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Empagliflozin (heart failure) –

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) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 October 2021). 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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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACE	angiotensin converting enzyme
ACT	appropriate comparator therapy
AE	adverse event
ARB	angiotensin receptor blocker
ARNI	angiotensin receptor neprilysin inhibitor
CRT	cardiac resynchronization therapy
eGFR	estimated glomerular filtration rate
EQ-5D	European Quality of Life-5 Dimensions
ESC	European Society of Cardiology
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
ICD	implantable cardioverter defibrillator
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
LOCF	last observation carried forward
LVEF	left ventricular ejection fraction
MRA	mineralocorticoid receptor antagonist
NT-proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OSS	overall summary score
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGLT	sodium-dependent glucose transporter
SOC	System Organ Class
SPC	Summary of Product Characteristics
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 13 July 2021.

Research question

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

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of empagliflozin

Therapeutic indication	**ACT**[a]
Adults with symptomatic chronic heart failure with reduced ejection fraction	Optimized standard therapy for the treatment of symptomatic chronic heart failure and underlying medical conditions, e.g. hypertension, cardiac arrhythmias, coronary heart disease, diabetes mellitus, hypercholesterolaemia, and concomitant symptoms[b]

a. Presented is the ACT specified by the G-BA.
b. The patients in both study arms are assumed to have received optimal treatment: guideline-compliant individualized treatment of heart failure and underlying medical conditions or risk factors such as hypertension, cardiac arrhythmias, or diabetes mellitus as well as the concomitant symptoms, e.g. oedema. It should be possible to adapt the baseline/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 is no further possibility for optimization, it has to be documented and explained that any other existing treatment options are unsuitable or have been exhausted.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company followed the G-BA's specification on the ACT.

The assessment was 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 were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

Results

The EMPEROR-Reduced study was used to assess the added benefit of empagliflozin in comparison with optimized standard therapy for the treatment of patients with symptomatic chronic heart failure with reduced ejection fraction.

Study design

The EMPEROR-Reduced study is a placebo-controlled, double-blind RCT. It included patients with chronic heart failure of New York Heart Association (NYHA) classes II through IV with reduced ejection fraction, defined as left ventricular ejection fraction (LVEF) ≤ 40%. There were additional further restrictions depending on the LVEF (see below). The patients had to be on adequate medical therapy for heart failure, which was stable for at least 1 week prior to visit 1 and during screening period until randomization (visit 2). The therapy for heart failure was to be individualized, consisting of combinations of the drug classes of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), beta-blockers, oral diuretics, mineralocorticoid receptor antagonists (MRAs), angiotensin receptor neprilysin inhibitors (ARNIs) and ivabradine, and had to be consistent with national and international recommendations. If there was a therapeutic indication, the patients had to be provided with implantable cardioverter defibrillators (ICDs) or a cardiac resynchronization therapy (CRT).

A total of 3730 patients were included in the study and randomly allocated in a 1:1 ratio either to treatment with empagliflozin (N = 1863) or to placebo (N = 1867).

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 a reduced LVEF ≤ 40%, patients in the EMPEROR-Reduced study had to meet the following inclusion criteria:

a) 36% ≤ LVEF ≤ 40%: elevated N-terminal pro-brain natriuretic peptide (NT-proBNP) at visit 1 ≥ 2500 pg/mL (≥ 5000 pg/mL for patients with atrial fibrillation or atrial flutter)
b) 31% ≤ LVEF ≤ 35%: elevated NT-proBNP at visit 1 ≥ 1000 pg/mL (≥ 2000 pg/mL for patients with atrial fibrillation or atrial flutter)
c) If LVEF ≤ 30%: elevated NT-proBNP at visit 1 ≥ 600 pg/mL (≥ 1200 pg/mL for patients with atrial fibrillation or atrial flutter)
d) For LVEF ≤ 40% and documented hospitalization for heart failure within 12 months prior to visit 1: elevated NT-proBNP at visit 1 ≥ 600 pg/mL (≥ 1200 pg/mL for patients with atrial fibrillation or atrial flutter)

As a result, for patients who had not previously been hospitalized for heart failure, the less pronounced the reduction in LVEF below the 40% threshold, the more elevated NT-proBNP values had to be to qualify for inclusion in the EMPEROR-Reduced study. For patients who had already been hospitalized for heart failure within the last 12 months, no further gradations below the 40% threshold were specified. These patients had to have NT-proBNP ≥ 600 pg/mL at visit 1. The inclusion criteria mentioned lead to a restricted study population both in relation

to the approved therapeutic indication and to the German health care context. The required NT-proBNP values in particular led to a selection of patients: About 36% of all patients who participated in the screening were not included in the EMPEROR-Reduced study solely because the NT-proBNP values were too low. It is therefore unclear whether the observed effects in the EMPEROR-Reduced study can also be transferred to patients with an LVEF ≤ 40% who do not fulfil the above-mentioned additional inclusion criteria, which are strict compared with other studies in the therapeutic indication.

Implementation of the appropriate comparator therapy

The comparator therapy of the included EMPEROR-Reduced study is an adequate implementation of the ACT only to a limited extent. A main limitation in the implementation of the ACT was that possibly not all therapeutic options were exhausted for a large proportion of patients.

In the EMPEROR-Reduced study, all patients were to receive individual therapy consistent with national and international guidelines. This applied both to the treatment of heart failure and to the treatment of other cardiovascular risk factors and comorbidities (especially type 2 diabetes mellitus). Therapy adjustments were possible in the course of the study, but therapy had to be stable for 1 week prior to visit 1 and during the screening period until randomization (visit 2). However, the extent to which an optimization of the standard therapy was ensured in the further course of study cannot be fully assessed.

Implementation of the recommendations for a treatment switch to sacubitril/valsartan

The recommendations of the National Care Guideline on the intensification of therapy in case of persisting symptoms under basic therapy for symptomatic heart failure with reduced ejection fraction were updated on 23 September 2021 with the amendment on sodium-dependent glucose transporter (SGLT)-2 inhibitors. This amendment also concerns the recommendation for a treatment switch from ACE inhibitors/ARBs to sacubitril/valsartan. The implementation of the ACT with regard to sacubitril/valsartan therapy in the EMPEROR-Reduced study is therefore assessed in light of this short-term change, taking into account the recommendations of the previous version 2 and the new version 3 of the National Care Guideline.

According to the National Care Guideline as well as the recently updated European Society of Cardiology (ESC) guideline, patients with symptomatic heart failure and reduced ejection fraction should be treated with a combination of an ACE inhibitor or an ARB, a beta-blocker, and an MRA. According to the National Care Guideline version 2, patients who continue to be symptomatic despite guideline-compliant therapy should be recommended a switch from ACE inhibitors/ARBs to the ARNI sacubitril/valsartan. Although, according to the inclusion criteria, patients in the EMPEROR-Reduced study were supposed to have NYHA class II through IV heart failure with concomitant stable and individually optimized therapy, only a small proportion received sacubitril/valsartan. The National Care Guideline version 2 comments with regard to a similar study with dapagliflozin in the same therapeutic indication that, from today's perspective, not all therapeutic options (referring to the use of sacubitril/valsartan) were

exhausted in a large proportion of the study population. Accordingly, this also applies to the EMPEROR-Reduced study presented here. However, it cannot be inferred from the available data for how many patients in the EMPEROR-Reduced study a switch to sacubitril/valsartan would actually have been indicated.

According to the National Care Guideline version 3 published on 23 September 2021, patients who continue to be symptomatic despite guideline-compliant therapy with ACE inhibitors/ARBs, beta-receptor blockers and MRAs should either be recommended therapy with an SGLT-2 inhibitor or a switch from ACE inhibitors/ARBs to the ARNI sacubitril/valsartan. If patients remain symptomatic despite intensification of therapy with sacubitril/valsartan or SGLT-2 inhibitors, the other drug/drug combination can also be offered as an additive. This updated recommendation was implemented accordingly for the patients in the intervention arm of the EMPEROR-Reduced study, as all patients received therapy with an SGLT-2 inhibitor (empagliflozin) or in some cases even a combination of empagliflozin and sacubitril/valsartan. For patients in the comparator arm, however, not all therapeutic options were exhausted, even taking into account these new recommendations, as only few patients received sacubitril/valsartan, and therapy with SGLT-2 inhibitors was not permitted in the comparator arm of the EMPEROR-Reduced study. The criticism of the low use of sacubitril/valsartan therefore remains valid for the comparator arm of the EMPEROR-Reduced study, even taking version 3 of the National Care Guideline into account.

