IQWiG Reports – Commission No. A22-39

Empagliflozin (heart failure with preserved ejection fraction) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Empagliflozin (Herzinsuffizienz mit erhaltener Ejektionsfraktion) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 June 2022). 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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Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HFmrEF	heart failure with mildly reduced ejection fraction
HFpEF	heart failure with preserved ejection fraction
HR	hazard ratio
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
JFM	joint frailty model
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	left ventricular ejection fraction
NT-proBNP	N-terminal pro-brain natriuretic peptide
NVL	Nationale VersorgungsLeitlinie (National Care Guideline)
NYHA	New York Heart Association
OECD	Organisation for Economic Co-operation and Development
OSS	overall summary score
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGLT	sodium-glucose cotransporter
SOC	System Organ Class
SPC	Summary of Product Characteristics
T2DM	type 2 diabetes mellitus
PT	Preferred Term
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug empagliflozin. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 31 March 2022.

Research question

The aim of the present report is the assessment of the added benefit of empagliflozin in comparison with optimized standard therapy of the underlying conditions as appropriate comparator therapy (ACT) in patients with symptomatic chronic heart failure with preserved ejection fraction (HFpEF).

In the context of the present assessment, HFpEF is defined as heart failure with left ventricular ejection fraction (LVEF) > 40%. This definition thus includes both patients with heart failure with mildly reduced ejection fraction (HFmrEF) (LVEF 40 to 49%) and with HFpEF (LVEF ≥ 50%) as defined in the current German National Care Guideline (NVL) on chronic heart failure.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of empagliflozin

Therapeutic indication	**ACT**[a]
Adults with symptomatic chronic heart failure with preserved ejection fraction (HFpEF)[b]	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[c]

a. Presented is the respective ACT specified by the GBA.
b. In the context of the present assessment, HFpEF is defined as heart failure with LVEF > 40%.
c. It is assumed that empagliflozin was generally administered in addition to standard therapy and that the patients in both study arms received optimal treatment: guideline-compliant individualized treatment of heart failure and underlying conditions or risk factors such as hypertension, cardiac arrhythmias, or diabetes mellitus as well as of the concomitant symptoms, e.g. oedema.
It should have been possible to adapt the basic/concomitant medication to the patient's individual needs in both study arms.
Unchanged continuation of an inadequate therapy does not concur with the ACT. If there was no further possibility for optimization, it had to be documented and explained that any other existing treatment options were unsuitable or had been exhausted.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction

The ACT cited by the company was individualized therapy of the underlying conditions such as hypertension, cardiac arrhythmias, or diabetes mellitus, as well as of the concomitant symptoms, that corresponds to current medical knowledge. This wording corresponds to the original specification of the ACT by the G-BA from 2016. The G-BA adjusted the wording of the ACT in 2019. The assessment of the added benefit is conducted in comparison with the updated ACT of the G-BA from 2019.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The EMPEROR-Preserved study is used to assess the added benefit of empagliflozin in comparison with optimized standard therapy for the treatment of patients with symptomatic chronic HFpEF.

The EMPEROR-Preserved study is a placebo-controlled, double-blind RCT. It included adult patients with chronic heart failure of New York Heart Association (NYHA) classes II through IV with preserved ejection fraction, defined as LVEF > 40%. Patients had to have predefined elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) levels (see below for a detailed description of this inclusion criterion) and either have structural heart disease or had been hospitalized for heart failure within the last 12 months prior to screening.

A total of 5988 patients were included in the study and randomly allocated in a 1:1 ratio either to treatment with empagliflozin (N = 2997) or to placebo (N = 2991). According to the study protocol, study participants had to be treated to the best standard of care in compliance with local guidelines and recommendations for heart failure, and diabetes mellitus if present.

The study's primary outcome was the composite outcome of cardiovascular death or hospitalization for heart failure. Further secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life and side effects.

Required inclusion criteria led to limited study population

In addition to LVEF > 40% and structural heart disease or previous hospitalization for heart failure ≤ 12 months prior to screening, patients in the EMPEROR-Preserved study had to have elevated NT-proBNP levels at screening as an inclusion criterion:

- > 300 pg/mL for patients without atrial fibrillation or atrial flutter
- > 900 pg/mL for patients with atrial fibrillation or atrial flutter

However, according to the current NVL on chronic heart failure, the threshold required to meet the diagnostic criteria for HFpEF is already exceeded at an NT-proBNP level > 125 pg/mL.

Patients in the present therapeutic indication with NT-proBNP levels between 125 pg/mL and 300 pg/mL were therefore not included in the EMPEROR-Preserved study. The required higher threshold values of the NT-proBNP in the inclusion criteria led to a strong selection of the study population: About 38% of all patients who participated in the screening were not included in the EMPEROR-Preserved study solely because the NT-proBNP values were too low. It is therefore unclear whether the observed effects in the EMPEROR-Preserved study can be transferred to all patients with HFpEF and whether the study population fully represents the total population in the German health care context.

Implementation of the appropriate comparator therapy

There are no effective specific therapies for HFpEF yet, so the treatment of the underlying conditions, such as hypertension, type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD), as well as of the concomitant symptoms, is of particular importance. The EMPEROR-Preserved study included a heterogeneous patient population with regard to underlying conditions. The ACT of the G-BA was not implemented for all subpopulations that can be defined on the basis of the underlying conditions. This is described below.

1) Patients without T2DM and without CKD

   Since there are no clear treatment recommendations for patients with HFpEF without T2DM and without CKD, and since the EMPEROR-Preserved study allowed any concomitant treatment except sodium-glucose cotransporter 2 (SGLT-2) inhibitors at the discretion of the investigator, adequate implementation of the ACT is assumed for this subpopulation in the EMPEROR-Preserved study.

2) Patients without T2DM and with CKD

   According to new findings, SGLT-2 inhibitors (dapagliflozin) also offer an added benefit for the treatment of CKD, regardless of the presence of T2DM, and are already recommended in some guidelines. It is unclear to what extent the use of SGLT-2 inhibitors for the treatment of CKD has already found its way into the German health care context. As SGLT-2 inhibitors were prohibited in the EMPEROR-Preserved study, with the exception of the study medication in the intervention arm, patients with CKD may not have received optimal treatment. Uncertainties therefore exist with regard to the implementation of the ACT in patients with CKD.

3) Patients with T2DM and with CKD

   The NVL for T2DM recommends treatment with metformin in combination with an SGLT-2 inhibitor or a GLP-1 receptor agonist for patients with T2DM and clinically relevant cardiovascular disease if drug therapy is indicated. However, as described in dossier assessment A21-109, there is only limited evidence for the treatment of T2DM with SGLT-2 inhibitors or GLP-1 receptor agonists in patients with concomitant CKD. This is due to the fact that the studies underlying these recommendations included mainly patients without CKD. However, according to new findings (see previous paragraph on

subpopulation 2), SGLT-2 inhibitors (dapagliflozin) are also recommended in the treatment of CKD regardless of the presence of T2DM. Therefore, due to the prohibition of SGLT-2 inhibitors in the comparator arm, the same uncertainties with regard to the implementation of the ACT exist for patients with T2DM and with CKD as for patients without T2DM and with CKD, as CKD may not have been optimally treated.

4) Patients with T2DM and without CKD

The NVL for T2DM recommends treatment with metformin in combination with an SGLT-2 inhibitor or a GLP-1 receptor agonist for patients with T2DM and clinically relevant cardiovascular disease with a therapeutic indication for drug therapy. For patients with T2DM and without concomitant CKD, there is thus a clear therapeutic indication for SGLT-2 inhibitors or GLP-1 receptor agonists. However, therapy with SGLT-2 inhibitors, with the exception of the investigational drug empagliflozin in the intervention arm, was not allowed. Although therapy with GLP-1 receptor agonists was possible, it was hardly carried out. Thus, the ACT was not implemented for patients with T2DM and without CKD in the EMPEROR-Preserved study.

In summary, the ACT in the EMPEROR-Preserved study was only adequately implemented for patients without T2DM and without CKD (subpopulation 1). The implementation for patients with/without T2DM and with CKD (subpopulations 2 and 3) is unclear because of uncertainties due to the lack of use of SGLT-2 inhibitors for the treatment of CKD. Due to this uncertainty, no more than hints, e.g. of an added benefit, can be derived for subpopulations 1 to 3. Since the ACT was not implemented for subpopulation 4, no added benefit can be derived for this subpopulation.

Furthermore, it is not clear from the presented analyses of the company how large the individual subpopulations are, so that the proportion of patients in the total population with adequate or unclear implementation of the ACT is unknown. Despite these limitations, the total population of the EMPEROR-Reduced study is used for the benefit assessment. This is justified below, and the consequences for the certainty of conclusions of the study are described.

Rationale for considering the total population of the EMPEROR-Preserved study

It is unclear how large the 4 subpopulations described above are in comparison with the total population, as no corresponding subgroup analyses are available. This means that it cannot be determined exactly for which proportions of the total population of the EMPEROR-Preserved study the ACT was not implemented, was implemented unclearly or was implemented adequately.

However, due to the pathogenesis of CKD, a relevant overlap of patients with T2DM and CKD can be assumed. This means that subpopulation 4 (T2DM without CKD), in which the ACT was not implemented, represents with sufficient certainty only a relatively small proportion of the total population of the EMPEROR-Preserved study. The company's dossier additionally contains subgroup analyses for patients with and without T2DM as well as for patients with and

without CKD. These show sufficiently consistent effects with regard to the characteristics of CKD and T2DM compared with the total population. Thus, the observed effects in the total population cannot be caused to an important degree by the only low proportion of patients from subpopulation 4 in whom the ACT was not implemented. Moreover, the observed effects in the total population for the assessment of the relevant subpopulations 1 to 3 are not called into question by these subgroup analyses. Therefore, despite the uncertainties described, the total population of the study is used to derive the added benefit. However, due to these uncertainties, the extent of the observed effects in the total population cannot be quantified. Quantification of the extent of the added benefit requires separate analyses for subpopulations 1 to 3 versus subpopulation 4 on the one hand, and individual analyses for the 4 subpopulations mentioned on the other hand, in order to finally ensure the consistency of the effects in subpopulations 1 to 3.

