IQWiG Reports – Commission No. A21-109

Dapagliflozin (kidney disease) –

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 (Niereninsuffizienz) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 November 2021). Please note: This document was translated by an external translator and 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 her 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.

Patient and family involvement

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

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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
CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate
ESRD	end-stage renal disease
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLP-1	glucagon-like peptide-1
HbA1c	glycosylated haemoglobin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KDIGO	Kidney Disease – Improving Global Outcomes
KDQoL-36	Kidney Disease Quality of Life
LVEF	left ventricular ejection fraction
MRA	mineralocorticoid receptor antagonist
NYHA	New York Heart Association
OR	odds ratio
PT	preferred term
RCT	randomized controlled trial
RR	relative risk
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGLT2	sodium-glucose cotransporter-2
UACR	urine albumin-to-creatinine ratio
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 27 August 2021.

Research question

The aim of this report is to assess the added benefit of dapagliflozin in comparison with optimized standard therapy as the appropriate comparator therapy (ACT) in adult patients with chronic kidney disease (CKD).

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 dapagliflozin

Therapeutic indication	**ACT**[a]
Adults with CKD	Optimized standard treatment of CKD, taking into account the underlying illness and common comorbidities (such as diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia) and sequelae[b]

a. Presented is the respective ACT specified by the G-BA.
b. Notes from the G-BA:
- In accordance with current medical knowledge, CKD treatment is assumed to comprise the use of ACE inhibitors or AT1-receptor antagonists (angiotensin receptor blockers [ARBs]), provided the patient is eligible for them, tolerates them, and is not contraindicated for them. Therefore, both study arms are to receive ACE inhibitors or AT1-receptor antagonists (ARBs) (as add-on therapy).
- In the context of the ACT, both treatment arms are assumed to include individualized treatment of the underlying illness and any comorbidities or sequelae while avoiding nephrotoxic substances in accordance with current medical knowledge. There is a discrepancy between the drugs approved for the treatment of CKD and drugs recommended by guidelines.
- For the target population to be treated, target levels for comorbidities (e.g. diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia) must be defined before the start of the study; these target levels should be reached by patients before enrolment or during a possible run-in phase and then maintained throughout the study with the aid of individualized therapy (e.g. dose modifications). Target levels should be based on the respective diseases' treatment standards and take into account multiple comorbidities, if applicable.
- For patients in the present therapeutic indication, the treatment goal of slowing the disease progression is assumed to still apply, thus excluding renal replacement therapy in the form of dialysis or transplantation for the time being.

ACE: angiotensin converting enzyme; ACT: appropriate comparator therapy; ARB: angiotensin receptor blocker; AT-1: angiotensin-1; G-BA: Federal Joint Committee

The company followed the G-BA's specification of 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 in comparison with the ACT specified by the G-BA. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for deriving any added benefit.

Below, the term kidney failure is used interchangeably with the internationally more common term chronic kidney disease or CKD.

Study pool

The study pool for the benefit assessment of dapagliflozin comprises the studies DAPA-CKD and DAPA-HF. In the DAPA-HF study, a subpopulation of patients with CKD represents the relevant subpopulation for this assessment (hereinafter referred to as "CKD subpopulation").

For deriving added benefit, the company uses primarily the DAPA-CKD study and supports this by a metaanalysis on the basis of individual patient data (IPD) from the DAPA-CKD study and CKD subpopulations of the DAPA-HF and DECLARE-TIMI 58 studies. As supplementary information, the company presents an additional metaanalysis of the renal safety studies DELIGHT, DERIVE, and MB102029, without using the same to derive added benefit. The data from the DECLARE-TIMI 58 study and the renal safety studies are unsuitable for the present benefit assessment since they did not adequately implement the ACT.

The ACT specifies for both CKD and comorbidities to be optimally treated in accordance with current medical knowledge. The current National Disease Management Guideline Type 2 Diabetes calls for additionally offering sodium-glucose cotransporter-2 (SGLT2) inhibitors (empagliflozin) and glucagon-like peptide-1 (GLP-1) receptor agonists (liraglutide) to type 2 diabetes patients with simultaneous cardiovascular disease or high cardiovascular risk. Patient treatment in the DECLARE-TIMI 58 comparator arm failed to comply with current recommendations since SGLT2 inhibitors were disallowed and liraglutide was rarely used. The renal safety studies DELIGHT, DERIVE, and MB102029 either generally disallowed modifications of background therapy, or study documents do not show whether adequate treatment modifications were possible. Hence, treatment in these studies' comparator arms failed to meet the treatment algorithm of the current National Disease Management Guideline Type 2 Diabetes as well as optimized standard therapy as per the ACT.

Study design

DAPA-CKD

DAPA-CKD is a randomized, double-blind, parallel group, placebo-controlled study on dapagliflozin. It included patients with CKD, an estimated glomerular filtration rate (eGFR) of ≥ 25 to ≤ 75 mL/min/1.73 m^2, and albuminuria (urine albumin-to-creatinine ratio [UACR]: ≥ 200 to ≤ 5000 mg/g). In addition to the study medication, patients were to receive individualized standard therapy of CKD as well as comorbidities, and they were to have been treated with the individual patient's maximum tolerated, stable dose of angiotensin-converting

enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) for at least 4 weeks before enrolment.

A total of 4304 patients were included and allocated in a 1:1 ratio to treatment with dapagliflozin (N = 2152) or placebo (N = 2152).

Dapagliflozin in the DAPA-CKD study was administered as approved. In addition, patients in both study arms received individualized therapy for CKD and comorbidities.

The primary outcome of the study is the composite outcome of ≥ 50% sustained decline in eGFR, reaching end-stage renal disease (ESRD), cardiovascular death, and renal death. Patient-relevant outcomes were overall survival, morbidity, health-related quality of life, and adverse events (AEs).

DAPA-HF

DAPA-HF is a parallel group, randomized, double-blind, placebo-controlled study on dapagliflozin. It included patients with symptomatic heart failure of New York Heart Association (NYHA) classes II to IV with reduced ejection fraction, defined as left ventricular ejection fraction (LVEF) ≤ 40%. The study's inclusion criteria specified for patients to have been treated with stable, optimized standard heart failure therapy for at least 4 weeks prior to enrolment. Unless contraindicated, therapy was to comprise ACE inhibitors, ARBs, or sacubitril/valsartan in combination with a beta blocker and, if appropriate, a mineralocorticoid receptor antagonist (MRA). The implementation of the ACT is discussed in detail below.

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

Dapagliflozin in the DAPA-HF study was administered as approved. In addition, patients in both study arms received individualized therapy for heart failure and comorbidities such as CKD or type 2 diabetes mellitus.

Primary outcome of the study is the composite outcome comprising cardiovascular death, hospitalization due to heart failure, and urgent visit due to heart failure. Patient-relevant secondary outcomes were overall survival, morbidity, health-related quality of life, and AEs.

Relevant subpopulation of the DAPA-HF study

Only a subpopulation of the DAPA-HF study is relevant for this benefit assessment. The company defined a relevant subpopulation on the basis of the diagnostic criteria of the "Kidney Disease – Improving Global Outcomes" (KDIGO) guideline. These criteria were eGFR < 60 mL/min/1.73 m^2 and/or UACR > 30 mg/g. This approach is appropriate. However, the DAPA-HF study did not survey UACR, and hence, no data are available on the percentage of study participants with albuminuria. The CKD subpopulation of the DAPA-HF study is therefore based solely on the criterion of eGFR. Hence, it remains unclear whether additional DAPA-HF participants might potentially belong to the target population. The benefit

assessment of dapagliflozin in CKD patients consequently used 41% of the DAPA-HF study population (dapagliflozin arm [n = 962]; comparator arm [n = 964]).

Implementation of the ACT

The comparator therapy used in the included studies can be considered an adequate implementation of the ACT only to a limited extent. Substantial limitations regarding the implementation of the ACT result from the company not having submitted any data showing whether and, if so, how therapy was optimized in the course of the study.

Patients in the DAPA-CKD and DAPA-HF studies were to receive individualized standard therapy in accordance with local guidelines. This applied to the treatment of CKD as well as any comorbidities such as cardiovascular disease or type 2 diabetes mellitus. In both studies, patients were to be treated with ACE inhibitors or ARBs or sacubitril/valsartan for ≥ 4 weeks before enrolment, and neither study restricted treatment switches or dose modifications of background therapy. However, the company did not submit any data on treatment optimization during the study. Hence, it remains largely unclear to what extent treatment was actually optimized in the course of both studies.