In summary, the ACT was only implemented to a limited extent. Despite these limitations, the EMPEROR-Reduced study was used for the benefit assessment. Consequences for the certainty of conclusions of the study are described below.

Risk of bias

The risk of bias across outcomes for the EMPEROR-Reduced study was rated as low. The risk of bias for the results of all outcomes was rated as low, except for the outcomes of health status (recorded using the visual analogue scale [VAS] of the European Quality of Life-5 Dimensions [EQ-5D]) and health-related quality of life (recorded using the overall summary score [OSS] of the Kansas City Cardiomyopathy Questionnaire [KCCQ]).

Assessment of the certainty of conclusions

Various aspects limit the certainty of conclusions of the present EMPEROR-Reduced study for the benefit assessment.

For the present benefit assessment, it remains unclear whether the concomitant treatment for heart failure used in the EMPEROR-Reduced study represents an adequate or full implementation of the ACT in the sense of an optimized standard therapy. On the one hand, this assessment is based on the lack of relevant data on therapy adjustments and on the fact that relatively few patients had their medical heart failure therapy adjusted during the course of the study. On the other hand, it is unclear how large the influence on the effect of empagliflozin would have been if a larger proportion of patients had been treated with sacubitril/valsartan.

Overall, at most hints, e.g. of an added benefit, can be determined for all outcomes due to these limitations. Further, it is unclear to what extent the potentially insufficient proportion of patients who switched to sacubitril/valsartan therapy (according to the new recommendations of the National Care Guideline version 3 only referring to the comparator arm) impacted the effects on patient-relevant outcomes in the EMPEROR-Reduced study. Therefore, the effects on the individual outcomes cannot be quantified.

Results

Mortality

There was no statistically significant difference between treatment groups for the outcome of all-cause mortality. This results in no hint of added benefit of empagliflozin + optimized standard therapy in comparison with placebo + 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 was shown for the outcome of hospitalization for heart failure. However, there is an effect modification for heart failure severity according to NYHA class. This results in a hint of an added benefit of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy for patients with NYHA class II. For patients with NYHA classes III/IV, there is 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 patient group.

Myocardial infarction

For the composite outcome of myocardial infarction, consisting of nonfatal myocardial infarction and fatal myocardial infarction, as well as for the 2 individual components, there is no statistically significant difference between the treatment groups. This results in no hint of added benefit of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy. An added benefit is therefore not proven for this outcome.

Stroke

For the composite outcome of stroke, consisting of nonfatal stroke and fatal stroke, as well as for the 2 individual components, there is no statistically significant difference between the treatment groups. This results in no hint of added benefit of empagliflozin + optimized standard therapy in comparison with placebo + 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 added benefit of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy; an added benefit is therefore not proven for this outcome.

Health status

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

Health-related quality of life

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 added benefit of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy. An added benefit is therefore not proven for these outcomes.

Side effects

Serious adverse events (SAEs)

A statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy was shown for the outcome of SAEs. However, there is an effect modification for heart failure severity according to NYHA class. This results in a hint of lesser harm from empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy for patients with NYHA class II. For patients with NYHA classes III/IV, there is no hint of greater or lesser harm from empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy; greater or lesser harm is therefore not proven for this patient group.

Discontinuation due to adverse events (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 from empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy; greater or lesser harm is therefore not proven for this outcome.

Urinary tract infection, reproductive system and breast disorders, diabetic ketoacidosis

No statistically significant difference between treatment groups was shown for the outcomes of urinary tract infection (Preferred Term [PT], AEs) and reproductive system and breast disorders (System Organ Class [SOC], AEs). The company presented no data for the outcome of diabetic

ketoacidosis (PT, AEs) in Module 4 A, because this event occurred in fewer than 1% of the patients per treatment arm. In each case, this results in no hint of greater or lesser harm from empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy; greater or lesser harm is therefore not proven.

Renal and urinary disorders (SOC, SAEs), hepatobiliary disorders (SOC, SAEs)

A statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy was shown for the outcomes of renal and urinary disorders (SOC, SAEs) and hepatobiliary disorders (SOC, SAEs). This results in a hint of lesser harm from empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy.

Atrial fibrillation (PT, SAEs)

A statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy was shown for the outcome of atrial fibrillation (PT, SAEs). However, there is an effect modification for heart failure severity according to NYHA class. This results in a hint of lesser harm from empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy for patients with NYHA class II. For patients with NYHA classes III/IV, there is no hint of greater or lesser harm from empagliflozin + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven for this patient group.

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

In the overall consideration, there are only positive effects of empagliflozin in comparison with optimized standard therapy for patients with symptomatic chronic heart failure with reduced ejection fraction.

For the total population, there are positive effects for the outcomes of hepatobiliary disorders (SOC, SAEs) and renal and urinary disorders (SOC, SAEs). For both of these outcomes, this results in a hint of non-quantifiable lesser harm from empagliflozin + optimized standard therapy for the total population.

Further positive effects were shown only for patients with NYHA class II severity. Thus, there is a hint of a non-quantifiable added benefit of empagliflozin + optimized standard therapy for this patient population for the outcome of hospitalization for heart failure. In the category of

[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].

side effects, there is a hint of non-quantifiable lesser harm from empagliflozin + optimized standard therapy for the outcomes of SAEs and atrial fibrillation (PT, SAEs).

As described above, some of the positive effects were shown only for patients with NYHA class II severity. However, since the observed effects in the EMPEROR-Reduced study are overall non-quantifiable and there are only positive effects also for the total population, the added benefit is derived on the basis of the total population regardless of these effect modifications.

In summary, there is therefore a hint of a non-quantifiable added benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy for patients with symptomatic chronic heart failure with reduced ejection fraction.

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 reduced ejection fraction[b]	Optimized standard therapy for the treatment of symptomatic chronic heart failure and underlying medical conditions, e.g. hypertension, cardiac arrhythmia, coronary heart disease, diabetes mellitus, hypercholesterolaemia and the concomitant symptoms	Hint of non-quantifiable added benefit

a. Presentation of the respective ACT specified by the G-BA.
b. The conclusion on added benefit is based on the results of the EMPEROR-Reduced study. To qualify for inclusion in the EMPEROR-Reduced study, patients had to exhibit an LVEF ≤ 40% and meet additional inclusion criteria (including certain NT-proBNP thresholds). It remains unclear whether the observed effects can be transferred to other patients in the target population.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide

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 as ACT in patients with symptomatic chronic heart failure with reduced ejection fraction.

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of empagliflozin

Therapeutic indication	**ACT**[a]
Adults with symptomatic chronic heart failure with reduced ejection fraction	Optimized standard therapy for the treatment of symptomatic chronic heart failure and underlying medical conditions, e.g. hypertension, cardiac arrhythmias, coronary heart disease, diabetes mellitus, hypercholesterolaemia, and concomitant symptoms[b]
a. Presented is the ACT specified by the G-BA. b. The patients in both study arms are assumed to have received optimal treatment: guideline-compliant individualized treatment of heart failure and underlying medical conditions or risk factors such as hypertension, cardiac arrhythmias, or diabetes mellitus as well as the concomitant symptoms, e.g. oedema. It should be possible to adapt the baseline/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 is no further possibility for optimization, it has to be documented and explained that any other existing treatment options are unsuitable or have been exhausted. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification on the ACT.

The assessment was 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 were 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: 1 June 2021)
- bibliographical literature search on empagliflozin (last search on 17 May 2021)
- search in trial registries/trial results databases for studies on empagliflozin (last search on 17 May 2021)
- search on the G-BA website for empagliflozin (last search on 1 July 2021)

To check the completeness of the study pool:

- search in trial registries for studies on empagliflozin (last search on 3 August 2021); 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-Reduced study is included in the present benefit assessment.

The company presented 2 additional studies (SUGAR-DM-HF [3] and EMPA-TROPISM [4]). The company presented the results of these studies only as supplementary information. The company justified this in particular by stating that the studies provided less detailed information on the implementation of the concomitant standard therapy.

The results of the studies SUGAR-DM-HF and EMPA-TROPISM are not used for the present benefit assessment. This is justified below.

