IQWiG Reports – Commission No. A20-113

Dapagliflozin (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 *Dapagliflozin (Herzinsuffizienz) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 25 February 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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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
eGFR	estimated glomerular filtration rate
EQ-5D	European Quality of Life-5 Dimensions
ESRD	end-stage renal disease
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KCCQ	Kansas City Cardiomyopathy Questionnaire
LVEF	left-ventricular ejection fraction
MRA	mineralocorticoid receptor antagonist
NYHA	New York Heart Association
OSS	overall summary score
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
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 dapagliflozin. 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 1 December 2020.

Research question

The aim of the present report was to assess the added benefit of dapagliflozin in comparison with optimized standard treatment as appropriate comparator therapy (ACT) in patients with symptomatic chronic heart failure with reduced ejection fraction.

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

Table 2: Research questions of the benefit assessment of dapagliflozin

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 arrhythmia, coronary heart disease, diabetes mellitus, hypercholesterolaemia and the concomitant symptoms[b]
a. Presentation of the respective ACT specified by the G-BA. b. It is assumed that the patients in both study arms received optimal treatment: guideline-compliant individual treatment of heart failure and underlying diseases or risk factors such as hypertension, cardiac arrhythmia or diabetes mellitus as well as the concomitant symptoms, for example oedema, is assumed. It should have been 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 was no further possibility for optimization, it had to be documented and explained that any other existing treatment options were unsuitable or had been exhausted. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

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 the added benefit.

Results

The DAPA-HF study is used to assess the added benefit of dapagliflozin in comparison with optimized standard therapy for the treatment of patients with symptomatic chronic heart failure with reduced ejection fraction.

Study design

The DAPA-HF study is a placebo-controlled, randomized parallel-group study on dapagliflozin. Patients with symptomatic heart failure of New York Heart Association (NYHA) classes II-IV and reduced ejection fraction, defined as left-ventricular ejection fraction (LVEF) ≤ 40%, were included. Patients should have received unchanged optimized standard therapy for the treatment of heart failure for at least 4 weeks prior to study inclusion. Unless contraindicated, this therapy had to include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) or sacubitril/valsartan in combination with a beta blocker and, if appropriate, a mineralocorticoid receptor antagonist (MRA).

A total of 4744 patients were included and assigned to treatment with dapagliflozin (N = 2373) or to the placebo group (N = 2371) in a 1:1 ratio.

Primary outcome of the study was the composite outcome of cardiovascular death, hospitalisation due to heart failure and emergency contact with a physician due to heart failure. Patient-relevant secondary outcomes were “overall survival”, “morbidity”, “health-related quality of life”, and “adverse events (AEs)”.

Implementation of the ACT

Adequate implementation of the comparator therapy of the included DAPA-HF study only took place to a limited extent. Hereby, the main limitation in the implementation of the ACT was that not all therapeutic options were exhausted for every patient.

In the DAPA-HF study, all patients were to receive individual therapy according to relevant guidelines. Treatment adjustments were possible at any time during the study, but therapy should have been optimized ≥ 4 weeks before study inclusion and was to remain as stable as possible. However, the extent to which the company had ensured an optimization of the standard therapy remains largely unclear.

According to the National Health Care Guideline, patients with symptomatic heart failure with reduced ejection fraction should be treated with a combination of an ACE inhibitor or an ARB, a beta blocker and an MRA. Moreover, patients who continue to show symptoms despite guideline-compliant treatment with ACE inhibitors/ARBs, beta-receptor blockers and MRAs should be recommended to switch from ACE inhibitors/ARBs to sacubitril/valsartan.

Although patients in the DAPA-HF study were supposed to have symptomatic heart failure according to the inclusion criteria, with stable and individually optimized therapy at the same time, only a small proportion received sacubitril/valsartan. The recommended treatment switch

from ACE inhibitors/ARBs to sacubitril/valsartan was only carried out in few patients. The National Health Care Guideline comments that, from today's perspective, not all therapeutic options had been exhausted in a large part of the DAPA-HF study population. However, the available data do not indicate for how many patients a switch to sacubitril/valsartan would actually have been indicated.

In summary, the ACT was only implemented to a limited extent. Despite these limitations, the DAPA-HF 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 was rated as low. Likewise, the risk of bias for the results for all outcomes included in the benefit assessment was rated as low.

Assessment of the certainty of conclusions

There are various aspects that limit the certainty of conclusions of the present DAPA-HF study for the benefit assessment.

For the present benefit assessment, it remains unclear whether the concomitant treatment of the heart failure applied in the DAPA-HF study represents a complete implementation of the ACT "optimized standard therapy". This assessment results from the fact that data on therapy adjustments are missing and the influence the small proportion of patients treated with sacubitril/valsartan has on the present effects in unclear. Moreover, the side effects cannot be fully assessed due to a lack of information on non-serious AEs.

Overall, at most hints, e.g. of an added benefit, can be determined for all outcomes due to these limitations. In addition, the extent of the impact the possibly insufficient proportion of patients who were switched to therapy with sacubitril/valsartan has on the effects on the patient-relevant outcomes in the DAPA-HF study is unclear. Therefore, the effects on the individual outcomes cannot be quantified.

Results

Mortality

A statistically significant difference in favour of dapagliflozin + optimized standard therapy was shown between the treatment groups for the outcome "all-cause mortality". However, there is an effect modification for the severity of the heart failure according to NYHA classification. This resulted in a hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy for patients with NYHA class II heart failure. For patients of the NYHA classes III/IV, there is no hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy; an added benefit is therefore not proven for this patient group.

Morbidity

Hospitalization due to cardiac failure

A statistically significant difference in favour of dapagliflozin + optimized standard therapy between the treatment groups was shown for the outcome "hospitalization due to cardiac failure". This resulted in a hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Renal morbidity

For the composite outcome "renal morbidity", consisting of the outcomes "persistent decrease of estimated glomerular filtration rate (eGFR) by 50%", "end-stage renal disease (ESRD)" and "renal death", there was no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for this outcome.

Myocardial infarction

For the composite outcome "myocardial infarction", consisting of "non-fatal myocardial infarction" and "fatal myocardial infarction", as well as for the two individual components, there is no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with the optimized standard therapy. An added benefit is therefore not proven for these outcomes.

Stroke

For the outcome "stroke", consisting of "non-fatal stroke" and "fatal stroke", as well as for the two individual components, there is no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with the optimized standard therapy. An added benefit is therefore not proven for these outcomes.