Risk of bias

The risk of bias of the results on all outcomes included in the present benefit assessment is rated as low.

Summary assessment of the certainty of conclusions

In the present benefit assessment, no more than indications, e.g. of an added benefit, can initially be derived on the basis of the single EMPEROR-Preserved study. However, various aspects further limit the certainty of conclusions of this study for the benefit assessment.

Based on the single EMPEROR-Preserved study, at most hints, e.g. of an added benefit, can be determined for all outcomes for subpopulations 1 to 3 due to the described uncertainties regarding the implementation of the ACT. Furthermore, only analyses that do not cover the entire observation period of the EMPEROR-Preserved study are available for adverse event (AE) outcomes. This also leads to limited certainty of conclusions, as the balancing of benefit and harm is subject to further uncertainty. This additionally justifies that no more than hints can be derived. In addition, the observed effects cannot be quantified due to the unclear sizes of the subpopulations. No added benefit can be derived for subpopulation 4.

Results

Mortality

All-cause mortality

There was no statistically significant difference between treatment groups for the outcome of all-cause mortality. This results in no hint of an added benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for this outcome.

Morbidity

Hospitalization for heart failure

A statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy was shown for the outcome of hospitalization for heart failure. This results in a hint of an added benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Myocardial infarction

For the composite outcome of myocardial infarction, consisting of nonfatal myocardial infarction and fatal myocardial infarction, as well as for both individual components, there was no statistically significant difference between the treatment groups. However, there is an effect modification by sex. For women, there is a hint of lesser benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. For men, however, there is no hint of an added benefit or lesser benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit or lesser benefit is therefore not proven for men for this outcome.

Stroke

For the composite outcome of stroke, consisting of nonfatal stroke and fatal stroke, as well as for both individual components, there was no statistically significant difference between the treatment groups. This results in no hint of an added benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for this outcome.

Renal morbidity

No usable data are available for the outcome of renal morbidity. This results in no hint of an added benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for this outcome.

Health status

EQ-5D VAS

For the outcome of health status, operationalized as EQ-5D visual analogue scale (VAS) improvement by ≥ 15 points at week 52, no statistically significant difference between treatment groups was found. This results in no hint of an added benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for this outcome.

Health-related quality of life

KCCQ OSS

For the outcome of health-related quality of life, operationalized as Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score (OSS) improvement by ≥ 15 points at week 52, no statistically significant difference between treatment groups was found. This results in no hint of an added benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for this outcome.

Side effects

SAEs

A statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy was shown for the outcome of serious AEs (SAEs). This results in a hint of lesser harm from empagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Discontinuation due to AEs

There was no statistically significant difference between treatment groups for the outcome of discontinuation due to AEs. This results in no hint of greater or lesser harm of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. Greater or lesser harm is therefore not proven for this outcome.

Specific AEs

Urinary tract infection

A statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy was shown for the outcome of urinary tract infection (Preferred Term [PT], AEs). This difference was no more than marginal, however. This results in no hint of greater or lesser harm of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. Greater or lesser harm is therefore not proven for this outcome.

Reproductive system and breast disorders, diabetic ketoacidosis

There was no statistically significant difference between treatment groups for the outcomes of reproductive system and breast disorders (System Organ Class [SOC], AEs) and diabetic ketoacidosis (PT, AEs). In each case, this results in no hint of greater or lesser harm of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. Greater or lesser harm is therefore not proven for these outcomes.

Metabolism and nutrition disorders (SOC, SAEs), musculoskeletal and connective tissue disorders (SOC, SAEs), blood and lymphatic system disorders (SOC, SAEs), respiratory, thoracic and mediastinal disorders (SOC, SAEs), hypertensive crisis (PT, SAEs), and basal cell carcinoma (PT, SAEs)

A statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy was shown for each of the outcomes of metabolism and nutrition disorders (SOC, SAEs), musculoskeletal and connective tissue disorders (SOC, SAEs), blood and lymphatic system disorders (SOC, SAEs), hypertensive crisis (PT, SAEs), and basal cell carcinoma (PT, SAEs). In each case, this results in a hint of lesser harm from empagliflozin + optimized standard therapy in comparison with optimized standard therapy.

A statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy was also shown for the outcome of respiratory, thoracic and mediastinal disorders (SOC, SAEs). However, there is an effect modification by age. For patients ≥ 70 years, there is a hint of lesser harm of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. For patients < 70 years, in contrast, there was no statistically significant difference between treatment groups. Greater or lesser harm for this outcome is therefore not proven for patients < 70 years.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

As described in the above sections, the EMPEROR-Preserved study included a heterogeneous patient population with regard to underlying conditions. The ACT was not adequately implemented for all patients in this heterogeneous patient population. The added benefit is therefore derived separately for the subpopulations with and without adequate or at least limited implementation of the ACT, in each case on the basis of the total population of the EMPEROR-Preserved study.

On the basis of the results presented, the probability and extent of added benefit of the drug empagliflozin in comparison with the ACT is assessed as follows:

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Patients with HFpEF without T2DM and without CKD as well as with/without T2DM and with CKD

Overall, there are several positive and one negative effect for empagliflozin + optimized standard therapy in comparison with optimized standard therapy.

On the side of positive effects, there is a hint of non-quantifiable added benefit in the outcome category of serious/severe secondary diseases for the outcome of hospitalization for heart failure. In addition, there is a hint of non-quantifiable lesser harm in the outcome category of serious/severe side effects for the outcome of SAEs and for various specific AEs contained in the overall rate of SAEs.

On the side of negative effects, however, there is a hint of non-quantifiable greater harm in the outcome category of serious/severe secondary diseases for the outcome of myocardial infarction only in women. However, this does not completely call into question the positive effect with regard to the outcome of hospitalization for heart failure in particular.

In summary, there is a hint of non-quantifiable added benefit of empagliflozin + optimized standard therapy in comparison with the ACT in the form of optimized standard therapy for patients with symptomatic chronic HFpEF (defined as heart failure with LVEF > 40%) without T2DM and without CKD as well as with/without T2DM and with CKD.

Patients with HFpEF with T2DM without CKD

There is no hint of an added benefit of empagliflozin + optimized standard therapy in comparison with the ACT in the form of optimized standard therapy for patients with symptomatic chronic HFpEF (defined as heart failure with LVEF > 40%) with T2DM and without CKD. An added benefit for these patients is therefore not proven.

Table 3 shows a summary of the probability and extent of added benefit of empagliflozin.

Table 3: 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; NVL: National Care Guideline; T2DM: type 2 diabetes mellitus

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of empagliflozin in comparison with optimized standard therapy of the underlying conditions as ACT in patients with symptomatic chronic HFpEF.

In the context of the present assessment, HFpEF is defined as heart failure with LVEF > 40%. This definition thus includes both patients with HFmrEF (LVEF 40 to 49%) and with HFpEF (LVEF ≥ 50%) as defined in the current NVL on chronic heart failure [3].

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of empagliflozin

Therapeutic indication	**ACT**[a]
Adults with symptomatic chronic heart failure with preserved ejection fraction (HFpEF)[b]	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[c]
a. Presented is the respective ACT specified by the GBA. b. In the context of the present assessment, HFpEF is defined as heart failure with LVEF > 40%. c. It is assumed that empagliflozin was generally administered in addition to standard therapy and that the patients in both study arms received optimal treatment: guideline-compliant individualized treatment of heart failure and underlying conditions or risk factors such as hypertension, cardiac arrhythmias, or diabetes mellitus as well as of the concomitant symptoms, e.g. oedema. It should have been possible to adapt the basic/concomitant medication to the patient's individual needs in both study arms. Unchanged continuation of an inadequate therapy does not concur with the ACT. If there was no further possibility for optimization, it had to be documented and explained that any other existing treatment options were unsuitable or had been exhausted. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction	

The ACT cited by the company was individualized therapy of the underlying conditions such as hypertension, cardiac arrhythmias, or diabetes mellitus, as well as of the concomitant symptoms, that corresponds to current medical knowledge. This wording corresponds to the original specification of the ACT by the G-BA from 2016. The G-BA adjusted the wording of the ACT in 2019. The assessment of the added benefit is conducted in comparison with the updated ACT of the G-BA from 2019 presented in Table 4 [4]. A detailed discussion of the implementation of the ACT is provided in Section 2.3.2.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on empagliflozin (status: 31 January 2022)
- bibliographical literature search on empagliflozin (last search on 31 January 2022)
- search in trial registries/trial results databases for studies on empagliflozin (last search on 31 January 2022)
- search on the G-BA website for empagliflozin (last search on 31 January 2022)

To check the completeness of the study pool:

- search in trial registries for studies on empagliflozin (last search on 21 April 2022); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

Concurring with the company, the EMPEROR-Preserved study is included in the present benefit assessment.

In addition, the EMPA-TROPISM study [5] is potentially relevant to the assessment but, in agreement with the company, is not used for the present benefit assessment. This is justified below.

EMPA-TROPISM study not used for benefit assessment

The RCT EMPA-TROPISM included 84 patients with symptomatic heart failure of NYHA classes II and III with LVEF < 50% without diabetes mellitus for a comparison of empagliflozin + standard therapy versus placebo + standard therapy. It thus also included patients with HFpEF as defined in the present benefit assessment (LVEF > 40%). There is no information about how many of the included patients in the EMPA-TROPISM study had an LVEF > 40%, however. Furthermore, there is no detailed information about the extent to which the treatment for heart failure and accompanying diseases conducted in the study was in line with an implementation of the ACT of the present benefit assessment. The relevance of the EMPA-TROPISM study for the present benefit assessment is therefore overall unclear.