Studies SUGAR-DM-HF and EMPA-TROPISM are not used for the benefit assessment

The RCT SUGAR-DM-HF included 105 patients with type 2 diabetes mellitus or prediabetes as well as symptomatic heart failure of NYHA classes II through IV with LVEF ≤ 40% for a comparison of empagliflozin + standard therapy versus placebo + standard therapy. Optimized treatment of concomitant diseases such as diabetes mellitus was not possible in this study because no change of antidiabetic medication, except insulin, was to be conducted in the first 12 weeks. Due to missing information, it also remains unclear to what extent the concomitant treatment for heart failure conducted in the study was in line with the ACT of the present benefit assessment. Thus, there was overall no sufficient implementation of the ACT in the SUGAR-DM-HF study, and the study is therefore unsuitable for the 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. An LVEF < 50% does not correspond to the definition of symptomatic chronic heart failure with reduced ejection fraction relevant for the present benefit assessment, which, according to the National Care Guideline, requires an LVEF < 40% [5]. There is no information about how many of the included patients in the EMPA-TROPISM study had an LVEF < 40%. Furthermore, there is no detailed information about the extent to which the treatment for heart failure 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 aspects mentioned above, the patient populations of the studies SUGAR-DM-HF (N = 105) and EMPA-TROPISM (N = 84) are overall only a small proportion (about 5%) of the number of patients in all 3 studies, including the EMPEROR-Reduced study (N = 3730), which is included in the benefit assessment. Therefore, it is not assumed that results from these studies would have a relevant influence on the result of the benefit assessment. The

exclusion of the studies SUGAR-DM-HF and EMPA-TROPISM is therefore without consequence for the conclusion of the present benefit assessment.

2.3.1 Studies included

The study presented in the following table was 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[c] (yes/no [citation])
1245.121 (EMPEROR-Reduced)[d]	Yes	Yes	No	Yes [6]	Yes [7-9]	Yes [10,11]

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. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to with this abbreviated form.

CSR: clinical study report; G-BA: Federal Joint Committee; 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-Reduced	RCT, double-blind, parallel	Adult patients[b] with chronic heart failure NYHA classes II–IV and reduced ejection fraction with LVEF ≤ 40%[d]	Empagliflozin (N = 1863) Placebo (N = 1867)	Screening: up to 4 weeks Treatment: event-driven study: end of study after 841 adjudicated events of the primary outcome Follow-up observation[e]: 30-day follow-up visit	520 centres in Argentina, Australia, Belgium, Brazil, Canada, China, Czech Republic, France, Germany, Hungary, India, Italy, Japan, Korea, Mexico, Netherlands, Poland, Spain, United Kingdom, USA 4/2017–5/2020	Primary: composite outcome of cardiovascular death or hospitalization for heart failure. Secondary: overall survival, 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 only include information on relevant available outcomes for this benefit assessment.
b. For Japan: age ≥ 20 years at screening.
c. The heart failure had to be present for ≥ 3 months prior to visit 1. Ongoing drug therapy for heart failure (such as ACE inhibitors, ARBs, beta blockers, oral diuretics, MRA, ARNI, ivabradine) had to be consistent with prevailing local and international guidelines for cardiovascular disease and stable for at least 1 week prior to visit 1 and during the screening phase until randomization (second visit) (except diuretics for symptom control, only 1 week before randomization).
d. In addition to LVEF ≤ 40%, patients had to have at least one of the following evidence of heart failure:
a) 36% ≤ LVEF ≤ 40%: elevated NT-proBNP at visit 1 ≥ 2500 pg/mL (≥ 5000 pg/mL for patients with atrial fibrillation or atrial flutter)
b) 31% ≤ LVEF ≤ 35%: elevated NT-proBNP at visit 1 ≥ 1000 pg/mL (≥ 2000 pg/mL for patients with atrial fibrillation or atrial flutter)
c) If LVEF ≤ 30%: elevated NT-proBNP at visit 1 ≥ 600 pg/mL (≥ 1200 pg/mL for patients with atrial fibrillation or atrial flutter)
d) For LVEF ≤ 40% and documented hospitalization for heart failure within 12 months prior to visit 1: elevated NT-proBNP at visit 1 ≥ 600 pg/mL (≥ 1200 pg/mL for patients with atrial fibrillation or atrial flutter)
e. Outcome-specific information is described in Table 10.

ACE: angiotensin converting enzyme; AE: adverse event; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; LVEF: left ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; 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-Reduced	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 and in accordance with prevailing local and international guidelines[b]: ▫ ACE inhibitors or ARBs ▫ beta-blockers ▫ oral diuretics ▫ MRAs ▫ ARNIs ▫ ivabradine ▪ Concomitant antidiabetic medications had to be adjusted individually as clinically indicated by the patient's usual diabetes care provider. ▪ Treatment of symptomatic and severe hypoglycaemic episodes ▪ If ketoacidosis was suspected, the study medication had to be discontinued. In patients requiring insulin, caution had to be taken when the dose of insulin was reduced. ▪ 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 visit and follow-up visit at the end of study) ▪ ICD or CRT implantation ≤ 3 months prior to visit 1 ▪ Heart transplantation or implanted left ventricular assist device (LVAD)	

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.
b. Therapy had to be stable for at least 1 week prior to visit 1 and during screening period until randomization (visit 2) (with the exception of diuretics which had to be stable for only 1 week before randomization to control symptoms).

ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; CRF: case report form; CRT: cardiac resynchronization therapy; ICD: implantable cardioverter defibrillator; LVAD: implanted left ventricular assist device; MRA: mineralocorticoid receptor antagonist; RCT: randomized controlled trial; SGLT: sodium-glucose cotransporter

The EMPEROR-Reduced study is a placebo-controlled, double-blind RCT. It included patients with chronic heart failure of NYHA classes II through IV with reduced ejection fraction, defined as LVEF ≤ 40%. There were additional further restrictions depending on the LVEF (see below for a detailed description of these inclusion criteria and the resulting consequences).

The patients had to be on adequate medical therapy for heart failure, which was stable for at least 1 week prior to visit 1 and during screening period until randomization (visit 2) – except diuretics, which had to be stable only 1 week before randomization (visit 2). The therapy for heart failure before study inclusion was to be individualized, consisting of combinations of the drug classes of ACE inhibitors, ARBs, beta-blockers, oral diuretics, MRAs, ARNIs and ivabradine, and had to be consistent with national and international recommendations. If there

was a therapeutic indication, the patients had to be provided with ICDs or a CRT. A detailed discussion of the implementation of the ACT in the course of the study can be found below.

A total of 3730 patients were included in the study and randomly allocated in a 1:1 ratio either to treatment with empagliflozin (N = 1863) or to placebo (N = 1867). 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) and estimated glomerular filtration rate (eGFR) at screening (< 60 mL/min/1.73 m^2 versus ≥ 60 mL/min/1.73 m^2).

Treatment with empagliflozin was in compliance with the recommendations of the Summary of Product Characteristics (SPC) [12]. In addition, patients in both study arms continued to receive individualized therapy for heart failure and any existing comorbidities such as type 2 diabetes mellitus after randomization.

The EMPEROR-Reduced study was event-driven and was planned to end after 841 events of the primary outcome. After reaching the required events, 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 at the end of treatment, 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 a reduced LVEF ≤ 40%, patients in the EMPEROR-Reduced study had to meet the following inclusion criteria:

a) 36% ≤ LVEF ≤ 40%: elevated NT-proBNP at visit 1 ≥ 2500 pg/mL (≥ 5000 pg/mL for patients with atrial fibrillation or atrial flutter)
b) 31% ≤ LVEF ≤ 35%: elevated NT-proBNP at visit 1 ≥ 1000 pg/mL (≥ 2000 pg/mL for patients with atrial fibrillation or atrial flutter)
c) If LVEF ≤ 30%: elevated NT-proBNP at visit 1 ≥ 600 pg/mL (≥ 1200 pg/mL for patients with atrial fibrillation or atrial flutter)
d) For LVEF ≤ 40% and documented hospitalization for heart failure within 12 months prior to visit 1: elevated NT-proBNP at visit 1 ≥ 600 pg/mL (≥ 1200 pg/mL for patients with atrial fibrillation or atrial flutter)