Health status

No usable data were available for the outcome "health status", recorded with the Patient Global Impression of Change [PGIC], Patient Global Impression of Severity (PGIS) and the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D). It is unclear how many patients were actually under observation at month 24 and included in the analyses at month 24. This resulted in no hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with the optimized standard therapy. An added benefit is therefore not proven for this outcome.

Health-related quality of life

No usable data were available for the outcome category "health-related quality of life", recorded using the overall summary score (OSS) of the Kansas City Cardiomyopathy Questionnaire (KCCQ). It is unclear how many patients were actually under observation at month 24 and

included in the analyses at month 24. This resulted in no hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with the optimized standard therapy. An added benefit is therefore not proven for this outcome.

Side effects

Serious adverse events (SAEs)

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

Discontinuation due to AEs

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from dapagliflozin + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

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

For the outcomes "urinary tract infection (Preferred Term [PT], AEs)", "reproductive system and breast disorders" (System Organ Class [SOC], AEs)", "diabetic ketoacidosis (PT, AEs)", there is no statistically significant difference between the treatment groups. This resulted in no hint of greater or lesser harm from dapagliflozin + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

Respiratory, thoracic and mediastinal disorders

A statistically significant difference in favour of dapagliflozin + optimized standard therapy was shown between the treatment groups for the outcome "respiratory, thoracic and mediastinal disorders (SOC, SAEs)". This resulted in a hint of lesser harm from dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. It cannot be ruled out that the SAE "respiratory, thoracic and mediastinal disorders" also includes events that may be due to the symptoms of the underlying disease, (e.g. dyspnoea).

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

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

[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).

Positive effects in the category “mortality” were only shown in patients with NYHA severity grade II. For the outcome ’”hospitalization due to cardiac failure”, this resulted in a hint of a non-quantifiable added benefit of dapagliflozin + optimized standard therapy for the total population. In addition, positive effects were shown in the outcome category “side effects”, which also concerned the total population. There was a hint of non-quantifiable lesser harm from dapagliflozin + optimized standard therapy both for the overall rate of SAEs and for respiratory, thoracic and mediastinal disorders (SOC, SAEs). It cannot be ruled out that the SAE “respiratory, thoracic and mediastinal disorders” also includes events that may be due to the symptoms of the underlying disease, (e.g. dyspnoea). No usable data were available for the outcomes “health status” and “health-related quality of life”.

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

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

Table 3: Dapagliflozin – 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	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. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

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 was to assess the added benefit of dapagliflozin in comparison with optimized standard treatment as ACT in patients with symptomatic chronic heart failure with reduced ejection fraction.

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

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].

Table 4: Research questions of the benefit assessment of dapagliflozin

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 arrhythmia, coronary heart disease, diabetes mellitus, hypercholesterolaemia and the concomitant symptoms[b]

a. Presentation of the respective ACT specified by the G-BA.
b. It is assumed that the patients in both study arms received optimal treatment: guideline-compliant individual treatment of heart failure and underlying diseases or risk factors such as hypertension, cardiac arrhythmia or diabetes mellitus as well as the concomitant symptoms, for example oedema, is assumed.
It should have been 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 was no further possibility for optimization, it had to be documented and explained that any other existing treatment options were unsuitable or had been exhausted.

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

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 the 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 dapagliflozin (status: 6 October 2020)
- bibliographical literature search on dapagliflozin (last search on 6 October 2020)
- search in trial registries/trial results databases for studies on dapagliflozin (last search on 8 October 2020)
- search on the G-BA website for dapagliflozin (last search on 23 October 2020)

To check the completeness of the study pool:

- search in trial registries for studies on dapagliflozin (last search on 10 December 2020)

The check did not identify any additional relevant studies.

In addition to the indication to be assessed here, dapagliflozin is also approved for the treatment of type 2 diabetes mellitus. For this purpose, the company conducted the cardiovascular outcome study DECLARE-TIMI 58 [3]. This study investigated the effect of dapagliflozin on cardiovascular outcomes in patients with type 2 diabetes mellitus. A proportion of the patient population included had heart failure in addition to type 2 diabetes mellitus. Of 17160 patients

included, 451 had symptomatic heart failure with reduced ejection fraction (NYHA classes II and III) [4]. If required, patients in both study arms were offered cardiovascular background therapy according to local standards in addition to dapagliflozin + metformin in the intervention arm and placebo + metformin in the comparator arm. The extent to which this therapy corresponded to the ACT of the present benefit assessment for patients with heart failure is unclear. The company did not include the study DECLARE-TIMI 58 in its benefit assessment. However, the potentially relevant patient population is only a small proportion (< 10%) compared to DAPA-HF (N = 4744). Therefore, it is not assumed that possible results from this study have a relevant influence on the result of the benefit assessment. The exclusion of the DECLARE-TIMI 58 study from the present benefit assessment is therefore without consequence.

2.3.1 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: dapagliflozin + 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 yes/no [citation])
D1699C00001 (DAPA-HF[c])	Yes	Yes	No	No[d]	Yes [5-8]	Yes [9-20]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.
d. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

CSR: Clinical Study Report; RCT: randomized controlled trial

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: dapagliflozin + 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]
DAPA-HF	RCT, double-blind, parallel	Adult patients with symptomatic heart failure of NYHA classes II-IV[b] and reduced ejection fraction with: ▪ LVEF ≤ 40% and ▪ NT-proBNP ▫ ≥ 600 pg/mL or ▫ ≥ 400 pg/mL in case of hospitalization due to cardiac failure within the last 12 months prior to study inclusion[c]	Dapagliflozin (N = 2373) placebo (N = 2371)	Screening: 14 ± 7 days Treatment: event-driven study: end of study after 844 events in the primary outcome follow-up observation[d]: 6 weeks	Argentina, Brazil, Bulgaria, Canada, China, Czech Republic, Denmark, Germany, Hungary, India, Japan, Netherlands, Poland, Russia, Slovakia, Sweden, Taiwan, United Kingdom, USA, Vietnam 02/2017–07/2019	Primary: composite outcome of cardiovascular death, hospitalization due to heart failure or emergency contact with a physician due to 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. The heart failure had to be present for ≥ 2 months. Treatment should be individually optimized, had to be stable ≥ 4 weeks prior to study inclusion and was to include an ACE inhibitor or ARB or sacubitril/valsartan, a beta-blocker and MRA if appropriate (unless contraindicated or not tolerated) according to locally accepted guidelines.
c. If there is concomitant atrial fibrillation or atrial flutter at visit 1, NT-proBNP must be ≥ 900 pg/mL.
d. Outcome-specific information is provided in Table 10.