All patients of the DAPA-HF study additionally had chronic heart failure with reduced ejection fraction. For patients who continued to exhibit symptoms despite guideline-compliant therapy with an ACE inhibitor or ARB, beta blocker, and MRA, a switch from ACE inhibitors / ARBs to sacubitril/valsartan or add-on SGLT2 inhibitor therapy was to be recommended. Only a few patients received the recommended treatment switch from ACE inhibitors / ARBs to sacubitril/valsartan. SGLT2 inhibitors were disallowed in the DAPA-HF study. Since only 11% of patients in the DAPA-CKD study exhibited heart failure, this aspect is less relevant for the overall evaluation of that study.

On the basis of the available information, the ACT of optimized standard therapy for CKD and particularly for the comorbidity of heart failure has presumably been implemented only to a limited extent. Despite these limitations, the DAPA-CKD study and the DAPA-HF study's CKD subpopulation are used in the benefit assessment. The resulting consequences for the benefit assessment (e.g. regarding the studies' certainties of results) are described below.

Risk of bias

The risk of bias at study level is rated as low, as is the risk of bias for the results on all outcomes included in the benefit assessment.

Assessment of the certainty of results

As far as the present benefit assessment is concerned, it seems safe to assume that the implementation of the ACT (as in optimized standard therapy) during the concomitant treatment of CKD and comorbidities in the DAPA-CKD and DAPA-HF studies was not all-encompassing. This reasoning results from the lack of information on treatment optimization in the course of the study. Further, side effects cannot be fully assessed because (1) the survey

of serious adverse events (SAEs) and discontinuation due to AEs included a large number of events associated with disease symptoms or comorbidities, (2) data on non-serious AEs were incomplete, and (3) data on AEs are not available for the full follow-up period.

Due to these limitations, the results of the individual studies can be used to derive at most hints, e.g. of an added benefit, for all outcomes. For patients with the additional comorbidity of heart failure, it is also unclear to what extent the potentially insufficient percentage of patients who were switched to sacubitril/valsartan therapy impacts the effects on patient-relevant outcomes. Since all patients in the DAPA-HF study exhibited symptomatic, chronic heart failure, it is impossible to quantify the effects on the individual outcomes for the DAPA-HF study's CKD subpopulation. In the DAPA-CKD study, in contrast, only 11% of the study population exhibited heart failure. Therefore, potentially insufficient treatment with sacubitril/valsartan for patients with heart failure is unlikely to affect the overall results of the DAPA-CKD study to a meaningful extent. Due to their differing percentages of patients with symptomatic chronic heart failure, conclusions, e.g. on added benefit, are drawn separately for the DAPA-CKD participants and the DAPA-HF study's CKD subpopulation. Another argument in favour of performing separate analyses is provided by the fact that all patients in the DAPA-CKD study exhibited albuminuria (≥ 200 mg/g), with half of them having a UACR of > 1000 mg/g. Since the DAPA-HF study did not survey UACR, the study's CKD subpopulation was selected based on eGFR (eGFR < 60 mL/min/1.73 m^2). Consequently, subgroup analyses by albuminuria category (e.g. microalbuminuria or macroalbuminuria) cannot be conducted for the DAPA-HF study's CKD subpopulation.

Results

Mortality

All-cause mortality

The DAPA-CKD study shows a statistically significant effect in favour of dapagliflozin + optimized standard therapy for the outcome of all-cause mortality. For the CKD subpopulation of the DAPA-HF study, no statistically significant difference between treatment groups was found. For the DAPA-CKD study population, this results in a hint of added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. Added benefit has not been proven for the DAPA-HF study's CKD subpopulation.

Morbidity

ESRD

For the composite outcome of ESRD, defined as sustained eGFR < 15 mL/min/1.73 m^2, chronic dialysis treatment, or receipt of a renal transplant, a statistically significant effect in favour of dapagliflozin + optimized standard therapy was found. No statistically significant difference between treatment groups was found for the DAPA-HF study's CKD subpopulation. For the DAPA-CKD study population, this results in a hint of added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. Added benefit has not been proven for the DAPA-HF study's CKD subpopulation.

Hospitalization for heart failure

Both for the DAPA-CKD study and for the DAPA-HF study's CKD subpopulation, a statistically significant effect in favour of dapagliflozin + optimized standard therapy was found for the outcome of hospitalization for heart failure. For both the DAPA-CKD study population and the CKD subpopulation of the DAPA-HF study, this results in a hint of added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Myocardial infarction, stroke

Neither the DAPA-CKD study nor the DAPA-HF study's CKD subpopulation showed any statistically significant difference between treatment groups for the outcomes of myocardial infarction or stroke. For these outcomes, this results in no hint of added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for these outcomes.

Health status (visual analogue scale [VAS] of European Quality of Life Questionnaire – 5 Dimensions [EQ-5D)

For the outcome of health status, operationalized as deterioration of EQ-5D VAS by 15 points, the company presented data only from the DAPA-CKD study, despite the fact that this outcome was also surveyed in the DAPA-HF study. Regarding this outcome, the DAPA-CKD study showed a statistically significant advantage in favour of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. However, the effect for this outcome of the non-serious/non-severe symptoms / late complications category is no more than marginal. An added benefit is therefore not proven. Similarly, added benefit has not been proven for the DAPA-HF study's CKD subpopulation.

Health-related quality of life

For the outcome category of health-related quality of life, no usable data were available. This results in no hint of added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for this outcome.

Side effects

SAEs, discontinuation due to AEs

In the survey of SAEs and discontinuation due to AEs, the studies included a large number of disease-related events. While the company also calculated SAEs and discontinuation due to AEs excluding renal events, AEs representing symptoms of the underlying illness or comorbidities are still included in the overall rates. The results for individual common AEs (e.g. myocardial infarction and heart failure in DAPA-CKD; heart failure in DAPA-HF) therefore show similar advantages of dapagliflozin as do the morbidity results. Consequently, the total rates of SAEs and discontinuation due to AEs are unusable for assessing the side effects of dapagliflozin. Based on the results on common SAEs and discontinuation due to AEs, however, dapagliflozin is not expected to be associated with unfavourable effects of an extent that might call into question the added benefit of dapagliflozin. Consequently, for the outcomes of SAEs

and discontinuation due to AEs, there is no hint of greater or lesser harm of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

Genital infection, urinary tract infection

No usable data are available on the outcomes of genital infection and urinary tract infection; this is because the studies did not systematically identify non-serious AEs and the events of interest are known to largely belong in the category of non-serious side effects.

Diabetic ketoacidosis

For the outcome of diabetic ketoacidosis, neither the DAPA-CKD study nor the DAPA-HF study's CKD subpopulation exhibit any statistically significant differences between treatment groups. Consequently, there is no hint of greater or lesser harm of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

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

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

DAPA-CKD

Overall, for patients with CKD (eGFR ≥ 25 to ≤ 75 mL/min/1.73 m^2 and albuminuria [UACR ≥ 200 to ≤ 5000 mg/g]) without the comorbidity of symptomatic chronic heart failure, exclusively favourable effects of dapagliflozin were found in comparison with optimized standard therapy. The effects were found for all-cause mortality and the outcomes of ESRD and hospitalization for heart failure. The favourable effect for the outcome of ESRD is supported by the results of the renal morbidity outcome, which was presented as supplementary information. No usable data are available for outcomes on health-related quality of life and the overall rates of AEs. On the basis of the available information on side effects, however, no unfavourable effects of an extent which might call into question an added benefit are expected.

In summary, for patients with CKD without chronic heart failure, there is a hint of considerable added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

[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].

CKD subpopulation of the DAPA-HF study

Overall, for patients with CKD (eGFR < 60 mL/min/1.73 m^2 irrespective of albuminuria since the study did not collect UACR data) and chronic heart failure, there is 1 favourable effect of dapagliflozin in comparison with optimized standard therapy. Regarding the outcome of hospitalization for heart failure, a hint of non-quantifiable added benefit of dapagliflozin + optimized standard therapy was found for the DAPA-HF study's CKD subpopulation. No usable data are available for outcomes on health-related quality of life and the overall rates of AEs. On the basis of the available information on side effects, however, no unfavourable effects of an extent which might call into question an added benefit are expected.