As a result, for patients who had not previously been hospitalized for heart failure, the less pronounced the reduction in LVEF below the 40% threshold, the more elevated NT-proBNP

values had to be to qualify for inclusion in the EMPEROR-Reduced study. For patients who had already been hospitalized for heart failure within the last 12 months, no further gradations below the 40% threshold were specified. These patients had to have NT-proBNP of 600 pg/mL at visit 1. The inclusion criteria mentioned lead to a restricted study population both in relation to the approved therapeutic indication and to the German health care context. A markedly reduced LVEF, increased NT-proBNP and previous hospitalizations for heart failure are listed in the National Care Guideline [5] as prognostically relevant factors for an unfavourable course of chronic heart failure. Thus, based the inclusion criteria chosen in the study, only patients with at least one prognostic factor for an unfavourable course were included. The required NT-proBNP values in particular led to a selection of the study population: About 36% of all patients who participated in the screening were not included in the EMPEROR-Reduced study solely because the NT-proBNP values were too low [10]. It is therefore unclear whether the observed effects in the EMPEROR-Reduced study can also be transferred to patients with an LVEF ≤ 40% who do not fulfil the above-mentioned additional inclusion criteria, which are strict compared with other studies in the therapeutic indication [13], or whether the study population is a complete representation of the total population in the German health care context. This is also addressed in the European Public Assessment Report of the European Medicines Agency [10], which points out that the NT-proBNP values required in the EMPEROR-Reduced study are often not achieved in clinical practice and the transferability of the study results to the total population remains unclear.

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

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

Study Characteristic Category	**Empagliflozin + optimized standard therapy N[a] = 1863**	**Placebo + optimized standard therapy N[a] = 1867**
EMPEROR-Reduced		
Age [years], mean (SD)	67 (11)	67 (11)
Sex [F/M], %	23/77	24/76
Family origin, n (%)		
White	1325 (71)	1304 (70)
Black/African American	123 (7)	134 (7)
Asian	337 (18)	335 (18)
Other (including mixed)	51 (3)	63 (3)
Geographical region, n (%)		
North America	212 (11)	213 (11)
Latin America	641 (34)	645 (35)
Europe	676 (36)	677 (36)
Asia	248 (13)	245 (13)
Other[b]	86 (5)	87 (5)
LVEF [%], mean (SD)	27.7 (6.0)	27.2 (6.1)
NT-proBNP level [pg/mL], median [Q1; Q3]	1887 [1077; 3429]	1926 [1153; 3525]
Systolic blood pressure (mmHg), mean (SD)	122.6 (15.9)	121.4 (15.4)
BMI [kg/m^2]		
Mean (SD)	28.0 (5.5)	27.8 (5.3)
< 30, n (%)	1263 (68)	1300 (70)
≥ 30, (%)	600 (32)	567 (30)
eGFR (CKD-EPI) [mL/min/1.73 m^3]		
Median [Q1; Q3]	61.0 [45.0; 77.5]	60.5 [45.5; 77.5]
Mean (SD)	61.8 (21.7)	62.2 (21.5)
< 60, n (%)	893 (48)	906 (49)
60-90, n (%)	740 (40)	740 (40)
≥ 90, n (%)	229 (12)	220 (12)
History of atrial fibrillation or atrial flutter[c], n (%)	703 (38)	738 (40)
Hospitalization for heart failure ≤ 12 months prior to visit 1	577 (31)	574 (31)
Type 2 diabetes mellitus at study inclusion, n (%)[d]	927 (50)	929 (50)
HbA1c [%], mean (SD)	7.4 (1.6)	7.4 (1.6)
NYHA class, n (%)		
II	1399 (75)	1401 (75)
III	455 (24)	455 (24)
IV	9 (< 1)	11 (< 1)

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

Study Characteristic Category	Empagliflozin + optimized standard therapy N[a] = 1863	Placebo + optimized standard therapy N[a] = 1867
Time since diagnosis of heart failure [years], median [Q1; Q3]	3.8 [1.4; 8.8]	4.1 [1.5; 9.0]
Aetiology of heart failure, n (%)		
Ischaemic	983 (53)	946 (51)
Hypertensive	233 (13)	220 (12)
Idiopathic	306 (16)	331 (18)
Other	341 (18)[e]	370 (20)[e]
Treatment discontinuation, n (%)	482 (26[e, f])	511 (27[e, f])
Study discontinuation, n (%)	22 (1[e])	20 (1[e])

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Includes patients from Australia and India.
c. According to the investor-reported medical history or ECG at baseline.
d. Patients without type 1 diabetes mellitus and with diabetes mellitus according to the investor-reported medical history or patients with previously undiagnosed diabetes mellitus (HbA1c ≥ 6.5% before the start of study treatment), or (if the aforementioned information is not available) patients in the "diabetes" stratum according to IRT.
e. Institute's calculation.
f. The most common reason for treatment discontinuation in both treatment arms was occurrence of AEs (70% vs. 67%; deterioration of the underlying disease or another pre-existing medical condition was also recorded as AE; the reasons were balanced between the treatment arms).

AE: adverse event; BMI: body mass index; CKD-EPI: chronic kidney disease epidemiology collaboration equation; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; F: female; HbA1c: glycosylated haemoglobin; IRT: interactive response technology; 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 67 years; most of them were male (76%) and most were from the regions of Europe and Latin America. Half of the patients had type 2 diabetes mellitus at study inclusion. 75% of the patients showed slight limitation in activity from their disease (NYHA class II), while about 1 quarter 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 (26% vs. 27%).

Implementation of the appropriate comparator therapy

The comparator therapy of the included EMPEROR-Reduced study is an adequate implementation of the ACT only to a limited extent. A main limitation in the implementation of the ACT was that possibly not all therapeutic options were exhausted for a large proportion of patients.

In the EMPEROR-Reduced study, all patients were to receive individual therapy consistent with national and international guidelines. This applied both to the treatment of heart failure and to the treatment of other cardiovascular risk factors and comorbidities (especially type 2 diabetes mellitus). Therapy adjustments were possible in the course of the study, but therapy had to be stable for 1 week prior to visit 1 and during the screening period until randomization (visit 2) – except diuretics, which had to be stable only 1 week before randomization (visit 2).

The extent to which an optimization of the standard therapy was ensured in the study cannot be fully assessed. In Module 4 A, the company presented which concomitant treatments the patients were receiving at the start of the study and which concomitant treatments were started or changed during the course of the study (see Table 9).

Table 9: Information on heart failure therapies, other antihypertensives, lipid-lowering drugs, antithrombotics, invasive therapies and antidiabetics – RCT, direct comparison: empagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study Characteristic / Category	At baseline		Started or changed therapies after study start	
	Empagliflozin + optimized standard therapy N = 1863	Placebo + optimized standard therapy N = 1867	Empagliflozin + optimized standard therapy N = 1863	Placebo + optimized standard therapy N = 1867
EMPEROR-Reduced				
Heart failure therapies, n (%)	1862 (100)	1866 (100)	603 (32)	723 (39)
ACE inhibitors/ARBs/ ARNIs	1641 (88)	1652 (88)	232 (12)	289 (15)
ACE inhibitors/ARBs	1314 (71)	1286 (69)	123 (7)	174 (9)
ARNIs	340 (18)	387 (21)	125 (7)	138 (7)
Beta-blockers	1765 (95)	1768 (95)	153 (8)	169 (9)
Diuretics	1755 (94)	1790 (96)	339 (18)	451 (24)
MRAs	1306 (70)	1355 (73)	122 (7)	167 (9)
Loop or high ceiling diuretics	1562 (84)	1588 (85)	191 (10)	248 (13)
Ivabradine	135 (7)	125 (7)	23 (1)	29 (2)
Cardiac glycosides	283 (15)	311 (17)	69 (4)	85 (5)
Nitrates	240 (13)	256 (14)	112 (6)	122 (7)
Hydralazine	61 (3)	65 (3)	36 (2)	37 (2)
Other anti-hypertensives, n (%)	151 (8)	131 (7)	58 (3)	69 (4)
Lipid-lowering drugs, n (%)	1311 (70)	1302 (70)	173 (9)	164 (9)
Antithrombotic drugs, n (%)	1538 (83)	1528 (82)	358 (19)	374 (20)
Invasive therapies, n (%)				
Defibrillator (ICD or CRT-D)	578 (31)	593 (32)	52 (3)	58 (3)
CRT (CRT-D or CRT-P)	220 (12)	222 (12)	39 (2)	30 (2)
Non-CRT pacemaker	52 (3)	62 (3)	9 (< 1)	5 (< 1)
Antidiabetics, n (%)	691 (37)	691 (37)	169 (9)	209 (11)
Blood-glucose lowering drugs, without insulins	590 (32)	564 (30)	106 (6)	135 (7)
Insulins and insulin analogues	225 (12)	248 (13)	80 (4)	107 (6)

ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; CRT-D: cardiac resynchronization therapy defibrillator; CRT-P: CRT pacemaker; ICD: implantable cardioverter defibrillator; MRA: mineralocorticoid receptor antagonist; n: number of patients with event; N: number of analysed patients; RCT: randomized controlled trial

The data show that 32% of the patients in the intervention arm and 39% of the patients in the comparator arm started or changed their heart failure medication, with the most frequent

adjustment concerning treatment with diuretics. However, regarding heart failure therapy, 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. In addition, regarding the treatment of comorbidities, detailed information is missing on the drug classes administered and the adjustments made in the categories of lipid-lowering drugs, antithrombotics and antidiabetics.

