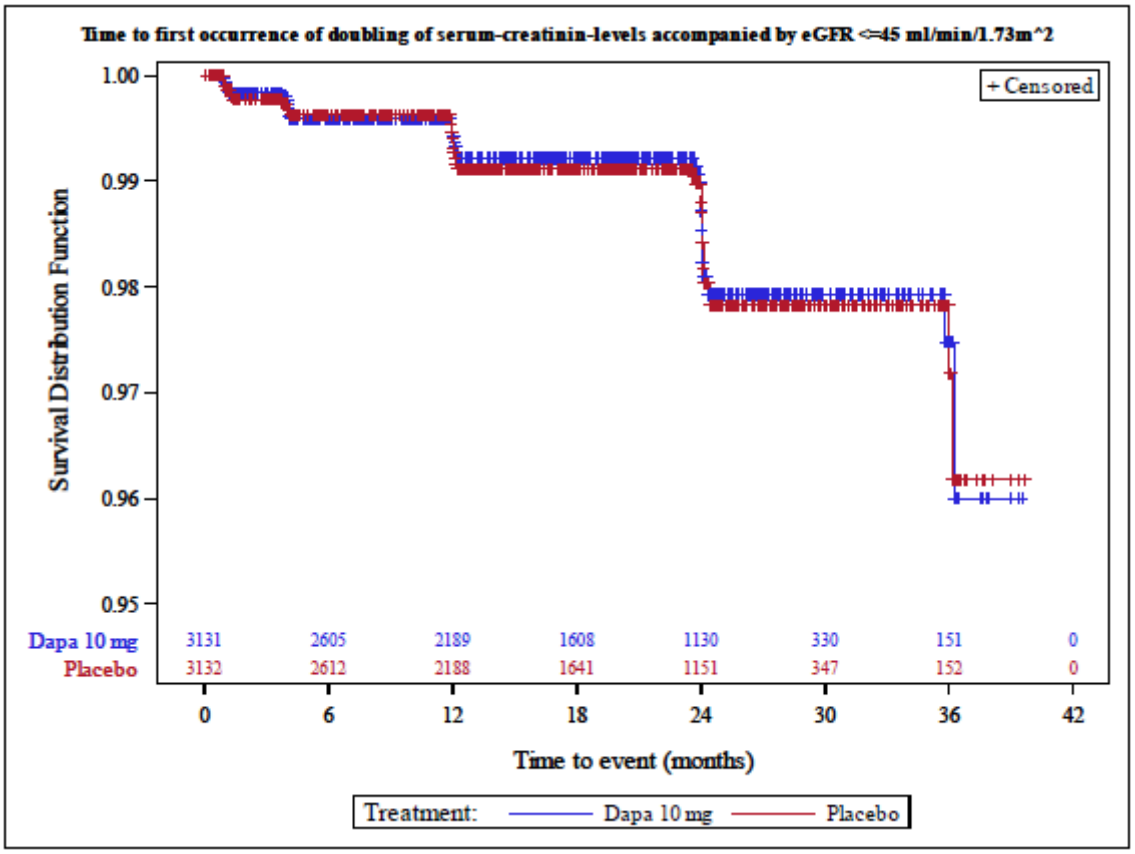

Figure 2: Kaplan-Meier curves for time to first occurrence of doubling of serum creatinine levels accompanied by eGFR ≤ 45 mL/min/1.73 m^2