In summary, for patients with CKD and additional chronic heart failure, there is a hint of non-quantifiable added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Table 3 presents a summary of the probability and extent of 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 CKD		
Without symptomatic chronic heart failure as a comorbidity	Optimized standard therapy for CKD taking into account the underlying illness and common comorbidities (such as diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia) and sequelae	Hint of considerable added benefit[b]
With additional symptomatic chronic heart failure as a comorbidity		Hint of non-quantifiable added benefit[c]

a. Presented is the respective ACT specified by the G-BA.
b. The conclusion on added benefit is based on the results of the DAPA-CKD study. DAPA-CKD included patients with eGFR ≥ 25 ≤ 75 mL/min/1.73 m^2 and albuminuria (UACR ≥ 200 to ≤ 5000 mg/g). It remains unclear whether the observed effects can be extrapolated to other patients in the target population. Only 11% of the patients showed heart failure at enrolment.
c. The conclusion on added benefit is based on the results of the DAPA-HF study's CKD subpopulation. The DAPA-HF study's CKD subpopulation included patients with symptomatic chronic heart failure involving reduced ejection fraction and an eGFR < 60 mL/min/1.73 m^2, irrespective of albuminuria (UACR data are not available from the study). It remains unclear whether the observed effects can be extrapolated to other patients in the target population.

ACT: appropriate comparator therapy; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; G-BA: Federal Joint Committee; UACR: urine albumin–creatinine ratio

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

2.2 Research question

The aim of this report is to assess the added benefit of dapagliflozin in comparison with optimized standard therapy as the ACT in adult patients with CKD.

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 dapagliflozin

Therapeutic indication	**ACT**[a]
Adults with CKD	Optimized standard treatment of CKD, taking into account the underlying illness and common comorbidities (such as diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia) and sequelae[b]

a. Presented is the respective ACT specified by the G-BA.
b. Comments by the G-BA:
- In accordance with current medical knowledge, CKD treatment is assumed to comprise the use of ACE inhibitors or AT1-receptor antagonists (angiotensin recept blockers [ARBs]), provided the patient is eligible for them, tolerates them, and is not contraindicated for them. Therefore, both study arms are to receive ACE inhibitors or AT1-receptor antagonists (ARBs) (as add-on therapy).
- In the context of the ACT, both treatment arms are assumed to include individualized treatment of the underlying illness and any comorbidities or sequelae while avoiding nephrotoxic substances in accordance with current medical knowledge. There is a discrepancy between the drugs approved for the treatment of CKD and drugs recommended by guidelines.
- For the target population to be treated, target levels for comorbidities (e.g. diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia) must be defined before the start of the study; these target levels should be reached by patients before enrolment or during a possible run-in phase and then maintained throughout the study with the aid of individualized therapy (e.g. dose modifications). Target levels should be based on the respective diseases' treatment standards and take into account multiple comorbidities, if applicable.
- For patients in the present therapeutic indication, the treatment goal of slowing the disease progression is assumed to still apply, thus excluding renal replacement therapy in the form of dialysis or transplantation for the time being.

ACE: angiotensin converting enzyme; ACT: appropriate comparator therapy; ARB: angiotensin receptor blocker; AT-1: angiotensin-1; G-BA: Federal Joint Committee

The company followed the G-BA's specification of 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 in comparison with the ACT specified by the G-BA. RCTs with a minimum duration of 24 weeks were used for deriving any added benefit. This concurs with the company's inclusion criteria.

Below, the term kidney failure is used interchangeably with the internationally more common term chronic kidney disease (CKD).

2.3 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on dapagliflozin (as of 25 June 2021)
- Bibliographic literature search on dapagliflozin (most recent search on 25 June 2021)
- Search in trial registries / study results databases on dapagliflozin (most recent search on 28 June 2021)
- Search on the G-BA website on dapagliflozin (most recent search on 29 June 2021)

To check the completeness of the study pool:

- Search in trial registries for studies on dapagliflozin (most recent search on 9 September 2021); see Appendix A of the full dossier assessment for search strategies.

The check did not identify any additional relevant studies.

2.3.1 Included studies

The studies included in the benefit assessment are listed in the table below.

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

Study	Study category			Available sources		
	Approval study for the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (yes/no [reference])	Registry entries[b] (yes/no [reference])	Publication and other sources[c] (yes/no [reference])
D169AC00001 (DAPA-CKD[d])	Yes	Yes	No	Yes [3]	Yes [4-6]	Yes [7]
D1699C00001 (DAPA-HF[d])	No	Yes	No	Yes [8]	Yes [9,10]	Yes [11-14]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the 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 tables below, the study will be referred to using this acronym.

G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool for the benefit assessment of dapagliflozin comprises the studies DAPA-CKD and DAPA-HF. In the DAPA-HF study, a subpopulation of patients with CKD represents the relevant subpopulation for this assessment (hereinafter referred to as “CKD subpopulation”).

The study pool only partially matches the study pool used by the company for the derivation of added benefit. The company used primarily the DAPA-CKD study and provided, as supporting information, a metaanalysis on the basis of individual patient data (IPD) from the DAPA-CKD study and CKD subpopulations of the DAPA-HF and DECLARE-TIMI 58 [15] studies. For supplementary information, the company presents an additional metaanalysis of the renal safety

studies DELIGHT [16], DERIVE [17], and MB102029 [18], without using this metaanalysis for deriving added benefit. For the reasons discussed below, this approach is only partially appropriate.

Dapagliflozin is approved not only for the indication of CKD to be assessed herein, but also for the treatment of chronic heart failure and diabetes mellitus type 2. Regarding these therapeutic indications, the company has previously conducted the approval study DAPA-HF in the indication of heart failure and the cardiovascular outcome study DECLARE-TIMI 58 in the indication of type 2 diabetes mellitus. In both studies, a substantial percentage of participants exhibited CKD. The company's dossier identifies these patients using an eGFR < 60 mL/min/1.73 m^2 for the DAPA-HF study, but primarily with a UACR > 30 mg/g for the DECLARE-TIMI 58 study. In principle, this is an appropriate approach since the KDIGO guideline [19] defines CKD via eGFR < 60 mL/min/1.73 m^2 and/or UACR > 30 mg/g.

However, the DECLARE-TIMI 58 study is disregarded for the benefit assessment of dapagliflozin in chronic CKD since the ACT specified by the G-BA's has not been implemented in this study. The ACT specifies that both CKD and comorbidities be optimally treated in accordance with current medical knowledge. For instance, the current National Disease Management Guideline Type 2 Diabetes [20] calls for type 2 diabetes patients with simultaneous cardiovascular disease or high cardiovascular risk to be additionally offered SGLT2 inhibitors (empagliflozin) and GLP-1 receptor agonists (liraglutide). All patients included in the DECLARE-TIMI 58 study met this definition. However, patient treatment in the DECLARE-TIMI 58 comparator arm failed to comply with current recommendations in that SGLT2 inhibitors were disallowed and liraglutide was rarely used. Hence, treatment in the comparator arm of this study met neither the treatment algorithm of the current National Disease Management Guideline Type 2 Diabetes nor optimized standard therapy as per the ACT. DAPA-CKD and DAPA-HF also excluded treatment with SGLT2 inhibitors, but their patient populations substantially differ in eGFR levels from those in the studies on which the recommendations for treatment with SGLT2 inhibitors (EMPA-REG study) and GLP-1 receptor agonists (LEADER study) are based. In both of these studies as well as in DECLARE-TIMI 58, a clear majority of patients had eGFR levels > 60 mL/min/1.73 m^2. Therefore, no evidence is available to support treating type 2 diabetes mellitus patients with eGFR levels < 60 mL/min/1.73 m^2 using SGLT2 inhibitors. Consequently, the DAPA-CKD and DAPA-HF studies can be deemed to have adequately implemented the ACT regarding type 2 diabetes mellitus, despite not offering SGLT2 inhibitor treatment (also see Section 2.3.2 on the implementation of the ACT).

As supplementary information, the company submitted the renal safety studies DELIGHT, DERIVE, and MB102029. These studies included patients with CKD and type 2 diabetes mellitus. The company justifies including the studies merely as supplementary information by citing the lack of patient-relevant effectiveness outcomes as well as a study duration of 24 weeks for DELIGHT and DERIVE. These studies are irrelevant for the present benefit assessment since they did not adequately implement the ACT. They either disallowed

modifications of background therapy, or study documents failed to show whether adequate treatment modifications were possible.