It should also be pointed out that there was a relatively high percentage of patients (about 65%) who did not receive any treatment modifications over the course of the study. Taking into account the unfavourable prognostic constellation of the patients due to the inclusion criteria (see above) and a similar study on dapagliflozin in the same therapeutic, in which about 50% of the patients received a therapy adjustment in the course of the study [13,14], it is at least questionable whether the optimization options were exhausted for all patients.

Implementation of the recommendations for a treatment switch to sacubitril/valsartan

The recommendations of the National Care Guideline on the intensification of therapy in case of persisting symptoms under basic therapy for symptomatic heart failure with reduced ejection fraction were updated on 23 September 2021 with the amendment on SGLT-2 inhibitors [15]. This amendment also concerns the recommendation for a treatment switch from ACE inhibitors/ARBs to sacubitril/valsartan. The implementation of the ACT with regard to sacubitril/valsartan therapy in the EMPEROR-Reduced study is therefore assessed in light of this short-term change, taking into account the recommendations of the previous version 2 [5] and the new version 3 [15] of the National Care Guideline.

According to the National Care Guideline [5,15] as well as the recently updated ESC guideline [16], patients with symptomatic heart failure and reduced ejection fraction should be treated with a combination of an ACE inhibitor or ARB, a beta-blocker, and an MRA. According to the National Care Guideline version 2, patients who continue to be symptomatic despite guideline-compliant therapy should be recommended a switch from ACE inhibitors/ARBs to the ARNI sacubitril/valsartan [5,16]. However, due to the current uncertainties regarding the long-term tolerability and side effect profile of sacubitril/valsartan, attention should be paid to contraindications and intolerances [5]. The G-BA also refers to this treatment switch in its notes on the ACT. Although, according to the inclusion criteria, patients in the EMPEROR-Reduced study had NYHA class II through IV heart failure with concomitant stable and individually optimized therapy, only a small proportion received sacubitril/valsartan. In the EMPEROR-Reduced study, a total of 73% of patients received treatment with ACE inhibitors/ARBs, 96% received beta-blockers and 77% additionally received MRAs. The treatment switch from ACE inhibitors/ARBs to sacubitril/valsartan recommended in the National Care Guideline version 2 was only carried out in few patients: At baseline, 19% of the patients had been pretreated with the ARNI sacubitril/valsartan. In the course of the study, sacubitril/valsartan treatment was adjusted or initiated in 7% of the patients. In Module 4 A, the company did not provide any information on the reasons why the other patients did not receive sacubitril/valsartan, but only argued that, in another study with dapagliflozin in the same therapeutic indication, fewer

patients were treated with sacubitril/valsartan [13]. The National Care Guideline version 2 comments with regard to the study cited by the company that, from today's perspective, not all therapeutic options (referring to the use of sacubitril/valsartan) were exhausted in a large proportion of this study population [5]. Accordingly, this also applies to the EMPEROR-Reduced study presented here. However, it cannot be inferred from the available data for how many patients in the EMPEROR-Reduced study a switch to sacubitril/valsartan would actually have been indicated.

According to the National Care Guideline version 3 [15], patients who continue to be symptomatic despite guideline-compliant therapy with ACE inhibitors/ARBs, beta-receptor blockers and MRAs should either be recommended therapy with an SGLT-2 inhibitor or a switch from ACE inhibitors/ARBs to the ARNI sacubitril/valsartan. If patients remain symptomatic despite intensification of therapy with sacubitril/valsartan or SGLT-2 inhibitors, the other drug/drug combination can also be offered as an additive. This updated recommendation was implemented accordingly for the patients in the intervention arm of the EMPEROR-Reduced study, as all patients received therapy with an SGLT-2 inhibitor (empagliflozin) or in some cases even a combination of empagliflozin and sacubitril/valsartan. For patients in the comparator arm, however, not all therapeutic options were exhausted, even taking into account these new recommendations, as only few patients received sacubitril/valsartan, and therapy with SGLT-2 inhibitors was not permitted in the comparator arm of the EMPEROR-Reduced study. The criticism of the low use of sacubitril/valsartan therefore remains valid for the comparator arm of the EMPEROR-Reduced study, even taking version 3 of the National Care Guideline into account.

In summary, the ACT was only implemented to a limited extent. Despite these limitations, the EMPEROR-Reduced study was used for the benefit assessment. Consequences for the certainty of conclusions of the study are described in Section 2.4.2.

Observation period and treatment duration

Table 10 shows the mean and median treatment duration of the patients.

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 = 1867**	**Placebo + optimized standard therapy** **N = 1863**
EMPEROR-Reduced		
Treatment duration [years]		
Median [min; max]	1.2 [ND]	1.2 [ND]
Mean (SD)	1.2 (0.6)	1.2 (0.6)
Observation period [years][a]		
Mortality, morbidity, health-related quality of life, side effects	Outcome-specific data are not available in Module 4 A[a]	
a. In Module 4 A of the dossier, the company only provided data for the period between randomization and the planned end of treatment after the occurrence of 841 events of the primary outcome: mean = 1.3 (SD = 0.6) years in both treatment arms. Thereafter, however, 2 visits (at the end of treatment and follow-up 30 days later) were still scheduled, which are to be taken into account when determining the observation period.		
max: maximum; min: minimum; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation		

The treatment duration was comparable between the two study arms. The median treatment duration in both study arms was 1.2 years. The company did not provide any outcome-specific data on the observation period in Module 4 A.

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-Reduced	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the EMPEROR-Reduced study was rated as low. This concurs with the company's assessment.

Transferability to the German health care context

To show the transferability of the study results of the EMPEROR-Reduced study to the German health care context, the company compared parameters from the EMPEROR-Reduced study with the respective available parameters from identified publications on various heart failure registries [17-19]. According to the company's assessment, taking into account the different study periods, there were essentially comparable patient characteristics between the EMPEROR-Reduced study and the publications on heart failure registries. Based on this, there were no indications that the results of the EMPEROR-Reduced study could not be transferred to the German health care context, according to the company. The company emphasized that, compared with other studies in the same therapeutic indication [13,20], a relatively high proportion of patients in the EMPEROR-Reduced study was receiving ARNI therapy already at the start of the study, which was further increased during the course of the study. It concluded that, for a relevant proportion of patients, the therapeutic options recommended in the National Care Guideline [5] regarding ARNIs were applied or exhausted. The company did not provide any further information on the transferability 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 with 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 A).

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

Table 12: Matrix of the 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-Reduced	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%, 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 (MedDRA coding) are considered: renal and urinary disorders (SOC, SAEs), hepatobiliary disorders (SOC, SAEs), and atrial fibrillation (PT, SAE).
e. No usable data available; for reasons, see following text.

AE: adverse event; eGFR: estimated glomerular filtration rate; EQ-5D: European Quality of Life-5 Dimensions; 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 was 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 was excluded from the benefit assessment.
- Hospitalization for heart failure: The operationalization using the time to first event was 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 [21]. 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 was not used for the benefit assessment. The composite outcome comprises the 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-Reduced 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. The analyses presented show that ≥ 85% of the events of the composite outcome are from

the component of sustained eGFR reduction by ≥ 40%. It is therefore not ensured that all events of the composite outcome represent a noticeable deterioration of the disease for the patients.