Regardless of the points mentioned above, the patient population of the EMPA-TROPISM study (N = 84) is very small compared with the EMPEROR-Preserved study (N = 5988) included in the benefit assessment (about 1.4%). The results of the EMPA-TROPISM study are therefore not expected to have a relevant influence on the result of the benefit assessment, even if they were included. The exclusion of the EMPA-TROPISM study is therefore without consequence for the conclusion of the present benefit assessment.

2.3.1 Studies included

The study presented in the following table is included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources (yes/no [citation])
1245.110 (EMPEROR-Preserved)[c]-	Yes	Yes	No	Yes [6]	Yes [7,8]	Yes [9,10]

a. Study for which the company was sponsor.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

CSR: clinical study report; RCT: randomized controlled trial

2.3.2 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
EMPEROR-Preserved	RCT, double-blind, parallel	Adult patients[b] with chronic heart failure[c] NYHA classes II–IV and preserved ejection fraction defined as LVEF > 40%[d]	Empagliflozin + optimized standard therapy (N = 2997) Placebo + optimized standard therapy (N = 2991)	Screening: up to 4 weeks[e] Treatment: event-driven study: end of study after 841 adjudicated events of the primary outcome Observation: 30-day follow-up visit	622 centres in Argentina, Australia, Belgium, Brazil, Canada, China, Colombia, Czech Republic, Germany, Hungary, India, Italy, Japan, Mexico, Netherlands, Poland, Romania, Singapore, South Africa, South Korea, Spain, United Kingdom, USA 3/2017–4/2021	Primary: composite outcome of cardiovascular death or hospitalization for heart failure Secondary: all-cause mortality, morbidity, health status, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. For Japan: age ≥ 20 years at screening.
c. Chronic heart failure must have been diagnosed for ≥ 3 months before visit 1 and had to be confirmed by ≥ 1 of the following:
1) structural heart disease (left atrial enlargement and/or left ventricular hypertrophy) documented by echocardiogram at visit 1 ≤ 6 prior to visit 1, or
2) documented hospitalization for heart failure ≤ 12 months
prior to visit 1 (the main reason had to be heart failure)
In addition, there had to be elevated NT-proBNP levels at visit 1 (analysed at the central laboratory): > 300 pg/mL for patients without atrial fibrillation or flutter, or > 900 pg/mL for patients with atrial fibrillation or flutter.
Oral diuretics, if prescribed to a patient according to local guideline, had to be stable for ≥ 1 week prior to randomization.
d. Demonstrated by echocardiography, radionuclide
ventriculography, invasive angiography, MRI or CT, and no prior measurement of LVEF ≤ 40% under stable conditions (investigator's assessment). A historical LVEF could be used if it had been measured within 6 months prior to visit 1, and more than 90 days after any myocardial infarction, or the LVEF could be measured after study consent had been obtained. The LVEF had to be documented in an official report prior to randomization.
e. With Amendment 1 (23 November 2017), the screening phase was extended by 7 days from the previous 21 days.

AE: adverse event; CT: computed tomography; LVEF: left ventricular ejection fraction; MRI: magnetic resonance imaging; N: number of randomized patients; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study	Intervention	Comparison
EMPEROR-Preserved	Empagliflozin 10 mg once daily, orally[a] + optimized standard therapy	Placebo once daily, orally[a] + optimized standard therapy
	Prior and concomitant treatment ▪ Treatment of heart failure was at the discretion of the investigator, in accordance with prevailing local and international guidelines ▪ Concomitant antidiabetic medications was to be adjusted individually as clinically indicated by the patient's usual diabetes care provider. ▪ Treatment of symptomatic and severe hypoglycaemia at the discretion of the investigator ▪ All concomitant medications and other therapies had to be recorded in the electronic CRF. **Prohibited prior and concomitant treatment** ▪ any SGLT-2 inhibitors or combined SGLT-1/2 inhibitors (except blinded study medication) ≤ 12 weeks prior to visit 1 and during the entire study duration (except for the 30-day period between end-of-treatment (EOT) visit and follow-up visit at the end of study) ▪ implanted CRT ▪ implantation of ICD ≤ 3 months prior to visit 1 ▪ heart transplantation	

a. The study medication had to be taken in the morning at approximately the same time every day. If a dose was missed by more than 12 hours, that dose had to be skipped and the next dose had to be taken as scheduled.

CRF: case report form; CRT: cardiac resynchronization therapy; ICD: implantable cardioverter defibrillator; RCT: randomized controlled trial; SGLT: sodium-glucose cotransporter

The EMPEROR-Preserved study is a placebo-controlled, double-blind RCT. It included adult patients with chronic heart failure of NYHA classes II through IV with preserved ejection fraction, defined as LVEF > 40%. Patients had to have predefined elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) levels (see below for a detailed description of this inclusion criterion) and either have structural heart disease (left atrial enlargement and/or left ventricular hypertrophy) or had been hospitalized for heart failure within the last 12 months prior to screening. Excluded were patients with heart failure based on infiltrative diseases, accumulation diseases, dystrophies, reversible conditions, hypertrophic obstructive cardiomyopathy or known pericardial constriction.

A total of 5988 patients were included in the study and randomly allocated in a 1:1 ratio either to treatment with empagliflozin (N = 2997) or to placebo (N = 2991). Randomization was stratified by geographical region (North America versus Latin America versus Europe versus Asia versus other), history of diabetes mellitus (diabetes mellitus versus prediabetes versus no diabetes mellitus), estimated glomerular filtration rate (eGFR) at screening (< 60 mL/min/1.73 m^2 versus ≥ 60 mL/min/1.73 m^2), and LVEF (< 50% versus ≥ 50%).

Treatment with empagliflozin was in compliance with the recommendations of the Summary of Product Characteristics (SPC) [11]. According to the study protocol, study participants had

to be treated to the best standard of care in compliance with local guidelines and recommendations for heart failure, and diabetes mellitus if present. The drugs and drug classes used are presented in Table 9. A detailed discussion of the implementation of the ACT in the course of the study can be found below.

The EMPEROR-Preserved study was event-driven and was terminated as planned after 841 events of the primary outcome. After reaching the required events, those patients who were still on study medication were scheduled for an end-of-treatment visit. A follow-up visit with another recording of outcomes was conducted 30 days after the end-of-treatment visit. Patients who prematurely discontinued study medication performed the end-of-treatment visit, and the follow-up visit 30 days after treatment discontinuation, and then continued to be observed until the end of study as they would have been had they remained on treatment.

The study's primary outcome was the composite outcome of cardiovascular death or hospitalization for heart failure. Further secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life and side effects.

Required inclusion criteria led to limited study population

In addition to LVEF > 40% and structural heart disease or previous hospitalization for heart failure ≤ 12 months prior to screening, patients in the EMPEROR-Preserved study had to have elevated NT-proBNP levels at screening as an inclusion criterion:

- > 300 pg/mL for patients without atrial fibrillation or atrial flutter
- > 900 pg/mL for patients with atrial fibrillation or atrial flutter

However, according to the current NVL on chronic heart failure, the threshold required to meet the diagnostic criteria for HFpEF is already exceeded at an NT-proBNP level > 125 pg/mL [3]. Patients in the present therapeutic indication with NT-proBNP levels between 125 pg/mL and 300 pg/mL were therefore not included in the EMPEROR-Preserved study. The required higher threshold values of the NT-proBNP in the inclusion criteria led to a strong selection of the study population: About 38% of all patients who participated in the screening were not included in the EMPEROR-Preserved study solely because the NT-proBNP values were too low [10]. It is therefore unclear whether the observed effects in the EMPEROR-Preserved study can be transferred to all patients with HFpEF and whether the study population fully represents the total population in the German health care context.

Table 8 shows the characteristics of the patients in the included study.

Table 8: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study Characteristic Category	**Empagliflozin + optimized standard therapy N[a] = 2997**	**Placebo + optimized standard therapy N[a] = 2991**
EMPEROR-Preserved		
Age [years], mean (SD)	72 (9)	72 (10)
Sex [F/M], %	45/55	45/55
Family origin n (%)		
White	2286 (76)	2256 (75)
Black/African American	133 (4)	125 (4)
Asian	413 (14)	411 (14)
Other (including mixed)	164 (6)	198 (7)
Region, n (%)		
North America	360 (12)	359 (12)
Latin America	758 (25)	757 (25)
Europe	1346 (45)	1343 (45)
Asia	343 (11)	343 (12)
Other[b]	190 (6)	189 (6)
LVEF [%]		
Mean (SD)	54.3 (8.8)	54.3 (8.8)
< 50, n (%)	995 (33)	988 (33)
50 to < 60, n (%)	1028 (34)	1030 (34)
≥ 60, n (%)	974 (33)	973 (33)
NT-proBNP [pg/mL], median [Q1; Q3]	994 [501; 1740]	946 [498; 1725]
NYHA class at baseline, n (%)		
I	3 (< 1)	1 (< 1)
II	2432 (81)	2451 (82)
III	552 (18)	531 (18)
IV	10 (< 1)	8 (< 1)
Time since diagnosis of heart failure [years], mean (SD)	4.5 (5.2)	4.3 (5.0)
Aetiology of heart failure, n (%)		
Ischaemic	1079 (36)	1038 (35)
Hypertensive	1066 (36)	1120 (37)
Valvular heart disease	187 (6)	168 (6)
Diabetic	67 (2)	58 (2)
Alcoholism	6 (< 1)	7 (< 1)
Idiopathic	289 (10)	262 (9)
Other	302 (10)	338 (11)