ACE: angiotensin converting enzyme; AE: adverse event; ARB: angiotensin receptor blocker; LVEF: left-ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; N: number of randomized (included) 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: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study	Intervention	Comparison
DAPA-HF	Dapagliflozin 10 mg once daily, orally + optimized standard therapy	Placebo once daily, orally + optimized standard therapy
	Dose adjustments due to AEs ▪ in the event of AEs such as volume depletion, hypotension and/or unexpected deterioration of renal function that cannot be remedied by adjustment of the concomitant treatment, the dapagliflozin dose may be reduced to 5 mg. After stabilization of the condition, the dose is to be increased to 10 mg again. **Prior and concomitant treatment** ▪ according to locally accepted guidelines, individually optimized standard therapy of heart failure with[a]: ▫ ACE inhibitors or ARB or sacubitril/valsartan ▫ beta-blockers ▫ if applicable, MRA ▫ if applicable, diuretics ▪ type 2 diabetes mellitus ▫ treatment according to the guidelines of the ADA and the EASD ▫ in case of therapy with insulin and insulin secretagogues, the daily dose should be reduced[b] ▪ additional necessary medications can be administered at the investigator's discretion **Prohibited prior and concomitant treatment** ▪ SGLT2 inhibitors ≤ 8 weeks before study inclusion ▪ coronary revascularization (PCI or CABG) or valve reconstruction/replacement(s) ≤ 12 weeks prior to study inclusion ▪ CRT implantation ≤ 12 weeks before study inclusion ▪ heart transplantation or implantation of a ventricular assist device	

a. Treatment was to be individually optimized and had to be stable ≥ 4 weeks before study inclusion. Dose reductions or discontinuation of effective therapy had to be avoided. Therapy switch and dose adjustments were possible at the investigator's discretion.
b. Reduction in the daily insulin dose by 10%-20% and in the insulin secretagogue dose by 25%-50% as well as more frequent blood glucose monitoring should be considered for patients with HbA1c < 7% at randomisation.

ACE: angiotensin converting enzyme; ADA: American Diabetes Association; AE: adverse event; ARB: angiotensin receptor blocker; CABG: coronary artery bypass grafting; CRT: cardiac resynchronization therapy; EASD: European Association for the Study of Diabetes; HbA1c: haemoglobin A1c; MRA: mineralocorticoid receptor antagonist; PCI: percutaneous coronary intervention; RCT: randomized controlled trial; SGLT-2: sodium glucose cotransporter 2

The DAPA- HF study is a placebo-controlled, double-blind, randomized parallel-group study on dapagliflozin. Patients with symptomatic heart failure of NYHA classes II-IV and reduced ejection fraction, defined as LVEF ≤ 40%, were included. Patients should have received unchanged optimized standard therapy for the treatment of heart failure for at least 4 weeks prior to study inclusion. Unless contraindicated, this therapy had to include ACE inhibitors, ARBs or sacubitril/valsartan in combination with a beta-blocker and, if appropriate, an MRA. A detailed discussion on the implementation of the ACT can be found below.

A total of 4744 patients were included and assigned to treatment with dapagliflozin (N = 2373) or to the placebo group (N = 2371) in a 1:1 ratio. Randomization was stratified according to the simultaneous presence of type 2 diabetes mellitus.

In the DAPA-HF study, dapagliflozin was administered in compliance with the approval [21]. In addition, patients in both study arms received individually adapted therapy for heart failure and other comorbidities such as type 2 diabetes mellitus.

The DAPA-HF study was event-driven and was planned to end after 844 events of the primary outcome. After the end of the study, all outcomes should be followed up for up to 6 weeks. Patients who discontinued the study medication prematurely after randomization were subject to further observation and were also followed up for up to 6 weeks after the end of the study.

Primary outcome of the study was the combined outcome of "cardiovascular death", "hospitalization due to heart failure" and "emergency contact with a physician due to heart failure". Patient-relevant secondary outcomes were "overall survival", "morbidity", "health-related quality of life", and "AEs".

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

Table 8: Characteristics of the study population – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study characteristic category	Dapagliflozin + optimized standard therapy N[a] = 2373	Placebo + optimized standard therapy N[a] = 2371
DAPA-HF		
Age [years], mean (SD)	66 (11)	67 (11)
Sex [F/M], %	24/76	23/77
Geographical region, n (%)		
North America	335 (14)	342 (14)
South America	401 (17)	416 (18)
Asia/Pacific	543 (23)	553 (23)
Europe	1094 (46)	1060 (45)
BMI, n (%)		
< 30 kg/m²	1537 (65)	1533 (65)
≥ 30 kg/m²	834 (35)	838 (35)
Type 2 diabetes mellitus at study inclusion, n (%)	993 (42)	990 (42)
Systolic blood pressure (mmHg), mean (SD)	122.0 (16.3)	121.6 (16.3)
eGFR (mL/min/1.73 m²)		
≥ 60	1410 (59)	1406 (59)
< 60	962 (41)	964 (41)
Missing	1	1
Aetiology of heart failure, n (%)		
Ischaemic	1316 (55)	1358 (57)
Not ischaemic/unknown	1057 (45)	1013 (43)
NYHA class, n (%)		
II	1606 (68)	1597 (67)
III	747 (31)	751 (32)
IV	20 (1)	23 (1)
LVEF, mean (SD)	31.2 (6.7)	30.9 (6.9)
Treatment discontinuation, n (%)	249 (10)	258 (11)
Study discontinuation, n (%)	ND	ND

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.

eGFR: estimated glomerular filtration rate; F: female; ND: no data; LVEF: left-ventricular ejection fraction; M: male; n: number of patients in the category; N: number of randomized (or included) patients; NYHA: New York Heart Association; RCT: randomized controlled trial; SD: standard deviation

Patient characteristics were sufficiently balanced between the treatment arms. The mean age of the patients was 66 years; most of them were male (77%) and of European family origin. 42% had type 2 diabetes mellitus diagnosis at study inclusion. A majority of the patients showed

slightly limited performance due to their disease, whereas almost 1 third of the patients showed severe limitations in performance (NYHA class III) and only 1% also showed limitations at rest (NYHA class IV).