- Health status (EQ-5D VAS) and health-related quality of life (KCCQ OSS):

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

  - EQ-5D VAS: improvement and deterioration by ≥ 7 or ≥ 10 points as well as stability (deterioration by < 7 or < 10 points or improvement) at week 52 (scale range of EQ-5D VAS: 0 to 100 points)
  - KCCQ OSS: improvement and deterioration by ≥ 5 points as well as stability (deterioration by < 5 points or improvement) at week 52 (scale range of KCCQ OSS: 0 to 100 points)
  - as sensitivity analysis (EQ-5D VAS) or supplementary analysis (KCCQ OSS): improvement and deterioration by ≥ 15 points of the scale range as well as stability (deterioration by < 15 points of the scale range or improvement) at week 52

  As explained in the *General Methods* of the Institute [1,22], 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). To derive the added benefit, therefore, the sensitivity analysis (EQ-5D VAS) or the supplementary analysis (KCCQ OSS) performed by the company on improvement by ≥ 15 points each (exactly 15% of the scale range) at week 52 were used. The analyses of improvement of EQ-5D VAS by ≥ 7 or ≥ 10 points and KCCQ OSS by ≥ 5 points are presented as supplementary information in Appendix D of the full dossier assessment.

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-Reduced	L	L	L	L	L	–[e]	H[f]	H[f]	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%, 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 (MedDRA coding) are considered: renal and urinary disorders (SOC, SAEs), hepatobiliary disorders (SOC, SAEs), and atrial fibrillation (PT, SAE).
e. No usable data available; see Section 2.4.1 for reasons.
f. Large proportion of LOCF-imputed values (27% vs. 28%); in addition, patients without a value at baseline or without at least one further value in the subsequent course of the study were not included in the analysis (7% vs. 8%).

AE: adverse event; eGFR: estimated glomerular filtration rate; EQ-5D: European Quality of Life-5 Dimensions; H: high; KCCQ: Kansas City Cardiomyopathy Questionnaire; L: low; LOCF: last observation carried forward; 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 company rated the risk of bias of the results as low for each of the outcomes included in the present benefit assessment. With the exception of the outcomes of health status (recorded using EQ-5D VAS) and health-related quality of life (recorded using KCCQ OSS), this assessment is accepted. The risk of bias of the results for these 2 outcomes is rated as high due to the high proportion of last observation carried forward (LOCF)-imputed values (27% versus 26%) and due to the additional patients not included in the analysis (7% versus 8% without a value at baseline or without at least one further value in the subsequent course of the study). With such a high proportion of imputed values – and in addition using a non-prespecified imputation strategy – sensitivity analyses, i.e. the use of other imputation strategies, are useful to check the robustness of the results. Besides, it is a general problem of the imputation method that the increase in sample size tends to increase the precision of the resulting effect estimation, although uncertainty tends to be increased by the imputation of missing values. This increased uncertainty can be taken into account by the estimation of the missing values using Higgins' modified estimation of variance [23]. It was not possible for the Institute to conduct its own sensitivity analyses, as the company provided no data on the responders actually observed at week 52 (observed cases) in Module 4 A.

Summary assessment of the certainty of conclusions

In the present benefit assessment, only indications, e.g. of an added benefit, can be derived on the basis of the individual EMPEROR-Reduced study. However, various aspects further limit the certainty of conclusions of the present EMPEROR-Reduced study for the benefit assessment.

For the present benefit assessment, it remains unclear whether the concomitant treatment for heart failure used in the EMPEROR-Reduced study represents an adequate or full implementation of the ACT in the sense of an optimized standard therapy. On the one hand, this assessment is based on the lack of relevant data on therapy adjustments and on the fact that relatively few patients had their medical heart failure therapy adjusted during the course of the study. On the other hand, it is unclear how large the influence on the effect of empagliflozin would be if, as noted in the National Care Guideline [5] for another study in the same therapeutic indication, a larger proportion of patients had been treated with sacubitril/valsartan.

Overall, at most hints, e.g. of an added benefit, can be determined for all outcomes due to these limitations. Further, it is unclear to what extent the potentially insufficient proportion of patients (according to the new recommendations of the National Care Guideline version 3 [15] only referring to the comparator arm) who switched to sacubitril/valsartan therapy impacted the effects on patient-relevant outcomes in the EMPEROR-Reduced study. Therefore, the effects on the individual outcomes cannot be quantified.

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 reduced 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 on the included outcomes are presented in Appendix B of the full dossier assessment, and the results on common AEs, SAEs, and discontinuation due to AEs are presented in Appendix C of the full dossier assessment. Supplementary analyses on the outcome of total hospitalization and responder analyses on the outcomes of EQ-5D VAS (improvement by ≥ 7 or ≥ 10 points) and KCCQ OSS (improvement by ≥ 5 points) are presented 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-Reduced					
Mortality					
All-cause mortality	1863	ND 249 (13.4)	1867	ND 266 (14.2)	0.92 [0.77; 1.10]; 0.354
Cardiovascular death	1863	ND 187 (10.0)	1867	ND 202 (10.8)	0.92 [0.75; 1.12]; 0.413
Morbidity					
Hospitalization for heart failure					
First event	1863	ND 246 (13.2)	1867	ND 342 (18.3)	0.69 [0.59; 0.81]; < 0.001
Including repeat events (presented as supplementary information)	*1863*	*Number of events* *388*	*1867*	*Number of events* *553*	*HR_{JFM}[b]: 0.70 [0.58; 0.85]; < 0.001*
Myocardial infarction (composite outcome)	1863	ND 19 (1.0)	1867	ND 18 (1.0)	1.04 [0.54; 1.98]; 0.917
Nonfatal	1863	ND 16 (0.9)	1867	ND 16 (0.9)	0.98 [0.49; 1.96]; 0.945
Fatal	1863	ND 3 (0.2)	1867	ND 2 (0.1)	1.51 [0.25; 9.10]; 0.650
Stroke (composite outcome)	1863	ND 40 (2.1)	1867	ND 35 (1.9)	1.13 [0.72; 1.78]; 0.591
Nonfatal	1863	ND 34 (1.8)	1867	ND 24 (1.3)	1.40 [0.83; 2.37]; 0.206
Fatal	1863	ND 6 (0.3)	1867	ND 12 (0.6)	0.50 [0.19; 1.35]; 0.172
Renal morbidity (composite outcome)	No usable data[c]				

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. See Section 2.4.1 for reasons.

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]**
CI: confidence interval; 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-Reduced					
Morbidity					
Improvement ≥ 15 points[c]					
Health status (EQ-5D VAS)	1733	495 (28.6)	1710	420 (24.6)	1.13 [1.02; 1.25]; 0.021
Health-related quality of life					
Improvement ≥ 15 points[c]					
KCCQ OSS	1740	445 (25.6)	1709	402 (23.5)	1.06 [0.95; 1.19]; 0.264
Domains (supplementary information)					
Physical limitation	*ND*	*ND*	*ND*	*ND*	*ND*
Symptoms (KCCQ TSS)	*1740*	*466 (26.8)*	*1709*	*396 (23.2)*	*1.11 [0.99; 1.23]*
Social limitation	*ND*	*ND*	*ND*	*ND*	*ND*
Psychological limitation	*ND*	*ND*	*ND*	*ND*	*ND*
Side effects					
AEs (supplementary information)[d]	1863	1325 (71.1)	1863	1362 (73.1)	–
SAEs[d]	1863	540 (29.0)	1863	605 (32.5)	0.89 [0.81; 0.98]; 0.023
Discontinuation due to AEs	1863	322 (17.3)	1863	328 (17.6)	0.98 [0.85; 1.13]; 0.855
Urinary tract infection (PT, AEs)	1863	69 (3.7)	1863	72 (3.9)	0.96 [0.69; 1.32]; 0.866
Reproductive system and breast disorders (SOC, AEs)	1863	57 (3.1)	1863	49 (2.6)	1.16 [0.80; 1.69]; 0.533
Diabetic ketoacidosis (PT, AEs)[e]	ND	ND	ND	ND	ND
Renal and urinary disorders (SOC, SAEs)	1863	71 (3.8)	1863	107 (5.7)	0.66 [0.49; 0.89]; 0.006
Hepatobiliary disorders (SOC, SAEs)	1863	16 (0.9)	1863	30 (1.6)	0.53 [0.29; 0.98]; 0.040
Atrial fibrillation (PT, SAEs)	1863	24 (1.3)	1863	44 (2.4)	0.55 [0.33; 0.89]; 0.015

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]
a. Outcomes of the categories of morbidity and health-related quality of life: missing values were imputed using LOCF (27% vs- 26%). 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 baseline value; outcomes of the category of side effects: p-value: Institute's calculation (unconditional exact test [CSZ method according to [24]]). c. Defined as increase of the score by ≥ 15 points compared with baseline at week 52 (scale range: 0-100 points). d. Without consideration of the following (disease-related) events: death from any cause, hospitalization for heart failure, myocardial infarction, stroke, nonfatal transient ischaemic attack, atrial fibrillation (serious), acute renal failure (serious), unstable angina pectoris. e. Module 4 A contains no data for this outcome, as the event occurred in fewer than 1% of the patients per treatment arm. AE: adverse event; CI: confidence interval; eGFR: estimated glomerular filtration rate; KCCQ: Kansas City Cardiomyopathy Questionnaire; LOCF: last observation carried forward; LVEF: left ventricular ejection fraction; n: number of patients with (at least one) event; N: number of analysed patients; OSS: overall summary score; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TSS: total symptom score					

Based on the available data, at most hints, e.g. of an added benefit, can be derived for all outcomes due to the above limitations in the implementation of the ACT (see Sections 2.3.2 and 2.4.2).