Hence, the present benefit assessment is based on the approval study DAPA-CKD and the DAPA-HF study's CKD subpopulation.

2.3.2 Study characteristics

Table 6 and Table 7 present the studies used in the benefit assessment.

Table 6: Characterization of the included studies – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]
DAPA-CKD	RCT, double-blind, parallel-group	Adult patients with CKD[b] with ▪ eGFR ≥ 25 to ≤ 75 ml/min/1.73 m^2 and ▪ albuminuria (UACR ≥ 200 to ≤ 5000 mg/g)[c]	Dapagliflozin (N = 2152) Placebo (N = 2152)	Screening: 14 ± 7 days Treatment: event-driven study, study end planned to occur after 681 events in the primary outcome; completed early after 509 events due to definitive treatment advantages of dapagliflozin Follow-up: for a maximum of 6 weeks after study end	A total of 405 centres in Argentina, Brazil, Canada, China, Denmark, Germany, Hungary, India, Japan, Mexico, Peru, Philippines, Poland, Russia, Spain, South Korea, Sweden, Ukraine, United Kingdom, United States, Vietnam 02/2017–06/2020	Primary: composite outcome of ≥ 50% sustained decline in eGFR, ESRD[d], cardiovascular death, or renal death Secondary: overall survival, morbidity, health status, health-related quality of life, AEs
DAPA-HF	RCT, double-blind, parallel-group	Adult patients with symptomatic heart failure of NYHA class II-IV[e] and reduced ejection fraction with: ▪ LVEF ≤ 40% and ▪ NT-proBNP ▫ ≥ 600 pg/mL or ▫ ≥ 400 pg/mL in case of hospitalization for heart failure within 12 months before enrolment[f]	Dapagliflozin (N = 2373) Placebo (N = 2371) Relevant subpopulation thereof[g]: Dapagliflozin (n = 962) Placebo (n = 964)	Screening: 14 ± 7 days Treatment: event-driven study: Study end after 844 events in the primary outcome Follow-up: for a maximum of 6 weeks after study end	Argentina, Brazil, Bulgaria, Canada, China, Czech Republic, Denmark, Germany, India, Japan, Netherlands, Poland, Russia, Slovakia, Sweden, Taiwan, United Kingdom, United States, Vietnam 02/2017–07/2019	Primary: composite outcome comprising cardiovascular death, hospitalization for heart failure, and urgent visit due to heart failure Secondary: overall survival, morbidity, health status, health-related quality of life, AEs

Table 6: Characterization of the included studies – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and time period conducted	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Patients with autosomal dominant or autosomal recessive polycystic kidney disease, lupus nephritis, or ANCA-associated vasculitis were excluded from the study, as were patients with type 1 diabetes mellitus.
c. Increased albuminuria ≥ 3 months before visit 1.
d. Defined as confirmed sustained eGFR < 15 mL/min/1.73 m^2 or chronic dialysis treatment, or receipt of a renal transplant.
e. Heart failure had to have persisted for ≥ 2 months.
f. If atrial fibrillation or flutter was simultaneously found at visit 1, NT-proBNP had to be ≥ 900 pg/mL.
g. Patients of the CKD subpopulation had to have eGFR < 60 mL/min/1.73 m^2 and/or UACR > 30 mg/g. Since the DAPA-HF study did not survey UACR, the selection is based only on the eGFR criterion.

AE: adverse event; ANCA: antineutrophil cytoplasmic antibodies; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease, LVEF: left ventricular ejection fraction; N: number of randomized patients; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; RCT: randomized controlled trial; UACR: urine albumin–creatinine ratio

Table 7: Characterization of the intervention – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study	Intervention	Comparison
DAPA-CKD	Dapagliflozin 10 mg, once daily, orally[a] + optimized standard therapy	Placebo once daily, orally + optimized standard therapy
	Pretreatment and concomitant treatment ▪ Standard therapy based on locally recognized guidelines ▫ of cardiovascular risk factors ▫ of type 2 diabetes mellitus[b] ▫ of symptoms and sequelae of kidney disease ▪ ACE inhibitors or ARB at the individual patient's maximum tolerated, stable dose for ≥ 4 weeks before enrolment No limitations of treatment switches or dose modifications **Non-permitted prior and concomitant treatment** ▪ SGLT2 inhibitors within 8 weeks prior to enrolment and during the study ▪ Coronary revascularization (PCI or CABG) or valve reconstruction/replacement ≤ 12 weeks prior to enrolment ▪ Cytotoxic therapy, immunosuppressive therapy, or other immunotherapy for primary or secondary renal disease ≤ 6 months prior to enrolment ▪ Organ transplantation ▪ Nonsteroidal anti-inflammatory drugs were to be avoided	
DAPA-HF	Dapagliflozin 10 mg, once daily, orally[a] + optimized standard therapy	Placebo once daily, orally + optimized standard therapy
	Pretreatment and concomitant treatment ▪ In compliance with locally recognized guidelines, individually optimized standard therapy for heart failure at a stable dose for ≥ 4 weeks prior to enrolment[c] with: ▫ ACE inhibitors or ARBs or sacubitril/valsartan ▫ Beta blockers ▫ MRAs, if necessary ▫ Diuretics, if necessary ▫ Treatment switches and dose modifications upon the investigator's discretion are allowed[d] ▪ Type 2 diabetes mellitus ▫ Treatment in accordance with the glycaemic target levels recommended by ADA and EASD ▫ Treatment modification based on local standards allowed ▫ In case of treatment with insulin and insulin secretagogues, reduction of the daily dose was to be considered[b] ▪ Additionally necessary medications were allowed upon the investigator's discretion **Non-permitted prior and concomitant treatment** ▪ SGLT2 inhibitors within 8 weeks prior to enrolment and during the study ▪ Coronary revascularization (PCI or CABG) or valve reconstruction/replacement ≤ 12 weeks prior to enrolment ▪ CRT implantation ≤ 12 weeks prior to enrolment ▪ Heart transplantation or implantation of a ventricular assist device	

Table 7: Characterization of the intervention – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study	Intervention	Comparison
a. Reducing the dapagliflozin dose to 5 mg was allowed in case of AEs such as hypovolaemia, hypotension, and/or abrupt declines in kidney function which persisted despite modifications of the concomitant medication. After patient stabilization, the dose was increased to 10 mg. b. For patients with HbA1c levels ≤ 7% (DAPA-CKD) or < 7% (DAPA-HF) at randomization, a 10–20% reduction of the daily insulin dose and a 25–50% reduction of the insulin secretagogue dose as well as more frequent blood glucose readings were to be considered. c. Diuretics did not have to be administered at a stable dose. d. Dose reductions or discontinuations of effective therapies were to be carried out only if other measures did not improve the patient's situation. ACE: angiotensin converting enzyme; ADA: American Diabetes Association; AE: adverse event; ARB: angiotensin receptor blocker; CABG: coronary artery bypass graft; CRT: cardiac resynchronization therapy; EASD: European Association for the Study of Diabetes; HbA1c: glycosylated haemoglobin; MRA: mineralocorticoid receptor antagonist; PCI: percutaneous coronary intervention; RCT: randomized controlled trial; SGLT-2: sodium-glucose cotransporter protein 2		

DAPA-CKD

DAPA-CKD is a randomized, double-blind, parallel group, placebo-controlled study on dapagliflozin. It included patients with CKD and an eGFR of ≥ 25 to ≤ 75 mL/min/1.73 m^2 and albuminuria (UACR: ≥ 200 to ≤ 5000 mg/g). In addition to the study medication, patients were to receive individualized standard therapy of CKD as well as comorbidities, and they were to have been treated with a stable, for the patient maximum tolerated dose of ACE inhibitor or ARB for at least 4 weeks before enrolment. A detailed discussion of the implementation of the ACT is found below.

A total of 4304 patients were included and allocated in a 1:1 ratio to treatment with dapagliflozin (N = 2152) or placebo (N = 2152). Randomization was stratified by the presence of type 2 diabetes mellitus and by UACR (≤ 1000 mg/g versus > 1000 mg/g).

The DAPA-CKD study administered dapagliflozin on label [21]. In addition, patients in both study arms received individualized therapy of CKD and comorbidities.

Being an event-driven study, DAPA-CKD study was terminated early after 33 months due to definitive treatment advantages of dapagliflozin. After study end, all outcomes were to be followed up for a maximum of 6 weeks. Patients who discontinued the study medication early continued to be observed, and after the end of the study, they were also followed up for a maximum of 6 weeks. The median follow-up duration was 28.5 months in both intervention arm and placebo arm, and the median treatment duration was 27.3 months in the intervention arm and 27.0 months in the comparator arm.