Implementation of the ACT

The comparator therapy of the included DAPA-HF study is an adequate implementation of the ACT only to a limited extent. Hereby, a main limitation in the implementation of the ACT was that possibly not all therapeutic options had been exhausted for a large proportion of patients.

In the DAPA-HF study, all patients were to receive individual therapy according to relevant local guidelines. This applied to the treatment of heart failure as well as to the treatment of other cardiovascular risk factors and comorbidities and, if applicable, type 2 diabetes mellitus. Adjustments of the therapy were possible at any time during the course of the study, but the therapy should be optimized ≥ 4 weeks before study inclusion and remain as stable as possible. However, the extent to which an optimization of the standard therapy was ensured in the study remains largely unclear. Table 9 shows the data available on the pretreatment and concomitant treatment of heart failure as well as the proportions of patients for whom treatment was modified in the course of the study.

Table 9: Data on the therapies for heart failure – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study characteristic category	Dapagliflozin + optimized standard therapy N[a] = 2373	Placebo + optimized standard therapy N[a] = 2371
DAPA-HF		
Modification of heart failure therapy, n (%)	1104 (47)	1183 (50)
Pretreatment with ACE inhibitor, n (%)	1332 (56)	1329 (56)
Pretreatment with ARB, n (%)	675 (28)	632 (27)
Pretreatment with beta-blocker, n (%)	2278 (96)	2280 (96)
Pretreatment with MRA, n (%)	1696 (71)	1674 (71)
Pretreatment with diuretics, n (%)	2216 (93)	2217 (94)
Pretreatment with ARNI, n (%)	250 (11)	258 (11)
Pretreatment or concomitant treatment with ARNI, n (%)	354 (15)	389 (16)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.

ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; MRA: mineralocorticoid receptor antagonist; n: number of patients in the category; N: number of randomized (or included) patients; RCT: randomized controlled trial

The company reports that about half of the patients received adjustment of the heart failure therapy in the course of the study (47% of the patients in the intervention arm and 50% in the comparator arm). However, it does not provide any information on the type of adjustments, e.g.

which drugs patients switched to or how many patients had dose adjustments for individual active substances. In Module 4 A, the company only presents reasons for non-treatment or non-achievement of the target dose recommended in the guideline for the individual drugs. It is therefore unclear whether all patients received optimized therapy.

According to the National Health Care Guideline [22], patients with symptomatic heart failure with reduced ejection fraction should be treated with a combination of an ACE inhibitor or an ARB, a beta blocker and an MRA. Moreover, patients who continue to show symptoms despite guideline-compliant treatment with ACE inhibitors/ARBs, beta-receptor blockers and MRAs should be recommended to switch from ACE inhibitors/ARBs to the ARNI sacubitril/valsartan. However, due to the current uncertainties regarding the long-term tolerability and the side effect profile of sacubitril/valsartan, attention should be paid to contraindications and intolerances. The G-BA also refers to this treatment switch in its comments on the ACT.

Although patients in the DAPA-HF study were supposed to have symptomatic heart failure according to the inclusion criteria, with stable and individually optimized therapy at the same time, only a small proportion received sacubitril/valsartan. In the DAPA-HF study, a total of 83% of patients received treatment with ACE inhibitors/ARBs, about 96% received beta-blockers and about 71% additionally received MRAs. However, the treatment switch from ACE inhibitors/ARBs to sacubitril/valsartan recommended by the National Health Care Guideline was only carried out in a few patients: approx. 11% of the patients were pretreated with sacubitril/valsartan at the time of study inclusion and approx. 16% were treated with sacubitril/valsartan throughout the course of the study. In Module 4 A, the company presents reasons for non-treatment with ARNI (sacubitril/valsartan) or non-achievement of the target dose recommended in the guideline. The main reasons for non-treatment with ARNI were therefore treatment with ACE inhibitors (approx. 53%) or with ARBs (approx. 25%). However, it is not conclusive why treatment with ACE inhibitors/ARBs would speak against a switch from ACE inhibitors/ARBs to sacubitril/valsartan. The company did not provide any further information on the low proportion of patients treated with sacubitril/valsartan. The National Health Care Guideline [22] comments that, from today's perspective, not all therapeutic options had been exhausted in a large part of the DAPA-HF study population. However, the available data do not indicate for how many patients a switch to sacubitril/valsartan would actually have been indicated.

In summary, the ACT was only implemented to a limited extent. Despite these limitations, the DAPA-HF 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/median treatment duration of the patients and the mean/median observation period for individual outcomes.

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

Study **duration of the study phase** **outcome category**	**Dapagliflozin** **+ optimized standard therapy** **N = 2373**	**Placebo** **+ optimized standard therapy** **N = 2371**
DAPA-HF		
Treatment duration [months]		
Median [Q1; Q3]	17.8 [13.5; 21.5]	17.6 [13.2; 21.3]
Mean (SD)	16.8 (6.3)	16.6 (6.5)
Observation period [months]		
Overall survival		
Median [Q1; Q3]	18.3 [14.3; 21.5]	18.2 [14.1; 21.5]
Mean (SD)	17.7 (5.1)	17.5 (5.3)
Cardiovascular/cerebrovascular morbidity[a]		
Median [Q1; Q3]	18.2 [14.3; 21.5]	18.2 [14.0; 21.4]
Mean (SD)	17.6 (5.2)	17.4 (5.4)
Renal morbidity		
Median [Q1; Q3]	17.8 [13.5; 21.2]	17.6 [13.3; 21.1]
Mean (SD)	16.9 (5.8)	16.7 (6.0)
Health status		
PGIC		
Median [Q1; Q3]	18.2 [12.5; 21.7]	18.0 [12.4; 21.7]
Mean (SD)	17.4 (5.5)	17.1 (5.7)
PGIS		
Median [Q1; Q3]	17.8 [12.2; 21.5]	17.5 [12.1; 21.5]
Mean (SD)	16.5 (6.5)	16.2 (6.8)
EQ-5D VAS		
Median [Q1; Q3]	17.8 [12.2; 21.5]	17.5 [12.1; 21.5]
Mean (SD)	16.5 (6.5)	16.2 (6.8)
Health-related quality of life (KCCQ)		
Median [Q1; Q3]	17.8 [12.2; 21.5]	17.5 [12.1; 21.5]
Mean (SD)	16.5 (6.5)	16.2 (6.8)
Side effects		
Median [Q1; Q3]	18.7 [14.7; 21.9]	18.6 [14.5; 21.9]
Mean (SD)	18.0 (5.2)	17.9 (5.4)

a. Includes all outcomes on heart failure, strokes and myocardial infarctions.