Table 8: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study Characteristic Category	**Empagliflozin + optimized standard therapy N[a] = 2997**	**Placebo + optimized standard therapy N[a] = 2991**
HHF within 12 months before screening and/or structural heart disease, n (%)		
Only HHF within 12 months before screening	199 (7)	187 (6)
Only structural heart disease	2297 (77)	2317 (78)
Both	499 (17)	482 (16)
History of hypertension, n (%)	2721 (91)	2703 (90)
Blood pressure [mmHg]		
Systolic, mean (SD)	131.8 (15.6)	131.9 (15.7)
Systolic ≥ 140 or diastolic ≥ 90, n (%)	1088 (36)	1074 (36)
Atrial fibrillation or flutter[c], n (%)	1576 (53)	1559 (52)
History of hypercholesterolaemia, n (%)	2015 (67)	2047 (68)
eGFR $(CKD\text{-}EPI)_{cr}$ [mL/min/1.73 m^2]		
Mean (SD)	60.6 (19.8)	60.6 (19.9)
Median [Q1; Q3]	59.5 [45.5; 75.0]	60.0 [45.5; 75.0]
≥ 90, n (%)	231 (8)	237 (8)
60 to < 90, n (%)	1262 (42)	1268 (42)
45 to < 60, n (%)	792 (26)	773 (26)
30 to < 45, n (%)	564 (19)	550 (18)
< 30, n (%)	148 (5)	161 (5)
Type 2 diabetes mellitus[d], n (%)	1461 (49)	1467 (49)
HbA1c [%], mean (SD)	6.46 (1.31)	6.48 (1.35)
Patients with diabetes at baseline	7.24 (1.47)	7.27 (1.52)
Patients with prediabetes at baseline	5.92 (0.24)	5.91 (0.24)
Treatment discontinuation, n (%)[e]	945 (31.5[f])	943 (31.5[f])
Study discontinuation, n (%)[g]	84 (2.8[f])	88 (2.9[f])

a. Number of randomized patients.
b. Australia, India and South Africa
c. According to the investor-reported medical history or ECG at baseline.
d. Patients without type 1 diabetes mellitus and with diabetes according to the investigator-reported medical history, and patients with previously undiagnosed diabetes (HbA1c before start of study treatment ≥ 6.5%).
e. Common reasons for treatment discontinuation in the intervention vs. control arm were: AEs (19.2%[f] vs. 18.5%[f]) and patient refusal to continue, not due to an AE (9.5%[f] vs. 10.2%[f]).
f. Institute's calculation.
g. Most common reasons for study discontinuation in the intervention vs. control arm were: withdrawal of informed consent (0.9% vs. 0.8%) and consent to limited follow-up (0.8% vs. 1.1%).

Table 8: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study Characteristic Category	Empagliflozin + optimized standard therapy N[a] = 2997	Placebo + optimized standard therapy N[a] = 2991

AE: adverse event; $(CKD\text{-}EPI)_{cr}$: chronic kidney disease epidemiology collaboration equation, creatine-based; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; F: female; HbA1c: glycosylated haemoglobin; HHF: hospitalization for heart failure; LVEF: left ventricular ejection fraction; M: male; n: number of patients in the category; N: number of randomized patients; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

Patient characteristics were sufficiently balanced between the treatment arms. The mean age of the patients was 72 years; most of them were male (55%) and most were from the regions of Europe and Latin America. One third of the patients had an LVEF < 50%, two thirds had an LVEF ≥ 50%. Half of the patients had T2DM at study inclusion. Similarly, half of the patients had CKD defined as an eGFR of < 60 mL/min/1.73 m² at study inclusion. The extent to which the subpopulations with T2DM and CKD overlap is unclear. About 80% of the patients showed slight limitation in activity from their disease (NYHA class II), while about 20% of the patients showed significant limitation in activity (NYHA class III) and < 1% even showed limitations at rest (NYHA class IV). The high rate of treatment discontinuations is notable but balanced between treatment arms (31.5% each).

Implementation of the appropriate comparator therapy

There are no effective specific therapies for HFpEF yet [3], so the treatment of the underlying conditions, such as hypertension, T2DM and CKD, as well as of the concomitant symptoms, is of particular importance. The EMPEROR-Preserved study included a heterogeneous patient population with regard to underlying conditions. The ACT of the G-BA was not implemented in the same way for all subpopulations that can be defined on the basis of the underlying conditions. In the following, the concomitant treatment carried out is presented, the patient populations are characterized with regard to their underlying conditions, and any deficiencies in the implementation of the ACT in the subpopulations are described and discussed.

Concomitant treatments in the EMPEROR-Preserved study

In the EMPEROR-Preserved study, all patients were to receive individualized treatment of the underlying conditions and concomitant symptoms, which, according to the study protocol, had to correspond to the best standard of care in compliance with local guidelines and recommendations for heart failure, and diabetes mellitus if present. Adjustments to therapy were possible during the course of the study, but oral diuretics, if prescribed to a patient, had to be stable for at least 1 week prior to randomization (second visit). The use of any SGLT-2 inhibitors or combined SGLT-1/2 inhibitors, except blinded study medication (empagliflozin),

was not allowed in the intervention arm (see Table 7). Furthermore, there were no restrictions in the study regarding concomitant drug treatments.

In its dossier, the company presented which concomitant treatments the patients were receiving at baseline and which concomitant treatments were started or changed during the course of the study (see Table 9). In addition, it reported on a survey in the electronic case report form, in which the investigators had to indicate for each visit whether the respective patient was currently receiving the best possible or best tolerated treatment for HFpEF as well as concomitant treatments in accordance with current guidelines. According to this survey, 99.6% of the patients were already receiving the best possible therapy at baseline.

Table 9: Information on heart failure therapies and concomitant treatments, antihypertensives, anticoagulants, antidiabetics and lipid-lowering drugs – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study Therapy Category	At baseline		Started or changed therapies after study start[a]	
	Empagliflozin + optimized standard therapy N = 2997	Placebo + optimized standard therapy N = 2991	Empagliflozin + optimized standard therapy N = 2997	Placebo + optimized standard therapy N = 2991
EMPEROR-Preserved				
Antihypertensives				
ACE inhibitors/ARBs/ARNIs	2428 (81.0)	2404 (80.4)	111 (3.7)	131 (4.4)
ACE inhibitors/ARBs[b]	2367 (79.0)	2338 (78.2)	114 (3.8)	129 (4.3)
ARNIs[b]	65 (2.2)	69 (2.3)	51 (1.7)	79 (2.6)
Beta-blockers	2598 (86.7)	2569 (85.9)	88 (2.9)	92 (3.1)
Diuretics	2563 (85.5)	2600 (86.9)	140 (4.7)	146 (4.9)
MRAs	1119 (37.3)	1125 (37.6)	241 (8.0)	270 (9.0)
Diuretics except MRAs	2407 (80.3)	2402 (80.3)	153 (5.1)	195 (6.5)
Loop or high ceiling diuretics	2030 (67.7)	2024 (67.7)	197 (6.6)	269 (9.0)
Thiazide diuretics or low ceiling diuretics	615 (20.5)	624 (20.9)	160 (5.3)	174 (5.8)
Other diuretics	80 (2.7)	89 (3.0)	66 (2.2)	73 (2.4)
Unclassified diuretics	–	–	14 (0.5)	16 (0.5)
Hydralazine	82 (2.7)	74 (2.5)	49 (1.6)	55 (1.8)
Calcium channel blockers	942 (31.4)	883 (29.5)	193 (6.4)	259 (8.7)
Renin inhibitors (aliskiren)	4 (0.1)	1 (< 0.1)	0 (0)	1 (< 0.1)
Cardiac glycosides	293 (9.8)	263 (8.8)	84 (2.8)	98 (3.3)
Nitrates	408 (13.6)	338 (11.3)	140 (4.7)	198 (6.6)
Antithrombotics	2631 (87.8)	2609 (87.2)	97 (3.2)	101 (3.4)
Platelet aggregation inhibitors, without heparin	1411 (47.1)	1424 (47.6)	136 (4.5)	129 (4.3)
Anticoagulants	1477 (49.3)	1435 (48.0)	281 (9.4)	312 (10.4)

Table 9: Information on heart failure therapies and concomitant treatments, antihypertensives, anticoagulants, antidiabetics and lipid-lowering drugs – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study Therapy Category	At baseline		Started or changed therapies after study start[a]	
	Empagliflozin + optimized standard therapy N = 2997	Placebo + optimized standard therapy N = 2991	Empagliflozin + optimized standard therapy N = 2997	Placebo + optimized standard therapy N = 2991
Antidiabetics	1162 (38.8)	1193 (39.9)	393 (13.1)	473 (15.8)
Blood-glucose lowering drugs, without insulins	971 (32.4)	1019 (34.1)	276 (9.2)	339 (11.3)
GLP-1 receptor agonists				
Albiglutide	1 (< 0.1)	0 (0)	–	–
Dulaglutide	12 (0.4)	9 (0.3)	10 (0.3)	13 (0.4)
Exenatide	3 (0.1)	1 (< 0.1)	1 (< 0.1)	0 (0)
Liraglutide	11 (0.4)	18 (0.6)	10 (0.3)	16 (0.5)
Lixisenatide	2 (0.1)	0 (0)	4 (0.1)	0 (0)
Semaglutide	1 (< 0.1)	2 (0.1)	17 (0.6)	16 (0.5)
Insulins and insulin analogues	434 (14.5)	428 (14.3)	171 (5.7)	213 (7.1)
Lipid-lowering drugs	2103 (70.2)	2139 (71.5)	129 (4.3)	129 (4.3)

a. Newly introduced (defined as newly documented use of a drug within a class that was not documented at baseline) or changed therapies from baseline to the end of the planned treatment period; for the category of antidiabetics, the data refer only to newly introduced therapies from baseline to the end of the planned treatment period. Data on changes in therapies from baseline are not available for this category.
b. Patients treated with the fixed combination of valsartan and sacubitril (ARNI) are not assessed as patients on ARB therapy as sacubitril/valsartan is not approved for antihypertensive treatment.

ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; GLP-1: glucagon-like peptide 1; MRA: mineralocorticoid receptor antagonist; n: number of patients; N: number of analysed patients; RCT: randomized controlled trial

The concomitant drug therapies shown in Table 9 and administered in the study appear appropriate for the treatment of hypertension, cardiac arrhythmias, coronary heart disease and hypercholesterolaemia. The values for blood pressure and lipid parameters over the course of the study presented in the dossier also suggest that the treatment of these underlying conditions was adequate on average. However, regarding therapy of the underlying conditions, the company did not submit any information about the type of modification, e.g. the drug classes to which patients switched or the reasons for performing or foregoing treatment modifications. Thus, it cannot be inferred with complete certainty from the data whether all patients actually received an individually optimized treatment for these underlying conditions. The following section discusses in detail the partly inadequate therapy of T2DM and CKD in individual subpopulations.

Patient population separated according to underlying conditions T2DM and CKD

In addition to HFpEF, about 50% of patients had T2DM at baseline and about 50% of patients had CKD (see Table 8). Based on these patient characteristics, there are a total of 4 subpopulations in the EMPEROR-Preserved study, which are decisive for the assessment of the implementation of the ACT:

1) patients without T2DM and without CKD
2) patients without T2DM and with CKD
3) patients with T2DM and with CKD
4) patients with T2DM and without CKD

Subpopulation 1: patients without T2DM and without CKD

For patients with HFpEF without T2DM and without CKD, any concomitant treatment (except SGLT-2 inhibitors) could be used at the discretion of the investigator in the EMPEROR-Preserved study (see Table 9). Therefore, adequate implementation of the ACT for this subpopulation is assumed in the EMPEROR-Preserved study.

Subpopulation 2: patients without T2DM and with CKD

According to new findings [12], SGLT-2 inhibitors (dapagliflozin) also offer an added benefit for the treatment of CKD, regardless of the presence of T2DM, and are already recommended in some guidelines [13-15]. It is unclear to what extent the use of SGLT-2 inhibitors for the treatment of CKD has already found its way into the German health care context. As SGLT-2 inhibitors were prohibited in the EMPEROR-Preserved study, with the exception of the study medication in the intervention arm, patients with CKD may not have received optimal treatment. Uncertainties therefore exist with regard to the implementation of the ACT in patients with CKD, which are addressed in the certainty of conclusions in Section 2.4.2.

Subpopulation 3: patients with T2DM and with CKD

The NVL for T2DM recommends treatment with metformin in combination with an SGLT-2 inhibitor or a GLP-1 receptor agonist for patients with T2DM and clinically relevant cardiovascular disease if drug therapy is indicated [16]. However, as described in dossier assessment A21-109 [17], there is only limited evidence for the treatment of T2DM with SGLT-2 inhibitors or GLP-1 receptor agonists in patients with concomitant CKD. This is due to the fact that the studies underlying these recommendations LEADER on liraglutide, EMPA-REG on empagliflozin, DECLARE-TIMI 58 on dapagliflozin) included mainly patients without CKD. However, according to new findings (see previous paragraph on subpopulation 2), SGLT-2 inhibitors (dapagliflozin) are also recommended in the treatment of CKD regardless of the presence of T2DM. Therefore, due to the prohibition of SGLT-2 inhibitors in the comparator arm, the same uncertainties with regard to the implementation of the ACT exist for patients of subpopulation 3 as for patients of subpopulation 2, as CKD may not have been optimally treated.

Subpopulation 4: patients with T2DM and without CKD

As already described for subpopulation 3, the NVL for T2DM recommends treatment with metformin in combination with an SGLT-2 inhibitor or a GLP-1 receptor agonist for patients with T2DM and clinically relevant cardiovascular disease if drug therapy is indicated [16]. For patients with drug-treated T2DM and without concomitant CKD, there is thus a clear therapeutic indication for SGLT-2 inhibitors or GLP-1 receptor agonists. However, therapy with SGLT-2 inhibitors, with the exception of the investigational drug empagliflozin in the intervention arm, was not allowed. Although therapy with GLP-1 receptor agonists was possible, it was hardly carried out (see Table 9). Thus, the ACT was not implemented for subpopulation 4 in the EMPEROR-Preserved study.

Summary of the appropriate comparator therapy

In summary, the ACT in the EMPEROR-Preserved study is adequately implemented only for the subpopulation 1 described above; for subpopulations 2 and 3, implementation is unclear because of uncertainties due to the lack of use of SGLT-2 inhibitors for the treatment of CKD. Due to this uncertainty, no more than hints, e.g. of an added benefit, can be derived for subpopulations 1 to 3. Since the ACT was not implemented for subpopulation 4, no added benefit can be derived for this subpopulation.

It is not clear from the presented analyses of the company how large the individual subpopulations are, so that the proportion of patients in the total population with adequate or unclear implementation of the ACT is unknown. Despite these limitations, the total population of the EMPEROR-Reduced study is used for the benefit assessment. This is justified below, and the consequences for the certainty of conclusions of the study are described. A summary of the certainty of conclusions can be found in Section 2.4.2.

Rationale for considering the total population of the EMPEROR-Preserved study

It is unclear how large the 4 subpopulations described above are in comparison with the total population, as no corresponding subgroup analyses are available. This means that it cannot be determined exactly for which proportions of the total population of the EMPEROR-Preserved study the ACT was not implemented, was implemented unclearly or was implemented adequately.

However, due to the pathogenesis of CKD, a relevant overlap of patients with T2DM and CKD can be assumed. This means that subpopulation 4 (T2DM without CKD), in which the ACT was not implemented, represents with sufficient certainty only a relatively small proportion of the total population of the EMPEROR-Preserved study. The company's dossier additionally contains subgroup analyses for patients with and without T2DM as well as for patients with and without CKD. These show sufficiently consistent effects with regard to the characteristics of CKD and T2DM compared with the total population (see Appendix E of the full dossier assessment). Thus, the observed effects in the total population cannot be caused to an important degree by the only low proportion of patients from subpopulation 4 in whom the ACT was not

implemented. Moreover, the observed effects in the total population for the assessment of the relevant subpopulations 1 to 3 are not called into question by these subgroup analyses. Therefore, despite the uncertainties described, the total population of the study is used to derive the added benefit. However, due to these uncertainties, the extent of the observed effects in the total population cannot be quantified. Quantification of the extent of the added benefit requires separate analyses for subpopulations 1 to 3 versus subpopulation 4 on the one hand, and individual analyses for the 4 subpopulations mentioned on the other hand, in order to finally ensure the consistency of the effects in subpopulations 1 to 3.

Duration of treatment and follow-up observation

Table 10 shows the mean and median patient treatment duration and the mean and median observation period for the outcomes.

Table 10: Data on the course of the study – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study **Duration of the study phase** **Outcome category**	**Empagliflozin + optimized standard therapy** **N = 2997**	**Placebo + optimized standard therapy** **N = 2991**
EMPEROR-Preserved		
Treatment duration [months]		
Median [Q1; Q3]	23.3 [15.4; 31.4]	23.3 [15.3; 31.4]
Mean (SD)	22.7 (10.7)	22.7 (10.8)
Observation period [months][a]		
Mortality, morbidity, health-related quality of life, side effects		
Median [Q1; Q3]	27.4 [19.2; 34.1]	27.3 [19.4; 34.1]
Mean (SD)	26.7 (9.3)	26.8 (9.2)

a. The observation period is calculated on the basis of the observed time to event/censoring/end of study of all patients.

N: number of patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

Treatment duration and observation period are comparable between the 2 study arms. The median treatment duration was 23.3 months in both treatment arms. The median observation period for all outcomes was 27.4 versus 27.3 months.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
EMPEROR-Preserved	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the EMPEROR-Preserved study is rated as low.

Transferability of the study results to the German health care context

The company stated that the EMPEROR-Preserved study is a multinational study in which 44.9% of all study participants were randomized in Europe, and 71.4% in countries belonging to the Organisation for Economic Co-operation and Development (OECD). According to the company, OECD countries have a comparatively high per capita income and an efficient health care system. In addition, the OECD has been pursuing a joint reporting on selected quality indicators of health care since 2003 [18]. Since an important proportion or the majority of the patients included in the EMPEROR-Preserved study were randomized in a European or OECD country, the results of this study are transferable to the German health care context, the company added.

According to the company, effect modifications that suggest an added benefit that deviates from the total population with regard to the context of care or in a medically clearly definable subgroup were not observed. Therefore, all results observed in the EMPEROR-Preserved study were to be classified as an overall conclusion on the population relevant to the assessment.

In the opinion of the company, it can be concluded that the results of the EMPEROR-Preserved study are fully transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - hospitalization for heart failure
  - myocardial infarction
  - stroke
  - renal morbidity
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - KCCQ OSS
- Side effects
  - SAEs
  - discontinuation due to AEs
  - urinary tract infection (PT, AEs)
  - reproductive system and breast disorders (SOC, AEs)
  - diabetic ketoacidosis (PT, AEs)
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4).

Table 12 shows for which outcomes data were available in the included study.

Table 12: Matrix of outcomes – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study	Outcomes												
	All-cause mortality	Hospitalization for heart failure	Myocardial infarction[a]	Stroke[b]	Renal morbidity[c]	Health status (EQ-5D VAS)	Health-related quality of life (KCCQ OSS)	SAEs	Discontinuation due to AEs	Urinary tract infection (PT, AEs)	Reproductive system and breast disorders (SOC, AEs)	Diabetic ketoacidosis (PT, AEs)	Further specific AEs[d]
EMPEROR-Preserved	Yes	Yes	Yes	Yes	No[e]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. The composite outcome comprises nonfatal and fatal myocardial infarctions.
b. The composite outcome comprises nonfatal and fatal strokes.
c. The composite outcome comprises chronic dialysis, kidney transplant, sustained eGFR reduction by ≥ 40% from baseline, 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.
d. The following events are considered (MedDRA coding): metabolism and nutrition disorders (SOC, SAEs), musculoskeletal and connective tissue disorders (SOC, SAEs), blood and lymphatic system disorders (SOC, SAEs), respiratory, thoracic and mediastinal disorders (SOC, SAEs), hypertensive crisis (PT, SAEs) and basal cell carcinoma (PT, SAEs).
e. No usable data available; for reasoning, see text below.