The primary outcome of the study is the composite outcome of ≥ 50% sustained decline in eGFR, reaching ESRD, cardiovascular death, and renal death. Patient-relevant outcomes were overall survival, morbidity, health-related quality of life, and AEs.

DAPA-HF

DAPA-HF is a parallel group, randomized, double-blind, placebo-controlled study on dapagliflozin. It included patients with symptomatic heart failure of NYHA classes II to IV involving reduced ejection fraction defined as LVEF ≤ 40%. The study's inclusion criteria specified for patients to have been treated with stable, optimized standard heart failure therapy for at least 4 weeks prior to enrolment. Unless contraindicated, therapy was to comprise ACE inhibitors, ARBs, or sacubitril/valsartan in combination with a beta blocker and, if appropriate, an MRA. The implementation of the ACT is discussed in detail below.

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

Dapagliflozin in the DAPA-CKD study was administered as approved [21]. In addition, patients in both study arms received individualized therapy for heart failure and comorbidities such as CKD or type 2 diabetes mellitus.

Being an event-driven study, the DAPA-HF was planned to end after 844 events in the primary outcome. After study end, all outcomes were to be followed up for a maximum of 6 weeks. Patients who discontinued the study medication early after randomization continued to be observed and, after study end, were also followed up for a maximum of 6 weeks. The median follow-up duration for the study's total population was 18.3 months in the intervention arm versus 18.2 months in the comparator arm, while the median treatment duration was 17.8 months in the intervention arm versus 17.6 months in the comparator arm.

Primary outcome of the study is the composite outcome comprising cardiovascular death, hospitalization due to heart failure, and urgent visit due to heart failure. Patient-relevant secondary outcomes were overall survival, morbidity, health-related quality of life, and AEs.

Relevant subpopulation of the DAPA-HF study

Only a subpopulation of the DAPA-HF study is relevant for this benefit assessment. The approval of dapagliflozin comprises not only the present therapeutic indication but also chronic heart failure. The approval study for the therapeutic indication of heart failure, DAPA-HF, included patients with CKD. The company defined a relevant subpopulation on the basis of the diagnostic criteria of the KDIGO guideline [19]. These criteria were eGFR < 60 mL/min/1.73 m^2 and/or UACR > 30 mg/g. This approach is appropriate.

The DAPA-HF study did not survey UACR, and hence, no data are available on the percentage of patients with albuminuria in this study. The CKD subpopulation of the DAPA-HF study is therefore based solely on the criterion of eGFR. Hence, it remains unclear whether additional DAPA-HF participants might potentially belong to the target population. The benefit assessment of dapagliflozin in CKD patients consequently used 41% of the DAPA-HF study population (dapagliflozin arm [n = 962]; comparator arm [n = 964]).

The median follow-up duration of the CKD subpopulation of the DAPA-HF study was 18.7 months, and the median treatment duration 17.6 months.

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

Table 8: Characterization of the study populations – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study Characteristic Category	DAPA-CKD		DAPA-HF	
	Dapagliflozin + optimized standard therapy	Placebo + optimized standard therapy	Dapagliflozin + optimized standard therapy	Placebo + optimized standard therapy
	N[a] = 2152	N[a] = 2152	N[b] = 962	N[b] = 964
Age [years], mean (SD)	62 (12)	62 (12)	71 (9)	71 (9)
Sex [f/m], %	33/67	33/67	29/71	27/73
Ancestry, n (%)				
White	1124 (52)	1166 (54)	712 (74)	716 (74)
African American	104 (5)	87 (4)	44 (5)	46 (5)
Asian	749 (35)	718 (33)	187 (19)	187 (19)
Hawaiian or Pacific Islanders	1 (0)	1 (0)	–	–
Native Americans or Alaska Natives	62 (3)	74 (3)	–	–
Other	112 (5)	106 (5)	19 (2)	15 (2)
Region, n (%)				
Asia	692 (32)	654 (30)	184 (19)	181 (19)
Europe	610 (28)	623 (29)	455 (47)	436 (45)
North America	401 (19)	412 (19)	138 (14)	167 (17)
Latin and South America	449 (21)	463 (22)	185 (19)	180 (19)
Baseline eGFR (mL/min/1.73 m^2)				
Mean (SD)	43.2 (12.3)	43.0 (12.4)	47.0 (7.92)	47.0 (8.17)
Median [min; max]	41.0 [19; 86]	42.0 [20; 80]	48.0 [24; 59]	48.0 [26; 59]
< 30	293 (14)	331 (15)	13 (1)	11 (1)
30 to < 45	979 (45)	919 (43)	349 (36)	346 (36)
45 to < 60	646 (30)	682 (32)	600 (62)	607 (63)
≥ 60	234 (11)	220 (10)	–	–
Baseline UACR (mg/g)				
Mean (SD)	1370.6 (1197.9)	1356.4 (1171.5)	ND[c]	ND[c]
Median [min; max]	964.8 [23; 11 905]	933.8 [124; 8963]	ND[c]	ND[c]
Type 2 diabetes mellitus at enrolment, n (%)	1455 (68)	1451 (67)	450 (47)	472 (49)
Dyslipidaemia, n (%)	1488 (69)	1500 (70)	628 (65)	637 (66)
Heart failure at enrolment, n (%)	235 (11)	233 (11)	962 (100)[d]	964 (100)[d]
Systolic blood pressure (mmHg), mean (SD)	136.7 (17.5)	137.4 (17.3)	ND	ND
≤ 130	793 (37)	749 (35)	ND	ND
> 130	1359 (63)	1,403 (65)	ND	ND
Diastolic blood pressure (mmHg), mean (SD)	77.5 (10.7)	77.5 (10.3)	ND	ND

Table 8: Characterization of the study populations – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study Characteristic Category	DAPA-CKD		DAPA-HF	
	Dapagliflozin + optimized standard therapy	Placebo + optimized standard therapy	Dapagliflozin + optimized standard therapy	Placebo + optimized standard therapy
	N[a] = 2152	N[a] = 2152	N[b] = 962	N[b] = 964
BMI, n (%)				
< 30 kg/m²	1208 (56)	1171 (54)	604 (63)	596 (62)
≥ 30 kg/m²	941 (44)	976 (45)	358 (37)	368 (38)
Treatment discontinuation, n (%)	274 (12.7[e])[f]	309 (14.4[e])[e]	121 (12.6)[f]	130 (13.5)[f]
Study discontinuation, n (%)	10 (0.5[e])	5 (0.2[e])	ND[g]	ND[g]

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. Number of randomized patients of the CKD subpopulation with eGFR< 60 mL/min/1.73 m².
c. UACR levels were not surveyed in the DAPA-HF study.
d. Chronic heart failure (NYHA class II-IV) was an inclusion criterion of the DAPA-HF study.
e. IQWiG calculation.
f. The most common reasons for discontinuation were "patient decision" (6.6% in the intervention arm versus 7.4% in the comparator arm) and "AEs" (5.5% in the intervention arm versus 5.7% in the comparator arm). For the DAPA-HF study's CKD subpopulation, no data were available on reasons for discontinuation.
g. From the overall population, 5 patients in the intervention arm and 4 patients in the comparator arm discontinued the study.

AE: adverse event; BMI: body mass index; eGFR: estimated glomerular filtration rate; f: female; m: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; NYHA: New York Heart Association; RCT: randomized controlled trial; SD: standard deviation; UACR: urine albumin–creatinine ratio

In both studies, patient characteristics are sufficiently balanced between treatment arms. In both studies, the included patients were predominantly male and had a mean age of 62 years (DAPA-CKD) and 71 years (CKD subpopulation of the DAPA-HF study). Type 2 diabetes mellitus had been diagnosed in 68% of DAPA-CKD participants and 48% of the DAPA-HF study's CKD subpopulation. Median eGFR levels were slightly lower in DAPA-CKD patients at 41 and 42 mL/min/1.73 m², respectively, than in the DAPA-HF study's CKD subpopulation (median: 48 mL/min/1.73 m²). Heart failure had been diagnosed in all patients of the DAPA-HF study's CKD subpopulation, but in only about 11% of DAPA-CKD participants. In DAPA-CKD, the mean UACR was 965 mg/g (intervention arm) and 934 mg/g (comparator arm). DAPA-HF did not survey UACR.