EQ-5D: European Quality of Life-5 Dimensions; KCCQ: Kansas City Cardiomyopathy Questionnaire; N: number of analysed patients; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

Treatment duration was comparable between the two study arms. Median treatment duration was 17.8 months in the intervention arm and 17.6 months in the comparator arm. The observation periods for the individual outcome categories or outcomes were also comparable between both study arms.

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: dapagliflozin + 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			
DAPA-HF	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

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

Transferability to the German health care context

The company explained that according to a commissioned health insurance data analysis, the mean age of approx. 71 years of patients with symptomatic heart failure with reduced ejection fraction corresponds quite well to the age of the study population of the DAPA-HF study. With 23.4%, the proportion of women in the DAPA-HF study was somewhat smaller than the proportion of women in the target population of the health insurance data analysis (42%). Moreover, the company pointed out that 70% of the patients included in the DAPA-HF study were of Caucasian origin and 45.4% came from Europe. Subgroup analyses on the factors "age", "gender", "religion" and "ethnicity" had not shown any effect modifications relevant for the conclusion.

The individual background therapy for the treatment of heart failure, comorbidities and type 2 diabetes mellitus in the study was in line with the recommendations of the current guideline [22,23] and the approval of dapagliflozin [21]. Overall, the company therefore assumes a robust transferability of its results to the German health care context.

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

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - hospitalization due to cardiac failure
  - renal morbidity
  - myocardial infarction
  - stroke
  - health status
    - PGIC
    - PGIS
    - VAS of the EQ-5D
- 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 for which outcomes data were available in the study included.

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

Study	Outcomes												
	All-cause mortality	**Hospitalization due to cardiac failure**	**Renal morbidity[a]**	**Myocardial infarction[b]**	**Stroke[c]**	**Health status (PGIC, PGIS, 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)**	**Respiratory, thoracic and mediastinal disorders (SOC, SAEs)**
DAPA-HF	Yes	Yes	Yes	Yes	Yes	No[d]	No[d]	Yes	Yes	Yes	Yes	Yes	Yes

a. The composite outcome comprises persistent decrease of eGFR by ≥ 50%, ESRD and renal death.
b. The composite outcome comprises non-fatal and fatal myocardial infarctions.
c. The composite outcome comprises non-fatal and fatal strokes.
d. Data not usable; it is unclear how many patients were actually under observation at month 24 and included in the analyses at month 24.

AE: adverse event; eGFR: estimated glomerular filtration rate; EQ-5D: European Quality of Life-5 Dimensions; ESRD: end-stage renal disease; KCCQ: Kansas City Cardiomyopathy Questionnaire; OSS: overall summary score; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Primary composite outcome on cardiovascular morbidity not included

In its present operationalization, the composite outcome on cardiovascular morbidity was not used for the benefit assessment. The composite outcome comprises the components "cardiovascular mortality", "hospitalization due to heart failure" and "emergency contact with a physician due to heart failure". This operationalization only represents cardiovascular morbidity to a limited extent, as non-fatal myocardial infarctions and strokes are not recorded by this outcome. In contrast, fatal myocardial infarctions and strokes are represented via cardiovascular mortality. Therefore, the primary composite outcome on cardiovascular morbidity is not used for the benefit assessment.

Results on patient-reported outcomes not usable

For the outcome categories "morbidity" and "health-related quality of life", the company presented results from the EQ-5D VAS, PGIC, PGIS and KCCQ instruments. The results on these outcomes are not usable, as there are unexplained discrepancies for these outcomes regarding the patients included in the analysis. This is explained in more detail below.

The company reports that at month 24, values for the EQ-5D VAS were available for 1561 patients in the intervention arm and 1519 patients in the comparator arm. For PGIC and PGIS, values were available for 1569 (intervention arm) and 1525 (comparator arm) patients; for KCCQ, there were values for 1566 (intervention arm) and 1523 (comparator arm) patients. However, considering the Kaplan-Meier curves for all-cause mortality (see Figure 1 in Appendix A of the full dossier assessment), only 233 (intervention arm) and 235 (comparator arm) patients were at risk and thus under observation at month 24. The data on patients at risk are supported by the median observation period of 17.8 months (intervention arm) and 17.5 months (comparator arm) for EQ-5D VAS, PGIS and KCCQ, and by the median observation period of 18.2 months (intervention arm) and 18.0 months (comparator arm) for PGIC (see Table 10). In Module 4 A, the company does not explain the discrepancy between the response rates at month 24 and patients at risk at month 24. Therefore, the results on the patient-reported outcomes were not usable.

Recording of AEs incomplete

AEs (independent of severity) were not systematically recorded in the DAPA-HF study. Only non-serious AEs that resulted in treatment discontinuation or dose adjustment or belonged to a choice of AEs predefined by the company were recorded. The approach of the company was not appropriate. This approach does not enable systematic identification of common, patient-relevant non-serious AEs. Consequences of this approach are described in Section 2.4.2.

2.4.2 Risk of bias

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

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

Study	Study level	Outcomes												
		All-cause mortality	Hospitalization due to cardiac failure	Renal morbidity[a]	Myocardial infarction[b]	Stroke[b]	Health status (PGIC, PGIS, 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)	Respiratory, thoracic and mediastinal disorders (SOC, SAEs)
DAPA-HF	L	L	L	L	L	L	–[d]	–[d]	L	L	L	L	L	L

a. The composite outcome comprises persistent decrease of eGFR by ≥ 50%, ESRD and renal death.
b. The composite outcome comprises non-fatal and fatal myocardial infarctions.
c. The composite outcome comprises non-fatal and fatal strokes.
d. Data not usable; it is unclear how many patients were actually under observation at month 24 and included in the analyses at month 24.

AE: adverse event; eGFR: estimated glomerular filtration rate; EQ-5D: European Quality of Life-5 Dimensions; ESRD: end-stage renal disease; KCCQ: Kansas City Cardiomyopathy Questionnaire; L: low; OSS: Overall Summary Score; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

The risk of bias for the results of all outcomes included in the benefit assessment was rated as low. This assessment concurs with that of the company.