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 was 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 added benefit of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy. An added benefit is therefore not proven for this outcome.

This deviates from the assessment of the company, which, on the basis of numerical differences between the treatment groups and also including further operationalizations of this outcome, derived a hint of a non-quantifiable added benefit of empagliflozin + optimized standard

therapy in comparison with placebo + optimized standard therapy for the outcome category of mortality.

Morbidity

Hospitalization for heart failure

A statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy was shown for the outcome of hospitalization for heart failure. However, there is an effect modification for heart failure severity according to NYHA class. This results in a hint of an added benefit of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy for patients with NYHA class II. For patients with NYHA classes III/IV, there is 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 patient group (see Section 2.4.4).

This deviates from the assessment of the company, which summarized all presented operationalizations for this outcome or for composite outcomes with the component of hospitalizations on the basis of the total population and derived an indication of considerable added benefit of empagliflozin + optimized standard therapy in comparison with placebo + 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 the 2 individual components, there is no statistically significant difference between the treatment groups. This results in no hint of added benefit of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy. An added benefit is therefore not proven for this outcome.

This concurs with the company’s assessment.

Stroke

For the composite outcome of stroke, consisting of nonfatal stroke and fatal stroke, as well as for the 2 individual components, there is no statistically significant difference between the treatment groups. This results in no hint of added benefit of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy. An added benefit is therefore not proven for this outcome.

This concurs with the company’s assessment.

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 added benefit of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy; an added benefit is therefore not proven for this outcome.

This deviates from the assessment of the company, which derived considerable added benefit of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy for renal morbidity.

Health status

EQ-5D VAS

For the outcome of health status, operationalized as an improvement in EQ-5D VAS by ≥ 15 points at week 52, there was a statistically significant difference between the treatment groups in favour of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy. This difference was no more than marginal, however (see Section 2.5.1). This results in no hint of added benefit of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy. An added benefit is therefore not proven for this outcome.

This deviates from the assessment of the company, which, in summary, derived an indication of considerable added benefit of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy for the outcomes of health status and health-related quality of life with deviating response criteria.

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 added benefit of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy. An added benefit is therefore not proven for these outcomes.

This deviates from the assessment of the company, which, in summary, derived an indication of considerable added benefit of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy for the outcomes of health status and health-related quality of life with deviating response criteria.

Side effects

SAEs

A statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy was shown for the outcome of SAEs. However, there is an effect modification for heart failure severity according to NYHA class. This results in a hint of lesser harm from empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy for patients with NYHA class II. For patients with NYHA classes III/IV, there is no hint of greater or lesser harm from empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy; greater or lesser harm is therefore not proven for this patient group (see Section 2.4.4).

This deviates from the assessment of the company, which, on the basis of all results on SAEs, in summary for the total outcome category of side effects, derived an indication of considerable added benefit for empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy for the total population.

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 from empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy; greater or lesser harm is therefore not proven for this outcome.

This deviates from the assessment of the company, which, on the basis of all results on SAEs, in summary for the total outcome category of side effects, derived an indication of considerable added benefit for empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy for the total population.

Specific AEs

Urinary tract infection, reproductive system and breast disorders, diabetic ketoacidosis

No statistically significant difference between treatment groups was shown for the outcomes of urinary tract infection (PT, AEs) and reproductive system and breast disorders (SOC, AEs). The company presented no data for the outcome of diabetic ketoacidosis (PT, AEs) in Module 4 A, because this event occurred in fewer than 1% of the patients per treatment arm. In each case, this results in no hint of greater or lesser harm from empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy; greater or lesser harm is therefore not proven.

Renal and urinary disorders (SOC, SAEs), hepatobiliary disorders (SOC, SAEs)

A statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy was shown for the outcomes of renal and urinary disorders (SOC, SAEs) and hepatobiliary disorders (SOC, SAEs). This results in a hint of lesser harm from empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy. Since the study is placebo controlled, it is unclear whether the effects observed in the outcome of renal and urinary disorders (SOC, SAEs) actually represent side effects or rather manifestations of disease-related morbidity.

Atrial fibrillation (PT, SAEs)

A statistically significant difference between treatment groups in favour of empagliflozin + optimized standard therapy was shown for the outcome of atrial fibrillation (PT, SAEs). However, there is an effect modification for heart failure severity according to NYHA class. This results in a hint of lesser harm from empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy for patients with NYHA class II. For patients with NYHA classes III/IV, there is no hint of greater or lesser harm from

empagliflozin + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven for this patient group (see Section 2.4.4). Since the study is placebo controlled, it is unclear whether the effects observed in the outcome of atrial fibrillation (PT, SAEs) actually represent side effects or rather manifestations of disease-related morbidity.

Overall, the assessment of specific AEs deviates from that of the company, which derived an indication of considerable added benefit for empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy for the total population not on the basis of the results of individual specific AEs, but on the basis of all results on SAEs, in summary for the total outcome category of side effects.

2.4.4 Subgroups and other effect modifiers

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

- age (≤ 65 years versus > 65 years)
- sex (male versus female)
- severity of heart failure (NYHA class II versus III/IV)

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least one subgroup.

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only 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 heart failure with reduced ejection fraction.

Table 16: Subgroups (morbidity) – 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][a]	p-value[a]
EMPEROR-Reduced						
Hospitalization for heart failure						
NYHA						
II	1399	ND 142 (10.2)	1401	ND 230 (16.4)	0.59 [0.48; 0.73]	< 0.001
III/IV	464	ND 104 (22.4)	466	ND 112 (24.0)	0.89 [0.68; 1.16]	0.393
Total					Interaction:	0.0190

a. HR, 95% CI and p-value from interaction testing: Cox proportional hazards model; adjusted for region, sex, age, diabetes status, LVEF, and baseline eGFR, as well as the terms NYHA and treatment x NYHA.

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) – 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[a]
EMPEROR-Reduced						
SAEs[b]						
NYHA						
II	1399	359 (25.7)	1399	432 (30.9)	0.83 [0.74; 0.94]	0.002
III/IV	464	181 (39.0)	464	173 (37.3)	1.05 [0.89; 1.23]	0.683
Total					Interaction:	0.038[c]
Atrial fibrillation (PT, SAEs)						
NYHA						
II	1399	16 (1.1)	1399	39 (2.8)	0.41 [0.23; 0.73]	0.002
III/IV	464	8 (1.7)	464	5 (1.1)	1.60 [0.53; 4.85]	0.530
Total					Interaction:	0.026[c]

a. Institute's calculation (unconditional exact test [CSZ method according to [24]]).
b. Without consideration of the following (disease-related) events: death from any cause, hospitalization for heart failure, myocardial infarction, stroke, nonfatal transient ischaemic attack, atrial fibrillation (serious), acute renal failure (serious), unstable angina pectoris.
c. Breslow-Day test for homogeneity of odds ratio; see Section 2.4.4.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; n: number of patients with (at least one) event; N: number of analysed patients; NYHA: New York Heart Association; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Morbidity

Hospitalization for heart failure

For the outcome of hospitalization for heart failure, there was a statistically significant effect modification from the characteristic of heart failure severity according to NYHA class.