AE: adverse event; eGFR: estimated glomerular filtration rate; KCCQ: Kansas City Cardiomyopathy Questionnaire; MedDRA: Medical Dictionary for Regulatory Activities; OSS: overall summary score; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Primary composite outcome

In its present operationalization, the primary composite outcome on cardiovascular morbidity is not used for the benefit assessment. The composite outcome comprises the components of cardiovascular mortality and hospitalization for heart failure. This operationalization represents cardiovascular morbidity only to a limited extent, as nonfatal myocardial infarctions and strokes are not covered by this outcome, despite the fact that these events represent relevant components of cardiovascular morbidity. Fatal myocardial infarctions and strokes, in contrast, are covered by cardiovascular mortality. Therefore, the primary composite outcome on cardiovascular morbidity is excluded from the benefit assessment.

Hospitalization for heart failure

The operationalization using the time to first event is used. The recurrent event rate is presented as supplementary information. For the recurrent event rate, the company presented an analysis using the joint frailty model (JFM), in which recurrent hospitalization for heart failure and cardiovascular death were modelled together, thus taking into account possible dependencies between these events [19]. In this analysis, 2 hazard ratios (HR_{JFM}) were estimated simultaneously; one for recurrent hospitalization for heart failure and the other for cardiovascular death. The HR_{JFM} regarding recurrent hospitalizations for heart failure is presented and can be interpreted as the treatment effect on the rate of these recurrent hospitalizations, taking into account the competing risk of cardiovascular death.

Renal morbidity

In the present operationalization, the composite outcome on renal morbidity is not used for the benefit assessment. The composite outcome comprises the following components:

- chronic dialysis
- kidney transplant
- sustained (2 or more consecutive post-baseline measurements separated by at least 30 days)
  - eGFR reduction by ≥ 40%
  - eGFR < 15 mL/min/1.73 m^2 (for patients with a baseline eGFR ≥ 30 mL/min/1.73 m^2) or eGFR < 10 mL/min/1.73 m^2 (for patients with a baseline eGFR < 30 mL/min/1.73 m^2)

For a composite outcome to be eligible for inclusion in a benefit assessment, the individual components of the outcome must be both patient-relevant and of similar severity. In this case, this only applies to the components of chronic dialysis and sustained eGFR < 15 mL/min/1.73 m^2 (for patients with a baseline eGFR ≥ 30 mL/min/1.73 m^2) or eGFR < 10 mL/min/1.73 m^2 (for patients with a baseline eGFR < 30 mL/min/1.73 m^2). Given the high baseline eGFR levels in the EMPEROR-Preserved study (see Table 8), a relative eGFR reduction by ≥ 40% is not necessarily patient-relevant and its severity is therefore not comparable to that of the remaining components of this composite outcome. Approximately 90% of the events of the composite outcome are from the component of sustained eGFR reduction by ≥ 40% [10]. It is therefore not ensured that all events of the composite outcome represent a noticeable deterioration of the disease for the patients.

Health status and health-related quality of life (KCCQ OSS)

For the health status outcomes (surveyed via EQ-5D VAS) and health-related quality of life (surveyed via KCCQ OSS), the company submitted responder analyses, using the following response criteria:

- EQ-5D VAS: improvement and deterioration by ≥ 7, ≥ 10 and ≥ 15 points, each at week 52 and at the time of the last available value within the planned treatment period (scale range of EQ-5D VAS: 0 to 100 points)
- KCCQ OSS: improvement and deterioration by ≥ 5 and ≥ 15 points, each at week 52 and at the time of the last available value within the planned treatment period (scale range of KCCQ OSS: 0 to 100 points)
- In order to analyse the improvement by ≥ 15 points, an additional analysis was carried out for both the KCCQ OSS and the EQ-5D VAS, in which patients with > 85 points at baseline were rated as responders if their score remained > 85 points at the documentation time ("ceiling correction").

Since the patients included in the EMPEROR-Preserved study were symptomatic (NYHA class ≥ II) at baseline and additional treatment with empagliflozin could therefore in principle improve symptoms, the analysis of improvement is considered for both the EQ-5D VAS and the KCCQ OSS. Analogous to dossier assessment A21-93 [20], the analysis at the prespecified time point at week 52 is used. As explained in the *General Methods* of the Institute [1,21], for a response criterion to reflect with sufficient certainty a change noticeable for the patient, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post-hoc analyses exactly 15% of the scale range). Accordingly, the results for the improvement by ≥ 15 points (in each case exactly 15% of the scale range) at week 52 are used for the derivation of the added benefit for the outcomes of EQ-5D VAS and KCCQ OSS.

Side effects – SAEs and specific AEs

AEs were recorded in the EMPEROR-Preserved study over the entire observation period, regardless of whether the patients were still receiving treatment with the study medication. However, only events that occurred during treatment with the study medication and 7 days after the end of treatment were included in the analyses of side effects submitted by the company. Thus, patients who prematurely discontinued therapy with the study medication (31.5%, see Table 8) were not included in the analyses with their entire observation periods. This approach is not appropriate. In principle, analyses that include all events in the observation period are necessary for the benefit assessment. In the present case, however, the treatment duration with the study medication corresponds to 85% of the total observation period of the EMPEROR-Preserved study (see Table 10), so that a large part of the total observation period is covered by the analyses presented for SAEs and specific AEs. The analyses of SAEs and specific AEs submitted by the company are therefore nevertheless used for the benefit assessment, although they did not take into account the entire observation period (for the effect on the certainty of conclusions, see Section 2.4.2).

2.4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study	Study level	Outcomes												
		All-cause mortality	Hospitalization for heart failure	Myocardial infarction[a]	Stroke[b]	Renal morbidity[c]	Health status (EQ-5D VAS)	Health-related quality of life (KCCQ OSS)	SAEs	Discontinuation due to AEs	Urinary tract infection (PT, AEs)	Reproductive system and breast disorders (SOC, AEs)	Diabetic ketoacidosis (PT, AEs)	Further specific AEs[d]
EMPEROR-Preserved	L	L	L	L	L	–[e]	L	L	L	L	L	L	L	L

a. The composite outcome comprises nonfatal and fatal myocardial infarctions.
b. The composite outcome comprises nonfatal and fatal strokes.
c. The composite outcome comprises chronic dialysis, kidney transplant, sustained eGFR reduction by ≥ 40% from baseline, 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.
d. The following events are considered (MedDRA coding): metabolism and nutrition disorders (SOC, SAEs), musculoskeletal and connective tissue disorders (SOC, SAEs), blood and lymphatic system disorders (SOC, SAEs), respiratory, thoracic and mediastinal disorders (SOC, SAEs), hypertensive crisis (PT, SAEs) and basal cell carcinoma (PT, SAEs).
e. No usable data available; for reasoning, see Section 2.4.1.

AE: adverse event; eGFR: estimated glomerular filtration rate; H: high; KCCQ: Kansas City Cardiomyopathy Questionnaire; L: low; MedDRA: Medical Dictionary for Regulatory Activities; OSS: overall summary score; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the results on all outcomes included in the present benefit assessment is rated as low.

Summary assessment of the certainty of conclusions

In the present benefit assessment, no more than indications, e.g. of an added benefit, can initially be derived on the basis of the single EMPEROR-Preserved study. However, various aspects further limit the certainty of conclusions of this study for the benefit assessment.

As described in Section 2.3.2, no suitable data are available for subpopulation 4 (T2DM without CKD) due to the lack of implementation of the ACT in this subpopulation; an added benefit can therefore not be derived for these patients on the basis of the EMPEROR-Preserved study. An added benefit is therefore not proven for this subpopulation.

As also described in Section 2.3.2, for subpopulations 1 to 3 (without T2DM and without CKD as well as with/without T2DM with CKD), at most hints, e.g. of an added benefit, can be derived from the results of the total population due to the existing uncertainty in the implementation of the ACT in subpopulations 2 and 3 (with/without T2DM with CKD). Furthermore, only analyses that do not cover the entire observation period of the EMPEROR-Preserved study are available for AE outcomes (see Section 2.4.1). This also leads to limited certainty of conclusions, as the balancing of benefit and harm is subject to further uncertainty. This additionally justifies that no more than hints can be derived.

Despite the described uncertainties about the size of the individual subpopulations with missing, adequate or unclear implementation of the ACT (see Section 2.3.2), the total population of the EMPEROR-Preserved study is used for the derivation of the added benefit. However, due to the existing uncertainties, the extent of the observed effects in the total population cannot be quantified.

In summary, based on the single EMPEROR-Preserved study, at most hints, e.g. of an added benefit, can be determined for all outcomes for subpopulations 1 to 3 (without T2DM and without CKD as well as with/without T2DM with CKD) due to the described uncertainties regarding the implementation of the ACT. However, the observed effects cannot be quantified. No added benefit can be derived for subpopulation 4 (T2DM without CKD).

2.4.3 Results

Table 14 and Table 15 summarize the results on the comparison of empagliflozin + optimized standard therapy with placebo + optimized standard therapy in patients with symptomatic chronic heart failure with preserved ejection fraction. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s dossier.

The Kaplan-Meier curves and cumulative incidence curves on the included outcomes are presented in Appendix B, the results on common AEs, SAEs, and discontinuations due to AEs in Appendix C, and supplementary analyses on the outcome of total hospitalization in Appendix D of the full dossier assessment.