Overall assessment of the certainty of conclusions

In the present benefit assessment, only indications, e.g. of an added benefit, can at first be derived on the basis of the individual DAPA-HF study. However, there are various aspects that limit the certainty of conclusions of the present DAPA-HF study for the benefit assessment.

For the present benefit assessment, it remains unclear whether the concomitant treatment of the heart failure applied in the DAPA-HF study represents a complete implementation of the ACT in the sense of an optimized standard therapy. On the one hand, this assessment results from the fact that data on therapy adjustments are missing. On the other hand, it is unclear how large the influence on the effect of dapagliflozin would be if, as postulated in the National Health Care Guideline [22], a larger proportion of patients had been treated with sacubitril/valsartan. Moreover, the side effects cannot be fully assessed due to a lack of information on AEs independent of severity.

Overall, at most hints, e.g. of an added benefit, can be determined for all outcomes due to these limitations. In addition, the extent of the impact the possibly insufficient proportion of patients who were switched to therapy with sacubitril/valsartan has on the effects on the patient-relevant outcomes in the DAPA-HF study is unclear. Therefore, the effects on the individual outcomes cannot be quantified.

This deviates from the assessment of the company, which derived proof of considerable added benefit of dapagliflozin versus optimized standard therapy for patients with symptomatic chronic heart failure with reduced ejection fraction. It justifies the derivation of a proof by stating that the DAPA-HF study fulfils the requirements for the derivation of a proof based on 1 study described in the General Methods, Version 6.0 [1]. The derivation of a proof on the basis of 1 study is subject to certain conditions and is only possible in exceptional cases: For example, the present study[1] has to be multicentre, with ≥ 10 study centres and at least 1000 patients in each study arm. The p-values for the observed effect estimates had to be very small (< 0.001). Moreover, the results had to be consistent within the study. Thus, the analysis of relevant subpopulations had to yield assessable and sufficiently homogeneous effect estimates. The analyses for subpopulations had to be available for all relevant outcomes. For the DAPA-HF study, it is unclear whether all criteria were met. On the one hand, the company did not present sufficient data to justify the consistency of the effect estimates for different subpopulations for all relevant outcomes. In addition, results on patient-reported outcomes (EQ-5D VAS, PGIC, PGIS, KCCQ) are not usable. Therefore, in principle, no statements on the consistency of the results can be made for these outcomes in the present situation.

In summary, based on this single study at most hints, e.g. of an added benefit, can therefore be determined for all outcomes due to the uncertainties described with regard to the implementation of the ACT.

2.4.3 Results

Table 14 and Table 15 summarize the results on the comparison of dapagliflozin + optimized standard therapy with placebo + optimized standard therapy in patients with symptomatic chronic heart failure with reduced ejection fraction. Where necessary, data from the company's dossier are supplemented by Institute's calculations.

The Kaplan-Meier curves on the included outcomes are presented in Appendix A, and the results on common SAEs and discontinuation due to AEs can be found in Appendix B of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study outcome category outcome	Dapagliflozin + optimized standard therapy		Placebo + optimized standard therapy		Dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy
	N	Median time to event in months [95% CI] patients with event n (%)	N	Median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[a]
DAPA-HF					
Mortality					
All-cause mortality	2373	ND 276 (11.6)	2371	ND 329 (13.9)	0.83 [0.71; 0.97]; 0.022
Cardiovascular death	2373	ND 227 (9.6)	2371	ND 273 (11.5)	0.82 [0.69; 0.98]; 0.029[b]
Morbidity					
Hospitalization due to cardiac failure	2373	ND 231 (9.7)	2371	ND 318 (13.4)	0.70 [0.59; 0.83]; < 0.001[b]
Renal morbidity (composite outcome)[c]	2373	ND 28 (1.2)	2371	ND 39 (1.6)	0.71 [0.44; 1.16]; 0.168[d]
Persistent decrease of eGFR by 50%	2373	ND 14 (0.6)	2371	ND 23 (1.0)	0.60 [0.31; 1.16] 0.126[d]
ESRD	2373	ND 16 (0.7)	2371	ND 16 (0.7)	1.00 [0.50; 1.99] 0.995[d]
Renal death	2372	ND 0 (0)	2371	ND 1 (0)	–[e]
Myocardial infarction (composite outcome)[f]	2373	ND 46 (1.9)	2371	ND 41 (1.7)	1.11 [0.73; 1.69]; 0.625
Non-fatal	2373	ND 38 (1.6)	2371	ND 33 (1.4)	1.14 [0.71; 1.82]; 0.583
Fatal	2373	ND 8 (0.3)	2371	ND 8 (0.3)	0.99 [0.37; 2.63]; 0.982
Stroke (composite outcome)[g]	2373	ND 42 (1.8)	2371	ND 46 (1.9)	0.90 [0.59; 1.37]; 0.629
Non-fatal	2373	ND 36 (1.5)	2371	ND 37 (1.6)	0.96 [0.61; 1.52]; 0.865
Fatal	2373	ND 8 (0.3)	2371	ND 9 (0.4)	0.88 [0.34; 2.28]; 0.791
Health status (PGIC, PGIS, EQ-5D VAS)	No usable data[h]				
Health-related quality of life					
KCCQ OSS	No usable data[h]				

Table 14: Results (mortality, morbidity, health-related quality of life) – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study outcome category outcome	Dapagliflozin + optimized standard therapy		Placebo + optimized standard therapy		Dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy
	N	Median time to event in months [95% CI] patients with event n (%)	N	Median time to event in months [95% CI] patients with event n (%)	HR [95% CI]; p-value[a]

a. Unless otherwise stated: Cox proportional hazards model (score test) stratified by status of type 2 diabetes mellitus at randomization.
b. Cox proportional hazards model (score test) stratified by status of type 2 diabetes mellitus at randomization, adjusted for previous "hospitalization due to heart failure".
c. The composite outcome comprises persistent decrease of eGFR by ≥ 50%, ESRD and renal death.
d. Cox proportional hazards model (score test) stratified by status of type 2 diabetes mellitus at randomization, adjusted for eGFR at study inclusion.
e. Since no deaths occurred in one study arm, the HR cannot be estimated in a meaningful way.
f. The composite outcome comprises non-fatal and fatal myocardial infarctions.
g. The composite outcome comprises non-fatal and fatal strokes.
h. It is unclear how many patients were actually under observation at month 24 and included in the analyses at month 24.