Implementation of the ACT

For the present therapeutic indication, the ACT is optimized standard therapy of CKD, taking into account the underlying illness and common comorbidities (such as diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia) or sequelae. However, the comparator therapy used in the included studies can be considered an adequate implementation of the ACT only

with some limitations. Substantial limitations in the implementation of the ACT result from the company not having submitted any data to show whether and, if so, how therapy was optimized in the course of the study.

In DAPA-HF, patients were to receive individualized standard therapy in accordance with local guidelines. This applied to the treatment of CKD as well as any comorbidities such as cardiovascular disease or type 2 diabetes mellitus. All patients had to have been treated with ACE inhibitors or ARBS at a maximum tolerated dose ≥ 4 weeks prior to enrolment. In DAPA-HF, patients were to receive individualized standard therapy in accordance with local guidelines for heart failure, cardiovascular risk factors, and type 2 diabetes mellitus. Heart failure therapy had to have been administered at a stable dose for ≥ 4 weeks, including with ACE inhibitors or ARBs or sacubitril-valsartan. Any additionally necessary treatments were allowed upon the investigator's discretion.

While neither study restricted treatment switches or dose modifications for background therapy, the company did not submit any data on treatment optimization during the study. Hence, it remains largely unclear to what extent treatment was actually optimized in the course of both studies. Table 9 shows the available data on prior therapies.

Table 9: Information on prior therapies – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study	DAPA-CKD		DAPA-HF	
Drug class Drug	Dapagliflozin + optimized standard therapy	Placebo + optimized standard therapy	Dapagliflozin + optimized standard therapy	Placebo + optimized standard therapy
	N = 2152[a]	N = 2152[a]	N = 962[b]	N = 964[b]
Prior therapy for CKD and cardiovascular diseases				
Any CKD/CV medication	2146 (99.7)	2145 (99.7)	962 (100.0)	964 (100.0)
ACE inhibitors	673 (31.3)	681 (31.6)	478 (49.7)	497 (51.6)
ARBs	1444 (67.1)	1426 (66.3)	308 (32.0)	267 (27.7)
ACE inhibitors or ARBs	2094 (97.3)	2080 (96.7)	ND	ND
Renin inhibitors	3 (0.1)	0 (0.0)	ND	ND
ARNIs	1 (0.0)	2 (0.1)	111 (11.5)	110 (11.4)
MRAs	ND	ND	ND	ND
Calcium channel blockers	1074 (49.9)	1109 (51.5)	ND	ND
Beta blockers	846 (39.3)	834 (38.8)	912 (94.8)	926 (96.1)
Diuretics	928 (43.1)	954 (44.3)	ND	ND
Thiazide diuretics	ND	ND	ND	ND
Loop diuretics	ND	ND	817 (84.9)	817 (84.8)
Other diuretics + MRAs	ND	ND	659 (68.5)	637 (66.1)
Other diuretics	ND	ND	125 (13.0)	120 (12.4)
Phosphate binders	23 (1.1)	25 (1.2)	1 (0.1)	10 (1.0)
Potassium binders	51 (2.4)	66 (3.1)	0 (0.0)	2 (0.2)
Vasodilators	ND	ND	182 (18.9)	181 (18.8)
Digitalis glycosides	ND	ND	178 (18.5)	160 (16.6)
Antithrombotic agents	1022 (47.5)	1020 (47.4)	ND	ND
Any antiplatelet drugs	952 (44.2)	928 (43.1)	ND	ND
Dual antiplatelet therapy	ND	ND	ND	ND
Acetyl salicylic acid	ND	ND	429 (44.6)	443 (46.0)
Anticoagulants	ND	ND	ND	ND
Oral anticoagulants	ND	ND	455 (47.3)	452 (46.9)
Acetyl salicylic acid + other antiplatelet drugs	ND	ND	5 (0.5)	2 (0.2)
Other	109 (5.1)	116 (5.4)	176 (18.3)	188 (19.5)
Lipid-lowering agents	1495 (69.5)	4493 (69.4)	59 (6.1)	75 (7.8)
Statins	1395 (64.8)	1399 (65.0)	655 (68.1)	690 (71.6)
Ezetimib	ND	ND	ND	ND
Other	320 (14.9)	325 (15.1)	ND	ND

Table 9: Information on prior therapies – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Study	DAPA-CKD		DAPA-HF	
Drug class Drug	Dapagliflozin + optimized standard therapy	Placebo + optimized standard therapy	Dapagliflozin + optimized standard therapy	Placebo + optimized standard therapy
	N = 2152[a]	N = 2152[a]	N = 962[b]	N = 964[b]
Statins + lipid-lowering agents	ND	ND	3 (0.3)	2 (0.2)
Statins + acetyl salicylic acid	ND	ND	6 (0.6)	3 (0.3)
Statins + other antiplatelet drugs	ND	ND	0 (0.0)	1 (0.1)
Diabetes treatment before randomization				
	N[c] = 1455	N[c] = 1451	N[c] = 450	N[c] = 472
Any diabetes treatment	1363 (93.7)	1356 (93.5)	363 (80.7[d])	385 (81.6[d])
Insulin	814 (55.9)	784 (54.0)	151 (33.6[d])	153 (32.4[d])
Biguanides/metformin	631 (43.4)	613 (42.2)	190 (42.2[d])	213 (45.1[d])
Sulfonylureas	389 (26.7)	385 (26.5)	108 (24.0[d])	89 (18.9[d])
Alpha-glucosidase inhibitors	42 (2.9)	57 (3.9)	15 (3.3[d])	21 (4.4[d])
Thiazolidinediones	53 (3.6)	38 (2.6)	2 (0.4[d])	2 (0.4[d])
DPP-4 inhibitors	364 (25.0)	378 (26.1)	87 (19.3[d])	74 (15.7[d])
GLP-1 analogues	63 (4.3)	59 (4.1)	8 (1.8[d])	7 (1.5[d])
Glinides	ND	ND	12 (2.7[d])	10 (2.1[d])
Biguanides + DPP-4 inhibitors	ND	ND	0 (0)	3 (0.6[d])
Aldose reductase inhibitors	ND	ND	1 (0.2[d])	1 (0.2[d])
Biguanides + sulfonylureas	ND	ND	0 (0)	1 (0.2[d])
SGLT-2 inhibitors	ND	ND	0 (0)	1 (0.2[d])
Other	35 (2.4)	54 (3.7)	ND	ND

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line if the deviation is relevant.
b. Number of randomized patients of the CKD subpopulation with eGFR< 60 mL/min/1.73 m^2.
c. Patients with diabetes mellitus at baseline.
d. IQWiG calculations.

ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor-neprilysin inhibitor; CKD: chronic kidney disease; CV: cardiovascular; DPP-4: dipeptidyl-peptidase 4, GLP-1: glucagon-like peptide 1; MRA: mineralocorticoid receptor antagonist; N: number of analysed patients; n: number of patients with subsequent therapy; ND: no data; RCT: randomized controlled trial; SGLT2: sodium-glucose cotransporter-2

Treatment of kidney disease

CKD therapy aims to both treat the causes of the disease and slow its progression [22]. In addition, comorbidities and sequelae are to be treated. For instance, patients with an

eGFR < 60 mL/min/1.73 m^2 and a blood pressure > 140/90 mmHg should be offered methods to control blood pressure [22]. However, ACE inhibitor or ARB therapy is recommended for inhibiting disease progression even in proteinuria patients and/or diabetes patients who do not exhibit elevated blood pressure. This recommendation is also reflected by the G-BA's comments on the ACT. The G-BA expects CKD treatment to include the use of ACE inhibitors or ARBs. About 97% of patients in the DAPA-CKD study were on ACE inhibitor or ARB treatment at enrolment, while upwards of 90% of patients in the DAPA-HF study's CKD subpopulation received ACE inhibitor or ARB or angiotensin receptor-neprilysin inhibitor (ARNI) treatment at enrolment. The company did not provide any data on dosing during the study or on modifications of ACE inhibitor or ARB treatment.