Table 14: Results (mortality, morbidity, time to event) – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

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					
Mortality					
All-cause mortality	2997	ND 422 (14.1)	2991	ND 427 (14.3)	1.00 [0.87; 1.15]; 0.989
Cardiovascular death	2997	ND 219 (7.3)	2991	ND 244 (8.2)	0.91 [0.76; 1.09]; 0.295
Morbidity					
Hospitalization for heart failure					
First event	2997	ND 259 (8.6)	2991	ND 352 (11.8)	0.71 [0.60; 0.83]; < 0.001
		Number of events		*Number of events*	*HR_{JFM}[b]*
Including repeat events (presented as supplementary information)	*2997*	*407*	*2991*	*541*	*0.73 [0.61; 0.88]; 0.001*
Myocardial infarction (composite outcome)[c]	2997	ND 49 (1.6)	2991	ND 40 (1.3)	1.23 [0.81; 1.86]; 0.338
Nonfatal	2997	ND 42 (1.4)	2991	ND 36 (1.2)	1.17 [0.75; 1.83]; 0.487
Fatal	2997	ND 5 (0.2)	2991	ND 3 (0.1)	1.71 [0.41; 7.16]; 0.463
Stroke (composite outcome)	2997	ND 92 (3.1)	2991	ND 84 (2.8)	1.10 [0.82; 1.47]; 0.539
Nonfatal	2997	ND 78 (2.6)	2991	ND 69 (2.3)	1.13 [0.82; 1.56]; 0.463
Fatal	2997	ND 16 (0.5)	2991	ND 17 (0.6)	0.95 [0.48; 1.89]; 0.893
Renal morbidity (composite outcome)	No usable data[d]				

Table 14: Results (mortality, morbidity, time to event) – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

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]

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. HR_{JFM}, 95% CI und p-value: joint frailty model; adjusted for region, sex, age, diabetes status, LVEF and baseline eGFR; HR_{JFM} can be interpreted as treatment effect on the (recurrent) hospitalization rate.
c. Data from the CSR of the EMPEROR-Preserved study; the following deviating data can be found in Module 4 A of the company's dossier: 47 (1.6%) vs. 38 (1.3%), HR 1.24 [0.81;1.90]; p = 0.323.
d. See Section 2.4.1 for the reasoning.

CI: confidence interval; CSR: clinical study report; eGFR: estimated glomerular filtration rate; HR: hazard ratio; JFM: joint frailty model; LVEF: left ventricular ejection fraction; n: number of patients with event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial

Table 15: Results (morbidity, health-related quality of life, and side effects, dichotomous) – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

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					
Morbidity					
Health status (EQ-5D VAS)[c]	2886	668 (23.1)	2868	604 (21.1)	1.05 [0.96; 1.15]; 0.270
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	*ND*	*ND*	*ND*	*ND*	*ND*
Psychological quality of life	*ND*	*ND*	*ND*	*ND*	*ND*
Social limitation	*ND*	*ND*	*ND*	*ND*	*ND*
Symptoms (KCCQ TSS)[c]	*2884*	*754 (26.1)*	*2867*	*648 (22.6)*	*1.08 [0.99; 1.18]; 0.066*
Side effects					
AEs (supplementary information)[d]	2996	2512 (83.8)	2989	2507 (83.9)	–
SAEs[d]	2996	1157 (38.6)	2989	1243 (41.6)	0.93 [0.87; 0.99]; 0.019[e]
Discontinuation due to AEs	2996	571 (19.1)	2989	551 (18.4)	1.03 [0.93; 1.15]; 0.536[e]
Urinary tract infection (PT, AEs)	2996	236 (7.9)	2989	181 (6.1)	1.30 [1.08; 1.57]; 0.006[e]
Reproductive system and breast disorders (SOC, AEs)	2996	116 (3.9)	2989	117 (3.9)	0.99 [0.77; 1.27]; 0.932[e]
Diabetic ketoacidosis (PT, AEs)	2996	3 (0.1)	2989	2 (0.1)	1.50 [0.25; 8.95]; 0.753
Metabolic and nutritional disorders (SOC, SAEs)	2996	84 (2.8)	2989	114 (3.8)	0.74 [0.56; 0.97]; 0.029
Musculoskeletal and connective tissue disorders (SOC, SAEs)	2996	53 (1.8)	2989	76 (2.5)	0.70 [0.49; 0.98]; 0.040
Blood and lymphatic system disorders (SOC, SAEs)	2996	33 (1.1)	2989	60 (2.0)	0.55 [0.36; 0.84]; 0.005
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	2996	113 (3.8)	2989	151 (5.1)	0.75 [0.59; 0.95]; 0.016

Table 15: Results (morbidity, health-related quality of life, and side effects, dichotomous) – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

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]
Hypertensive crisis (PT, SAEs)	2996	13 (0.4)	2989	32 (1.1)	0.41 [0.21; 0.77]; 0.004
Basal cell carcinoma (PT, SAEs)	2996	17 (0.6)	2989	32 (1.1)	0.53 [0.29; 0.95]; 0.031

a. Outcomes of the categories of morbidity and health-related quality of life: Missing values were imputed using LOCF (KCCQ OSS: 14.3% each; EQ-5D VAS: 13.9% vs. 13.7%).
b. Outcomes of the categories of morbidity and health-related quality of life: log-link Poisson model with robust "estimators of variance", adjusted for region, sex, age, diabetes status, LVEF, eGFR and respective baseline value; outcomes of the category of side effects: Institute's calculation of RR, 95% CI (asymptotic) and p-value (unconditional exact test [CSZ method according to [22]]) unless stated otherwise.
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/health-related quality of life.
d. Without consideration of the following (disease-related) events: death from any cause, hospitalization for heart failure, myocardial infarction, stroke, transient ischaemic attack, atrial fibrillation (serious), acute renal failure (serious), unstable angina pectoris.
e. Chi-square test.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; 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; OSS: overall summary score; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; TSS: total symptom score; VAS: visual analogue scale

Due to the uncertainties described above (see Sections 2.3.2 and 2.4.2), at most hints, e.g. of added benefit, can be derived on the basis of the available information.

Mortality

The outcome of all-cause mortality represents mortality irrespective of the cause of death, thus providing a more comprehensive picture than the outcome of cardiovascular death. Hence, the outcome of all-cause mortality is used for the derivation of added benefit.

All-cause mortality

There was no statistically significant difference between treatment groups for the outcome of all-cause mortality. This results in no hint of an added benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for this outcome.

Morbidity

Hospitalization for heart failure

A statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy was shown for the outcome of hospitalization for heart failure. This results in a hint of an added benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Myocardial infarction

For the composite outcome of myocardial infarction, consisting of nonfatal myocardial infarction and fatal myocardial infarction, as well as for both individual components, there was no statistically significant difference between the treatment groups. However, there is an effect modification by sex. For women, there is a hint of lesser benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. For men, however, there is no hint of an added benefit or lesser benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit or lesser benefit is therefore not proven for men for this outcome (see Section 2.4.4).

Stroke

For the composite outcome of stroke, consisting of nonfatal stroke and fatal stroke, as well as for both individual components, there was no statistically significant difference between the treatment groups. This results in no hint of an added benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for this outcome.

Renal morbidity

No usable data are available for the outcome of renal morbidity. See Section 2.4.1 for reasons. This results in no hint of an added benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for this outcome.

Health status

EQ-5D VAS

For the outcome of health status, operationalized as EQ-5D VAS improvement by ≥ 15 points at week 52, no statistically significant difference between treatment groups was found. This results in no hint of an added benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for this outcome.

Health-related quality of life

KCCQ OSS

For the outcome of health-related quality of life, operationalized as improvement in KCCQ OSS by ≥ 15 points at week 52, no statistically significant difference between treatment groups was found. This results in no hint of an added benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for this outcome.

Side effects

Given that the study used for the assessment is a placebo-controlled study, it is unclear whether the observed effects in favour of empagliflozin in the side effect outcomes are actually attributable to side effects or rather to disease-related morbidity.

SAEs

A statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy was shown for the outcome of SAEs. This results in a hint of lesser harm from empagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Discontinuation due to AEs

There was no statistically significant difference between treatment groups for the outcome of discontinuation due to AEs. This results in no hint of greater or lesser harm of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. Greater or lesser harm is therefore not proven for this outcome.

Specific AEs

Urinary tract infection

A statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy was shown for the outcome of urinary tract infection (PT, AEs). This difference was no more than marginal, however (see Section 2.5.1). This results in no hint of greater or lesser harm of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. Greater or lesser harm is therefore not proven for this outcome.

Reproductive system and breast disorders, diabetic ketoacidosis

There was no statistically significant difference between treatment groups for the outcomes of reproductive system and breast disorders (SOC, AEs) and diabetic ketoacidosis (PT, AEs). In each case, this results in no hint of greater or lesser harm of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. Greater or lesser harm is therefore not proven for these outcomes.

Metabolism and nutrition disorders (SOC, SAEs), musculoskeletal and connective tissue disorders (SOC, SAEs), blood and lymphatic system disorders (SOC, SAEs), respiratory, thoracic and mediastinal disorders (SOC, SAEs), hypertensive crisis (PT, SAEs), and basal cell carcinoma (PT, SAEs)

A statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy was shown for each of the outcomes of metabolism and nutrition disorders (SOC, SAEs), musculoskeletal and connective tissue disorders (SOC, SAEs), blood and lymphatic system disorders (SOC, SAEs), hypertensive crisis (PT, SAEs), and basal cell carcinoma (PT, SAEs). In each case, this results in a hint of lesser harm from empagliflozin + optimized standard therapy in comparison with optimized standard therapy.

A statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy was also shown for the outcome of respiratory, thoracic and mediastinal disorders (SOC, SAEs). However, there is an effect modification by age. For patients ≥ 70 years, there is a hint of lesser harm of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. For patients < 70 years, in contrast, there was no statistically significant difference between treatment groups. Greater or lesser harm for this outcome is therefore not proven for patients < 70 years (see Section 2.4.4).

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present benefit assessment:

- age (< 70 years versus ≥ 70 years)
- sex (male versus female)
- LVEF at baseline < 50% versus ≥ 50%

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 16 and Table 17 summarize the subgroup results on the comparison of empagliflozin + optimized standard therapy with placebo + optimized standard therapy in adult patients with symptomatic chronic HFpEF.