A statistically significant difference in favour of empagliflozin + optimized standard therapy was shown for patients with NYHA class II. This results in a hint of an added benefit of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy for patients with NYHA class II. No statistically significant difference between the treatment groups was shown for patients with NYHA classes III/IV. This results in no hint of added benefit of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy. For this outcome, an added benefit is therefore not proven for patients with NYHA classes III/IV.

Side effects

Interaction tests on AEs performed by the company on the basis of the odds ratios

For the outcomes of the category of side effects, the company performed the interaction test using the Breslow-Day test for homogeneity of the odds ratios – and not a test for homogeneity of the relative risks. Especially in the case of higher risks for an event, this can lead to differences in the results. For this reason, an interaction test on the basis of the relative risks using a Q test was subsequently performed for the present assessment, provided that the company's analysis had produced a statistically significant effect modification to the level of 0.2. No qualitative difference between the test results on the basis of the odds ratios and of the relative risks were shown. The test results presented by the company were therefore used.

SAEs

For the outcome of SAEs, there was a statistically significant effect modification from the characteristic of heart failure severity according to NYHA class.

A statistically significant difference in favour of empagliflozin + optimized standard therapy was shown for patients with NYHA class II. This results in a hint of lesser harm from empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy for patients with NYHA class II. No statistically significant difference between the treatment groups was shown for patients with NYHA classes III/IV. This results in no hint of greater or lesser harm of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy. For this outcome, greater or lesser harm is therefore not proven for patients with NYHA classes III/IV.

Atrial fibrillation (PT, SAEs)

For the outcome of atrial fibrillation (PT, SAEs), there was a statistically significant effect modification from the characteristic of heart failure severity according to NYHA class.

A statistically significant difference in favour of empagliflozin + optimized standard therapy was shown for patients with NYHA class II. This results in a hint of lesser harm from empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy for patients with NYHA class II. No statistically significant difference between the treatment groups was shown for patients with NYHA classes III/IV. This results in no hint of greater or lesser harm of empagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy. For this outcome, greater or lesser harm is therefore not proven for patients with NYHA classes III/IV.

2.5 Probability and extent of added benefit

Probability and extent of the added benefit 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 was estimated from the results presented in Section 2.4 (see Table 18).

Determination of the outcome category for the outcomes on morbidity

It cannot be inferred from the dossier whether the following outcomes were serious/severe or non-serious/non-severe. The classification of 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 was assigned to the outcome category of serious/severe symptoms/late complications.

Health status (EQ-5D VAS)

There is no information on the assignment of the severity grade for the outcome of health status recorded using EQ-5D VAS. Therefore, this outcome was assigned to the outcome category of non-serious/non-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: 0.92 [0.77; 1.10] p = 0.354	Lesser benefit/added benefit not proven
Morbidity		
Hospitalization for heart failure Severity of heart failure NYHA II	ND vs. ND HR: 0.59 [0.48; 0.73] p < 0.001 Probability: "hint"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "non-quantifiable"
NYHA III/IV	ND vs. ND HR: 0.89 [0.68; 1.16] p = 0.393	Lesser benefit/added benefit not proven
Myocardial infarction	ND vs. ND HR: 1.04 [0.54; 1.98] p = 0.917	Lesser benefit/added benefit not proven
Stroke	ND vs. ND HR: 1.13 [0.72; 1.78] p = 0.591	Lesser benefit/added benefit not proven
Renal morbidity	No usable data	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS; improvement ≥ 15 points)	28.6% vs. 24.6% RR: 1.13 [1.02; 1.25] RR[c] 0.88 [0.80; 0.98] p = 0.021	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[d]
Health-related quality of life		
KCCQ OSS; improvement ≥ 15 points	25.6% vs. 23.5% RR: 1.06 [0.95; 1.19] p = 0.264	Lesser benefit/added benefit not proven

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]
Side effects		
SAEs Severity of heart failure NYHA II	25.7% vs. 30.9% RR: 0.83 [0.74; 0.94] p < 0.002 probability: "hint"	Outcome category: serious/severe side effects lesser harm; extent: "non-quantifiable"
NYHA III/IV	39.0% vs. 37.3% RR: 1.05 [0.89; 1.23] p = 0.683	Greater/lesser harm not proven
Discontinuation due to AEs	17.3% vs. 17.6% RR: 0.98 [0.85; 1.13] p = 0.855	Greater/lesser harm not proven
Urinary tract infection	3.7% vs. 3.9% RR: 0.96 [0.69; 1.32] p = 0.866	Greater/lesser harm not proven
Reproductive system and breast disorders	3.1% vs. 2.6% RR: 1.16 [0.80; 1.69] p = 0.533	Greater/lesser harm not proven
Diabetic ketoacidosis	ND vs. ND RR: ND p = ND	Greater/lesser harm not proven
Renal and urinary disorders	3.8% vs. 5.7% RR: 0.66 [0.49; 0.89] p = 0.006 probability: "hint"	Outcome category: serious/severe side effects lesser harm; extent: "non-quantifiable"
Hepatobiliary disorders	0.9% vs. 1.6% RR: 0.53 [0.29; 0.98] p = 0.040 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]
Atrial fibrillation Severity of heart failure NYHA II	1.1% vs. 2.8% RR: 0.41 [0.23; 0.73] p < 0.002 probability: "hint"	Outcome category: serious/severe side effects lesser harm; extent: "non-quantifiable"
NYHA III/IV	1.7% vs. 1.1% RR: 1.60 [0.53; 4.85] p = 0.530	Lesser benefit/added benefit not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; reversed 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; EQ-5D: European Quality of Life-5 Dimensions; KCCQ: Kansas City Cardiomyopathy Questionnaire; ND: no data; NYHA: New York Heart Association; 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 considered 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 ▫ NYHA II ▫ hint of added benefit – extent: "non-quantifiable"	–
▪ Serious/severe side effects ▪ SAEs: ▫ NYHA II ▫ hint of lesser harm – extent: "non-quantifiable" ▪ Hepatobiliary disorders (SOC, SAEs): hint of lesser harm – extent: "non-quantifiable" ▪ Renal and urinary disorders (SOC, SAEs): hint of lesser harm – extent: "non-quantifiable" ▪ Atrial fibrillation (PT, SAEs): ▫ NYHA II ▫ hint of lesser harm – extent: "non-quantifiable"	–
NYHA: New York Heart Association; PT: Preferred Term; SAE: serious adverse event; SOC: System Organ Class	

In the overall consideration, there are only positive effects of empagliflozin in comparison with optimized standard therapy for patients with symptomatic chronic heart failure with reduced ejection fraction.

For the total population, there are positive effects for the outcomes of hepatobiliary disorders (SOC, SAEs) and renal and urinary disorders (SOC, SAEs). For both of these outcomes, this results in a hint of non-quantifiable lesser harm from empagliflozin + optimized standard therapy for the total population.

Further positive effects were shown only for patients with NYHA class II severity. Thus, there is a hint of a non-quantifiable added benefit of empagliflozin + optimized standard therapy for this patient population for the outcome of hospitalization for heart failure. In the category of side effects, there is a hint of non-quantifiable lesser harm from empagliflozin + optimized standard therapy for the outcomes of SAEs and atrial fibrillation (PT, SAEs).

As described above, some of the positive effects were shown only for patients with NYHA class II severity. However, since the observed effects in the EMPEROR-Reduced study are overall non-quantifiable and there are only positive effects also for the total population, the added benefit is derived on the basis of the total population regardless of these effect modifications.

In summary, there is therefore a hint of a non-quantifiable added benefit of empagliflozin + optimized standard therapy in comparison with optimized standard therapy for patients with symptomatic chronic heart failure with reduced ejection fraction.

The result of the assessment of the added benefit of dapagliflozin 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 reduced ejection fraction[b]	Optimized standard therapy for the treatment of symptomatic chronic heart failure and underlying medical conditions, e.g. hypertension, cardiac arrhythmia, coronary heart disease, diabetes mellitus, hypercholesterolaemia and the concomitant symptoms	Hint of non-quantifiable added benefit

a. Presented is the ACT specified by the G-BA.
b. The conclusion on added benefit is based on the results of the EMPEROR-Reduced study. To qualify for inclusion in the EMPEROR-Reduced study, patients had to exhibit an LVEF ≤ 40% and meet additional inclusion criteria (including certain NT-proBNP thresholds). It remains unclear whether the observed effects can be transferred to other patients in the target population.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal pro-brain natriuretic peptide

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit.

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.

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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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