Treatment of type 2 diabetes mellitus

High levels of glycosylated haemoglobin (HbA1c) in diabetes patients increase the risk of progression of kidney disease. The current National Disease Management Guideline Type 2 Diabetes [20] no longer defines any HbA1c target levels or ranges. Instead, target levels are to be defined together with the individual patient within an HbA1c range of 6.5% to 8.5%. Both DAPA-CKD and DAPA-HF specified for type 2 diabetes mellitus to be treated in accordance with local guidelines. Treatment modifications were allowed in both studies. About 94% of type 2 diabetes mellitus patients in DAPA-CKD received such treatment at enrolment, compared with about 81% in the DAPA-HF study's CKD subpopulation. The mean baseline HbA1c level was 7.8% in both DAPA-CKD treatment groups and 6.6% in DAPA-HF. The company did not submit any information on diabetes medication received during the study or on its modifications during the study.

Treatment of chronic heart failure

DAPA-HF is the approval study for the indication of chronic heart failure with reduced ejection fraction; all patients in this study had this therapeutic indication. According to the National Disease Management Guideline Chronic Heart Failure [23], 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. For patients who continue to be symptomatic despite guideline-compliant therapy, the National Disease Management Guideline, version 3, recommends a switch from ACE inhibitors / ARBs to the ARNI sacubitril/valsartan or added SGLT-2 inhibitor treatment (empagliflozin). Despite the fact that the inclusion criteria require DAPA-HF patients to exhibit symptomatic heart failure while on stable, individually optimized therapy, only a small percentage of these patients were on sacubitril/valsartan. In total, about 81% of patients in the DAPA-HF study's CKD subpopulation were treated with ACE inhibitors or ARBs, and about 95% received beta blockers. Regarding MRAs, no data are available for the CKD subpopulation, but about 71% of the total population received additional MRAs. For about half of the patients not treated with MRAs, the reasons remain unclear. Treatment switches from ACE inhibitors or ARBs to sacubitril/valsartan as recommended by the National Disease Management Guideline were carried out in few patients: about 11% of patients in the CKD subpopulation had received prior sacubitril/valsartan therapy at enrolment. SGLT2

inhibitors were disallowed in the DAPA-HF study. The company did not submit any further information on the low percentage of patients with sacubitril/valsartan treatment.

In DAPA-CKD, 11% of patients additionally suffered from heart failure. However, the number of patients who would have been indicated for a switch to sacubitril/valsartan cannot be inferred from the available information. SGLT2 inhibitors were disallowed in the DAPA-CKD study as well.

For either study, the company did not submit any information on heart failure medication received during the study or on its modifications during the study. Both studies, however, apparently involved only a limited amount of treatment intensification as called for by the National Disease Management Guideline Chronic Heart Failure following maximization of guideline-compliant basic therapy.

Summary

The company's dossier provides insufficient information on the treatment of kidney failure and comorbidities in DAPA-CKD study participants and in the DAPA-HF study's CKD subpopulation after enrolment. On the basis of the available information, the ACT of optimized standard therapy can be assumed to have been implemented only to a limited degree. Despite these limitations, the DAPA-CKD study and the DAPA-HF study's CKD subpopulation are used in this benefit assessment. The resulting consequences for the benefit assessment (e.g. regarding the studies' certainties of results) are described in Section 2.4.2.

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: 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		Results-independent reporting	Lack of other aspects	Risk of bias at study level
			Patients	Treatment providers			
DAPA-CKD	Yes	Yes	Yes	Yes	Yes	Yes	Low
DAPA-HF	Yes	Yes	Yes	Yes	Yes	No[a]	Low

a. Results on the outcome of EQ-5D VAS surveyed in DAPA-HF were not presented.

RCT: randomized controlled trial; VAS: visual analogue scale

The risk of bias across outcomes was rated as low for both studies.

Transferability to the German healthcare context

According to the company, a commissioned health insurance data analysis has shown the mean age of CKD patients to be about 70 years. At 61.9 (± 12.1), the average age of the DAPA-CKD population was only slightly below that, while the average age of the DAPA-HF study's CKD population was comparable, at 70.9 years (± 9.0). The company adds that based on the health insurance data analysis, about 43.8% of the target population in Germany are women, a number slightly higher than in the DAPA-HF study's CKD subpopulation (27.7%) and close to the population of the DAPA-CKD study (33.1%). In addition, the company reports that 74.1% of the DAPA-HF study's CKD subpopulation and about half of DAPA-CKD participants (53.2%) are white. About one third (28.6%) of patients in the DAPA-CKD study and 46.3% of the DAPA-HF study's CKD subpopulation are from European countries, including Germany. Subgroup analyses on the factors of age, sex, region, and ethnicity reportedly revealed no effect modifications relevant for the conclusion.

Patients in the two included studies additionally exhibited comorbidities such as cardiovascular diseases and diabetes mellitus; these were reflected by the results of the health insurance data analysis regarding comorbidities of CKD patients. The company argues that, consistent with current medical knowledge, comorbidities were to be treated by individualized therapy. It also mentions that, in the DAPA-CKD study, the majority of patients received ACE inhibitor and ARB therapy in accordance with the currently valid guidelines. The company deems this treatment to be comparable with the results from the health insurance data analysis on the health care situation in Germany.

The company did not present any further information on the transferability of study results to the German healthcare 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
  - ESRD
  - Hospitalization for heart failure
  - Myocardial infarction
  - Stroke
  - Health status
    - Visual analogue scale (VAS) of EQ-5D

- Health-related quality of life
  - Kidney Disease Quality of Life (KDQOL-36)
- Side effects
  - SAEs
  - Discontinuation due to AEs
  - Genital infections (AEs)
  - Urinary tract infections (preferred term [PT], AEs)
  - Diabetic ketoacidosis (AEs)
  - Further specific AEs, if any

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

Table 11 shows for which outcomes data were available in the included study.

Table 11: Matrix of outcomes – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study	Outcomes												
	All-cause mortality	ESRD[a]	Hospitalization for heart failure	Myocardial infarction[b]	Stroke[b]	Health status (EQ-5D VAS)	Health-related quality of life (KDQOL-36)	SAEs	Discontinuation due to AEs	Genital infections (AEs)[c]	Urinary tract infections (PT, AEs)	Diabetic ketoacidosis (AEs)[d]	Further specific AEs
DAPA-CKD	Yes	Yes	Yes	Yes	Yes	Yes	No[e]	–[f]	–[f]	No[g]	No[g]	Yes	No[h]
DAPA-HF	Yes	Yes	Yes	Yes	Yes	No[i]	No[j]	–[f]	–[f]	No[g]	No[g]	Yes	No[h]

a. ESRD comprises confirmed sustained eGFR < 15 mL/min/1.73 m^2 or chronic dialysis treatment, or receipt of a renal transplant.
b. Fatal and non-fatal events.
c. Events for the AESI of genital infections listed by the company in the study report.
d. Probable and definite diabetic ketoacidosis adjudicated by an outcome committee were analysed.
e. Data unusable; it is unclear how many patients were actually being followed up at Month 36 and included in Month 36 analyses.
f. High percentage of disease-related events (see Section 2.4.1). Disease-related events were disregarded only if the company had surveyed them for the predefined AESI of renal events.
g. No usable data due to incomplete survey. Non-serious AEs were surveyed only if they led to treatment discontinuation or dose modification or were included in a selection of AEs predefined by the company. Genital infections and urinary tract infections were not included in the AEs predefined by the company and are particularly relevant as non-serious AEs.
h. No further specific AEs other than disease-related AEs were identified.
i. The outcome was surveyed, but the dossier contains no results for the relevant subpopulation.
j. Outcome not surveyed.

AE: adverse event; AESI: AE of special interest; eGFR: estimated glomerular filtration rate: ESRD: end-stage renal disease; KDQOL: Kidney Disease Quality of Life; PT: preferred term; RCT: randomized controlled study; SAE: serious adverse event; VAS: visual analogue scale

- ESRD: The company has presented analyses of various composite outcomes on renal morbidity. This benefit assessment uses the composite outcome of ESRD, consisting of the following components:
  - Chronic dialysis treatment
  - Kidney transplantation
  - Confirmed sustained eGFR < 15 mL/min/1.73 m^2

  The composite outcome consisting of confirmed ≥ 50% sustained decline in eGFR, ESRD, and renal death is presented as a supplementary outcome on renal morbidity. However, this outcome is associated with uncertainties. 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 the present case, it is unclear whether the component of ≥ 50% decline in eGFR of the composite outcomes on renal morbidity meets these criteria. A total of 11% of DAPA-CKD study participants have an eGFR ≥ 60 mL/min/1.73 m^2. Given such high baseline levels, a relative decline in eGFR by ≥ 50% is not necessarily patient relevant and hence not of comparable severity as the other components of the composite renal morbidity outcomes (e.g. ESRD and renal death).