Table 16: Subgroups (morbidity, time to event) – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study **Outcome** **Characteristic** **Subgroup**	**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						
Myocardial infarction (composite outcome)[b]						
Sex						
Women	1338	ND 24 (1.8)	1338	ND 12 (0.9)	2.13 [1.06; 4.26]	0.033
Men	1659	ND 23 (1.4)	1653	ND 26 (1.6)	0.85 [0.48; 1.49]	0.571
Total					Interaction:	0.044[c]

a. HR [95% CI] from Cox proportional hazards model with the covariates treatment, region, diabetes status, age, sex, LVEF and eGFR at baseline and the interaction term subgroup characteristic*treatment.
b. The composite outcome comprises nonfatal and fatal myocardial infarctions.
c. Wald chi-square statistic of the interaction effect of subgroup characteristic*treatment from Cox proportional hazards model.

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; NYHA: New York Heart Association; RCT: randomized controlled trial

Table 17: Subgroups (side effects, dichotomous) – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study Outcome Characteristic Subgroup	Empagliflozin + optimized standard therapy		Placebo + optimized standard therapy		Empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy	
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
EMPEROR-Preserved						
Side effects						
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)						
Age						
< 70 years	1066	48 (4.5)	1084	42 (3.9)	1.16 [0.77; 1.74]	0.467[a]
≥ 70 years	1930	65 (3.4)	1905	109 (5.7)	0.59 [0.44; 0.79]	< 0.001[a]
Total					Interaction:	0.008[b]

a. Chi-square test.
b. Cochran Q-test for homogeneity of RR (interaction: treatment*subgroup).

CI: confidence interval; LVEF: left ventricular ejection fraction; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Morbidity

Myocardial infarction (composite outcome)

There is a statistically significant effect modification by the characteristic of sex for the composite outcome of myocardial infarction, consisting of nonfatal myocardial infarction and fatal myocardial infarction. A statistically significant difference between treatment groups to the disadvantage of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy was shown for women. For women, this results in a hint of lesser benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy. For men, in contrast, there was no statistically significant difference between the treatment groups. This results in no hint of an added benefit or lesser benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy for men. An added benefit or lesser benefit is therefore not proven for men for this outcome.

Side effects

SAEs

For the specific AE of respiratory, thoracic and mediastinal disorders (SOC, SAEs) included in the overall rate of SAEs, there is a statistically significant effect modification by the characteristic of age. For patients ≥ 70 years of age, there was a statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy

in comparison with placebo + optimized standard therapy. This results in a hint of lesser harm of empagliflozin + optimized standard therapy in comparison with optimized standard therapy for patients ≥ 70 years of age. For patients < 70 years, in contrast, there was no statistically significant difference between treatment groups. This results in no hint of greater or lesser harm of empagliflozin + optimized standard therapy in comparison with optimized standard therapy for patients < 70 years of age. Greater or lesser harm for this outcome is therefore not proven for patients < 70 years.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit per subpopulation at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.4 (see Table 18).

Determination of the outcome category for the outcomes on morbidity

For the following morbidity outcome(s), it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. The classification for these outcomes is justified.

Hospitalization for heart failure

Events that are fatal or require inpatient treatment are considered severe or serious. Therefore, the outcome of hospitalization for heart failure is assigned to the outcome category of serious/severe symptoms/late complications.

Table 18: Extent of added benefit at outcome level: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

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]
Mortality		
All-cause mortality	ND vs. ND HR: 1.00 [0.87; 1.15] p = 0.989	Lesser benefit/added benefit not proven
Morbidity		
Hospitalization for heart failure	ND vs. ND HR: 0.71 [0.60; 0.83] p < 0.001 Probability: "hint"	Outcome category: serious/severe symptoms/late complications Added benefit, extent: "non-quantifiable"
Myocardial infarction Sex Women	ND vs. ND HR: 2.13 [1.06; 4.26] HR: 0.47 [0.23; 0.94][c] p = 0.033 Probability: "hint"	Outcome category: serious/severe symptoms/late complications lesser benefit, extent: "non-quantifiable"
Men	ND vs. ND HR: 0.85 [0.48; 1.49] p = 0.571	Lesser benefit/added benefit not proven
Stroke	ND vs. ND HR: 1.10 [0.82; 1.47] p = 0.539	Lesser benefit/added benefit not proven
Renal morbidity	No usable data	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS; improvement by ≥ 15 points)	23.1% vs. 21.1% RR: 1.05 [0.96; 1.15] p = 0.270	Lesser benefit/added benefit not proven
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
Side effects		
SAEs	38.6% vs. 41.6% RR: 0.93 [0.87; 0.99] p = 0.019 Probability: "hint"	Outcome category: serious/severe side effects Lesser harm, extent: "non-quantifiable"

Table 18: Extent of added benefit at outcome level: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

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]
Discontinuation due to AEs	19.1% vs. 18.4% RR: 1.03 [0.93; 1.15] p = 0.536	Greater/lesser harm not proven
Urinary tract infection (AEs)	7.9% vs. 6.1% RR: 1.30 [1.08; 1.57] RR: 0.77 [0.64; 0.93][c] p = 0.006	Outcome category: non-serious/non-severe side effects $0.90 \leq CI_u < 1.00$ Greater/lesser harm not proven[d]
Reproductive system and breast disorders (AEs)	3.9% vs. 3.9% RR: 0.99 [0.77; 1.27] p = 0.932	Greater/lesser harm not proven
Diabetic ketoacidosis (AEs)	0.1% vs. 0.1% RR: 1.50 [0.25; 8.95] p = 0.753	Greater/lesser harm not proven
Metabolic and nutritional disorders (SAEs)	2.8% vs. 3.8% RR: 0.74 [0.56; 0.97] p = 0.029 Probability: "hint"	Outcome category: serious/severe side effects Lesser harm, extent: "non-quantifiable"
Musculoskeletal and connective tissue disorders (SAEs)	1.8% vs. 2.5% RR: 0.70 [0.49; 0.98] p = 0.040 Probability: "hint"	Outcome category: serious/severe side effects Lesser harm, extent: "non-quantifiable"
Blood and lymphatic system disorders (SAEs)	1.1% vs. 2.0% RR: 0.55 [0.36; 0.84] p = 0.005 Probability: "hint"	Outcome category: serious/severe side effects Lesser harm, extent: "non-quantifiable"
Respiratory, thoracic and mediastinal disorders (SAEs) Age		
< 70 years	4.5% vs. 3.9% RR: 1.16 [0.77; 1.74] p = 0.467	Greater/lesser harm not proven
≥ 70 years	3.4% vs. 5.7% RR: 0.59 [0.44; 0.79] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects Lesser harm, extent: "non-quantifiable"
Hypertensive crisis (SAEs)	0.4% vs. 1.1% RR: 0.41 [0.21; 0.77] p = 0.004 Probability: "hint"	Outcome category: serious/severe side effects Lesser harm, extent: "non-quantifiable"

Table 18: Extent of added benefit at outcome level: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

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]
Basal cell carcinoma (SAEs)	0.6% vs. 1.1% RR: 0.53 [0.29; 0.95] p = 0.031 Probability: "hint"	Outcome category: serious/severe side effects Lesser harm, extent: "non-quantifiable"

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; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 19 summarizes the results included in the overall conclusion on the extent of added benefit.

Table 19: Positive and negative effects from the assessment of empagliflozin + optimized standard therapy in comparison with optimized standard therapy

Positive effects	Negative effects
Morbidity Serious/severe secondary diseases ▪ Hospitalization for heart failure: hint of an added benefit – extent: "non-quantifiable"	Morbidity Serious/severe secondary diseases ▪ Myocardial infarction ▫ Sex (women): hint of lesser benefit – extent: "non-quantifiable"
Serious/severe side effects ▪ SAEs: hint of lesser harm – extent: "non-quantifiable"[a] ▫ 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"	–
a. It is questionable whether the effect is in fact attributable to the outcome category of side effects or reflects symptoms of the underlying diseases. SAE: serious adverse event	

As described in Sections 2.3.2 and 2.4.2, the EMPEROR-Preserved study included a heterogeneous patient population with regard to underlying conditions. The ACT was not adequately implemented for all patients in this heterogeneous patient population. The added benefit is therefore derived separately for the subpopulations with and without adequate or at least limited implementation of the ACT, as defined in Section 2.3.2, in each case on the basis of the total population of the EMPEROR-Preserved study.

Patients with HFpEF without T2DM and without CKD as well as with/without T2DM and with CKD

Overall, there are several positive and one negative effect for empagliflozin + optimized standard therapy in comparison with optimized standard therapy.

On the side of positive effects, there is a hint of non-quantifiable added benefit in the outcome category of serious/severe secondary diseases for the outcome of hospitalization for heart failure. In addition, there is a hint of non-quantifiable lesser harm in the outcome category of serious/severe side effects for the outcome of SAEs and for various specific AEs contained in the overall rate of SAEs.

On the side of negative effects, however, there is a hint of non-quantifiable greater harm in the outcome category of serious/severe secondary diseases for the outcome of myocardial

infarction only in women. However, this does not completely call into question the positive effect with regard to the outcome of hospitalization for heart failure in particular.

In summary, there is a hint of non-quantifiable added benefit of empagliflozin + optimized standard therapy in comparison with the ACT in the form of optimized standard therapy for patients with symptomatic chronic HFpEF (defined as heart failure with LVEF > 40%) without T2DM and without CKD as well as with/without T2DM and with CKD.

Patients with HFpEF with T2DM without CKD (concurring with subpopulation 4)

There is no hint of an added benefit of empagliflozin + optimized standard therapy in comparison with the ACT in the form of optimized standard therapy for patients with symptomatic chronic HFpEF (defined as heart failure with LVEF > 40%) with T2DM and without CKD. An added benefit for these patients is therefore not proven.

The result of the assessment of the added benefit of empagliflozin in comparison with the ACT is summarized in Table 20.

Table 20: 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; NVL: National Care Guideline; T2DM: type 2 diabetes mellitus

The assessment described above deviates from that of the company, which derived proof of considerable added benefit in comparison with the ACT.

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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