CI: confidence interval; eGFR: estimated glomerular filtration rate; EQ-5D: European Quality of Life-5 Dimensions; ESRD: end-stage renal disease; HR: hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; OSS: Overall Summary Score; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity: RCT: randomized controlled trial; VAS: visual analogue scale

Table 15: Results (side effects) – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study outcome category outcome	Dapagliflozin + optimized standard therapy		Placebo + optimized standard therapy		Dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
DAPA-HF					
Side effects					
AEs (supplementary information)	Outcome not recorded[b]				
SAEs[c]	2368	659 (27.8)	2368	728 (30.7)	0.90 [0.83; 0.99]; 0.025
Discontinuation due to AEs	2368	111 (4.7)	2368	116 (4.9)	0.96 [0.74; 1.23]; 0.733
Urinary tract infection (PT, AEs)	2368	44 (1.9)	2368	47 (2.0)	0.94 [0.62; 1.41]; 0.750
Reproductive system and breast disorders (SOC, AEs)	2368	33 (1.4)	2368	33 (1.4)	1.00 [0.62; 1.62]; 0.999
Diabetic ketoacidosis (PT, AEs)	2368	3 (0.1)	2368	0 (0)	7.00 [0.36; 135.44]; 0.097[d]
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	2368	57 (2.4)	2368	88 (3.7)	0.65 [0.47; 0.90]; 0.010

a. Logistic regression with log-link, adjusted for status of type 2 diabetes mellitus at study inclusion.
b. Only non-serious AEs that resulted in treatment discontinuation or dose adjustment or belonged to a choice of AEs predefined by the company were recorded.
c. Without events adjudicated to the primary cardiovascular outcome, myocardial infarction, stroke, or to the secondary and exploratory renal outcomes.
d. Institute‘s calculation of RR, 95%- CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [24]).

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

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

Mortality

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

All-cause mortality

A statistically significant difference in favour of dapagliflozin + optimized standard therapy was shown between the treatment groups for the outcome "all-cause mortality". However, there is an effect modification for the severity of the heart failure according to NYHA classification. This resulted in a hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy for patients with NYHA class II heart failure. For patients of the NYHA classes III/IV, there is no hint of an added benefit of dapagliflozin + 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 company's assessment, which derived proof of a considerable added benefit for the total population.

Morbidity

Hospitalization due to cardiac failure

A statistically significant difference in favour of dapagliflozin + optimized standard therapy between the treatment groups was shown for the outcome "hospitalization due to cardiac failure". This resulted in a hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

This deviates from the assessment of the company, which derived proof of major added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Renal morbidity

For the composite outcome "renal morbidity", consisting of the outcomes "persistent decrease of eGFR by 50%", "ESRD" and "renal death", there was no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for this outcome.

This concurs with the company's assessment.

Myocardial infarction

For the composite outcome "myocardial infarction", consisting of "non-fatal myocardial infarction" and "fatal myocardial infarction", as well as for the two individual components, there is no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for these outcomes.

This concurs with the company's assessment.

Stroke

For the outcome "stroke", consisting of "non-fatal stroke" and "fatal stroke", as well as for the two individual components, there is no statistically significant difference between the treatment groups. This resulted in no hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for these outcomes.

This concurs with the company's assessment.

Health status

There are no usable data for the outcome "health status" (see Section 2.3.2). This resulted in no hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for this outcome.

This partly deviates from the assessment of the company, which derived proof of minor added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy based on the results of the PGIS. For the EQ-5D VAS, it derived a non-clinically relevant advantage of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Health-related quality of life

No usable data were available for the outcome category "health-related quality of life" (see Section 2.3.2). This resulted in no hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for this outcome.

This deviates from the assessment of the company, which derived proof of considerable added benefit of dapagliflozin + optimized standard therapy versus optimized standard therapy on the basis of responder analyses for an improvement by 5 points as well as for a deterioration by 5 points for the KCCQ-OSS and the KCCQ symptom score. The company presented no responder analyses for the remaining 3 valid domains of the KCCQ (physical limitation, social limitation and psychological quality of life).

Side effects

SAEs

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

This deviates from the assessment of the company, which derived proof of considerable added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Discontinuation due to AEs

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from dapagliflozin + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

Specific AEs

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

There is no statistically significant difference between the treatment groups for the outcomes "urinary tract infection (PT, AEs)", "reproductive system and breast disorders (SOC, AEs)", "diabetic ketoacidosis (PT, AEs)". This resulted in no hint of greater or lesser harm from dapagliflozin + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

This partly deviates from the company's assessment. The company did not use the outcomes "urinary tract infection (PT, AEs)" and "reproductive system and breast disorders (SOC, AEs)" to derive greater or lesser harm. For the outcome "diabetic ketoacidosis", the company derived no added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Respiratory, thoracic and mediastinal disorders

A statistically significant difference in favour of dapagliflozin + optimized standard therapy was shown between the treatment groups for the outcome "respiratory, thoracic and mediastinal disorders (SOC, SAEs)". This resulted in a hint of lesser harm from dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. It cannot be ruled out that the SAE "respiratory, thoracic and mediastinal disorders" also includes events that may be due to the symptoms of the underlying disease, (e.g. dyspnoea).

This deviates from the assessment of the company, which derived proof of considerable added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

2.4.4 Subgroups and other effect modifiers

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

- age (≤ 65 years versus > 65 years)
- sex (male versus female)
- severity of heart failure (NYHA class II vs. 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 10 events in at least one subgroup.

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

Table 16 summarizes the subgroup results on the comparison of dapagliflozin + optimized standard therapy with placebo + optimized standard therapy in adult patients with symptomatic heart failure with reduced ejection fraction.

Table 16: Subgroups (mortality) – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study **outcome** **characteristic** **subgroup**	**Dapagliflozin + optimized standard therapy**		**Placebo + optimized standard therapy**		**Dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy**	
	N	**Median time to event in months [95 % CI]** **patients with event n (%)**	**N**	**Median time to event in months [95 % CI]** **patients with event n (%)**	**HR [95% CI]**	**p-value**
DAPA-HF						
Mortality						
All-cause mortality						
Severity						
NYHA II	1606	ND 125 (7.8)	1597	ND 192 (12.0)	0.64 [0.51; 0.80]	< 0.001
NYHA III/IV	767	ND 151 (19.7)	774	ND 137 (17.7)	1.12 [0.89; 1.42]	0.326
Total					Interaction:	< 0.001

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NYHA: New York Heart Association; RCT: randomized controlled trial

Mortality

All-cause mortality

For the outcome "all-cause mortality", a statistically significant interaction is shown by the characteristic "severity of cardiac failure according to NYHA class".

A statistically significant difference in favour of dapagliflozin + optimized standard therapy was shown for patients with NYHA severity class II. This resulted in a hint of an added benefit

of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy for patients with NYHA class II heart failure. No statistically significant difference between the treatment groups was shown for patients with NYHA severity classes III and IV. This resulted in no hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for these outcomes of the category "mortality" for patients in 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 17).

Determination of the outcome category for the outcomes on morbidity

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they are serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Hospitalization due to cardiac failure

Fatal events or events that require inpatient treatment are considered severe or serious. Therefore, the outcome "hospitalization due to heart failure" was assigned to the outcome category "serious/severe symptoms/late complications".

Table 17: Extent of added benefit at outcome level: dapagliflozin + optimized standard therapy vs. optimized standard therapy (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Dapagliflozin + optimized standard therapy vs. optimized standard therapy** **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		
Severity of heart failure		
NYHA II	ND vs. ND HR: 0.64 [0.51; 0.80] p < 0.001 probability: "hint"	Outcome category: mortality added benefit, extent: "non-quantifiable"
NYHA III/IV	ND vs. ND HR: 1.12 [0.89; 1.42] p = 0.326	Lesser benefit/added benefit not proven
Morbidity		
Hospitalization due to cardiac failure	ND vs. ND HR: 0.70 [0.59; 0.83] p < 0.001 probability: "hint"	Outcome category: serious/severe symptoms/late complications added benefit, extent: "non-quantifiable"
Renal morbidity	ND vs. ND HR: 0.71 [0.44; 1.16] p = 0.168	Lesser benefit/added benefit not proven
Myocardial infarction	ND vs. ND HR: 1.11 [0.73; 1.69] p = 0.625	Lesser benefit/added benefit not proven
Stroke	ND vs. ND HR: 0.90 [0.59; 1.37] p = 0.629	Lesser benefit/added benefit not proven
Health status (PGIC, PGIS, EQ-5D VAS)	No usable data[c]	Lesser benefit/added benefit not proven
Health-related quality of life		
KCCQ OSS	No usable data[c]	Lesser benefit/added benefit not proven
Side effects		
SAEs	27.8% vs. 30.7% RR: 0.90 [0.83; 0.99] p = 0.025 probability: "hint"	Outcome category: serious/severe side effects lesser harm, extent: "non-quantifiable"
Discontinuation due to AEs	4.7% vs. 4.9% RR: 0.96 [0.74; 1.23] p = 0.733	Greater/lesser harm not proven

Table 17: Extent of added benefit at outcome level: dapagliflozin + optimized standard therapy vs. optimized standard therapy (multipage table)

Outcome category **outcome** **effect modifier** **subgroup**	**Dapagliflozin + optimized standard therapy vs. optimized standard therapy** **median time to event (months) or proportion of events (%)** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Urinary tract infection (PT, AEs)	1.9 % vs. 2.0 % RR: 0.94 [0.62; 1.41] p = 0.750	Greater/lesser harm not proven
Reproductive system and breast disorders (SOC, AEs)	1.4% vs. 1.4% RR: 1.00 [0.62; 1.62] p = 0.999	Greater/lesser harm not proven
Diabetic ketoacidosis (PT, AEs)	0.1% vs. 0.0% RR: 7.00 [0.36; 135.44] p = 0.097	Greater/lesser harm not proven
Respiratory, thoracic and mediastinal disorders (SOC, SAEs)	2.4% vs. 3.7% RR: 0.65 [0.47; 0.90] p = 0.010 probability: "hint"	Outcome category: serious/severe side effects lesser harm, extent: "non-quantifiable"

a. Probability provided if there is a statistically significant and relevant effect.
b. Based on the DAPA-HF study, no quantifiable assessments of the effect size can be made (see Section 2.4.2).
c. It is unclear how many patients were actually under observation at month 24 and included in the analyses at month 24.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; ND: no data; NYHA: New York Heart Association; OSS: Overall Summary Score; PGIC: Patient Global Impression of Change; PGIS: Patient Global Impression of Severity; PT: Preferred Term; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

Table 18 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy

Positive effects	**Negative effects**
Mortality ▪ all-cause mortality ▫ NYHA II hint of added benefit – extent: “non-quantifiable”	–
Morbidity serious/severe secondary diseases ▪ hospitalization due to cardiac failure: hint of an added benefit – extent: “non-quantifiable”	–
Serious/severe side effects ▪ SAEs: hint of lesser harm – extent: “non-quantifiable” ▪ respiratory, thoracic and mediastinal disorders (SOC, SAEs): hint of lesser harm – extent: “non-quantifiable”	–
No usable data were available for the outcomes “health status” and “health-related quality of life”. AEs independent of severity were not systematically recorded in the DAPA-HF study.	
NYHA: New York Heart Association; SAE: serious adverse event; SOC: System Organ Class	

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

Positive effects in the category “mortality” were only shown in patients with NYHA severity grade II. For the outcome ‘”hospitalization due to cardiac failure”, this resulted in a hint of a non-quantifiable added benefit of dapagliflozin + optimized standard therapy for the total population. In addition, positive effects were shown in the outcome category “side effects”, which also concerned the total population. There was a hint of non-quantifiable lesser harm from dapagliflozin + optimized standard therapy both for the overall rate of SAEs and for respiratory, thoracic and mediastinal disorders (SOC, SAEs). It cannot be ruled out that the SAE “respiratory, thoracic and mediastinal disorders” also includes events that may be due to the symptoms of the underlying disease, (e.g. dyspnoea). No usable data were available for the outcomes “health status” and “health-related quality of life”.

In summary, there is a hint of a non-quantifiable added benefit of dapagliflozin + optimized standard therapy versus 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 19.

Table 19: Dapagliflozin – 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	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. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived proof of considerable added benefit for the total population.

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

References for English extract

Please see full dossier assessment for full reference list.

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

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