The present benefit assessment therefore relies on the composite ESRD outcome and presents the broader composite renal morbidity outcome (consisting of confirmed sustained ≥ 50% decline in eGFR, ESRD, and renal death) as supplementary information.

- Health status (EQ-5D VAS): Data on the patient-reported outcome of health status (EQ-5D VAS) is available only for the DAPA-CKD study. The company has not presented any results on EQ-5D VAS for the DAPA-HF study's CDK subpopulation despite the fact that the outcome was surveyed in this study. For DAPA-CKD, the company presents responder analyses on improvement by 15 points, deterioration by 15 points, and on mean differences. The EQ-5D VAS response criterion of 15 points (scale range 0 to 100), which was used in the analyses presented by the company, meets the requirements for response criteria of reflecting with sufficient certainty a change that is perceivable for patients, as defined by the IQWiG General Methods [1]. Due to the progressive course of disease to be expected in the present therapeutic indication and taking into account the distribution of absolute values on the scales at baseline, an analysis of the deterioration of health status is of key relevance in the present benefit assessment. This benefit assessment relied on the EQ-5D VAS responder analysis of deterioration.
- Health-related quality of life (KDQOL-36): Only the DAPA-CKD study surveyed data on health-related quality of life using KDQOL-36. For the KDQOL-36 domains, the company has likewise presented mean differences and analyses with a response criterion of 15 points. The KDQOL-36 contains the SF-12, version 1 (Physical Component Summary [PCS] and Mental Component Summary [MCS]) as well as 3 kidney disease-specific subscales (Burden of Kidney Disease, Symptoms and Problems of Kidney Disease, and Effects of Kidney Disease). For the subscales of SF-12, version 1, the company assumes a scale range of 0 to 100. This scale range is not plausible because according to the SF-12, version 1, scoring manual [24], the PCS and MCS are transformed based on a distribution with a mean of 50 and a standard deviation of 10, and the values for the items are associated with positive and negative weights. As discussed in dossier assessment A21-84 [25], it is not permissible to use the theoretical range for determining the response criterion of 15% of the scale range. In line with A21-84, therefore, the response criteria were calculated on the basis of the empirical scale ranges reported in the scoring manual, which were derived from the US general population. They equal 13 to 69 points for PCS and 10 to 70 points for MCS, and 15% of the scale range

equals 8.4 points (rounded to 8) for PCS ([69 − 13] * 0.15 = 8.4) and 9.0 points for MCS ([70 − 10] * 0.15 = 9.0).
The differences in mean values are likewise unusable in this benefit assessment because these outcomes exhibit unexplained discrepancies with regard to the patients included in the analysis. The reason is explained in more detail below.
The company reports that, by Month 36, results for the individual KDQOL-36 domains are available from 998 patients in the intervention arm and 956 patients in the comparator arm. Based on the Kaplan-Meier curves for all-cause mortality in DAPA-CKD (see Figure 2 in Appendix B of the full dossier assessment), however, only 43 patients (intervention arm) and 44 patients (comparator arm) were under risk and hence being followed up at Month 36. The data on patients under risk are supported by the mean follow-up duration of 28.5 months. The company's Module 4 A does not explain the discrepancy between return rates for Month 36 and patients under risk at Month 36. Therefore, the results on KDQOL-36 mean differences cannot be used.

- Side effects:
  - Non-serious AEs were not systematically surveyed in DAPA-CKD or DAPA-HF. Non-serious AEs were surveyed only if they led to treatment discontinuation or dose modification or if they belonged to a selection of AEs predefined by the company (AESIs). The company's approach is inappropriate because it does not allow systematically identifying common, patient-relevant, non-serious AEs in the study. Further, the company did not specify the follow-up period during which the AE events presented in Module 4 A had occurred. A comparison with the DAPA-CKD study report reveals that the company has presented data only for AEs occurring within 30 days after treatment discontinuation. In both studies, AEs were followed up for up to 6 weeks, however, and even randomized patients who discontinued the study medication early continued to be observed and followed up for a maximum of 6 weeks after study end. An appropriate assessment of side effects would require data from the studies' entire follow-up periods.
  - The survey of SAEs and discontinuation due to AEs apparently included a large number of events associated with the symptoms of disease or comorbidities (e.g. myocardial infarction, heart failure in DAPA-CKD and heart failure in DAPA-HF). The company excluded as disease-related events only renal events which were identified in the predefined survey of the AESI renal events and listed in the study report. However, an adequate assessment of side effects would also require an analysis of the total rates of SAEs and discontinuation due to AEs excluding disease-related events due to comorbidities (such as heart failure). All in all, the available total rates of SAEs and discontinuations due to AEs are unusable in the present situation and have therefore been disregarded in this benefit assessment.
  - For this benefit assessment, the AEs of genital infection and urinary tract infection are of special interest. The company's dossier analyses the AE of genital infection as an

AE of special interest (AESI) and reports that events on this AESI were obtained from the study report rather than having been surveyed directly. However, the study protocols do not list AEs belonging to the complexes of genital infection and urinary tract infections as AESIs. It thus seems safe to assume that non-serious AEs have not been surveyed fully. In this indication, however, primarily non-serious genital infections and urinary tract infections would be expected since they were found to be significantly more common in previous studies on SGLT-2. Therefore, the data on the AEs of genital infections and urinary tract infections are not usable.
The consequences of this approach are described in Section 2.4.2.

2.4.2 Risk of bias

Table 12 presents the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias at study and outcome levels – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy

Study	Outcomes													
	Study level	All-cause mortality	ESRD[a]	Hospitalization for heart failure	Myocardial infarction[b]	Stroke[b]	Health status (EQ-5D VAS)	Health-related quality of life (KDQOL-36)	SAEs	Discontinuation due to AEs	Genital infections (AEs)[c]	Urinary tract infections (PT, AEs)	Diabetic ketoacidosis (AEs)[d]	Further specific AEs
DAPA-CKD	L	L	L	L	L	L	L	–[e]	–[f]	–[f]	–[g]	–[g]	L	–[h]
DAPA-HF	L	L	L	L	L	L	–[i]	–[j]	–[f]	–[f]	–[g]	–[g]	L	–[h]

a. ESRD comprises confirmed sustained eGFR < 15 mL/min/1.73 m^2 or chronic dialysis treatment, or receipt of a renal transplant.
b. Fatal and non-fatal events.
c. Events for the AESI of genital infections listed by the company in the study report.
d. Probable and definite diabetic ketoacidosis adjudicated by an outcome committee were analysed.
e. Data unusable; it is unclear how many patients were actually being followed up at Month 36 and included in Month 36 analyses.
f. High percentage of disease-related events (see Section 2.4.1). Disease-related events were disregarded only if the company had surveyed them for the predefined AESI of renal events.
g. No usable data due to incomplete survey. Non-serious AEs were surveyed only if they had led to treatment discontinuation or dose modification or been included in a selection of AEs predefined by the company. Genital infections and urinary tract infections were not included in the AEs predefined by the company and are particularly relevant as non-serious AEs.
h. No further specific AEs other than disease-related AEs were identified.
i. The outcome was surveyed, but the dossier contains no results for the relevant subpopulation.
j. Outcome not surveyed.

AE: adverse event; AESI: AE of special interest; eGFR: estimated glomerular filtration rate: ESRD: end-stage renal disease; KDQOL: Kidney Disease Quality of Life; L: low; PT: preferred term; RCT: randomized controlled study; SAE: serious adverse event; VAS: visual analogue scale

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

Summary assessment of the certainty of results

On the basis of the single study DAPA-CKD and the DAPA-HF study's CKD subpopulation, the present benefit assessment can initially derive only indications, e.g. of an added benefit. However, various aspects further reduce the certainty of results of the available studies DAPA-CKD and DAPA-HF for the benefit assessment.

As far as the present benefit assessment is concerned, it seems safe to assume that the implementation of the ACT (as in optimized standard therapy), as used for the concomitant

treatment of CKD and comorbidities during the DAPA-CKD and DAPA-HF studies, was not all-encompassing. This reasoning results from the lack of information on treatment optimization in the course of the study. Further, side effects cannot be fully assessed because (1) the survey of SAEs and discontinuation due to AEs included a large number of the events associated with disease symptoms or comorbidities, (2) data on non-serious AEs were missing, and (3) data on AEs are not available for the full follow-up period.

Due to these limitations, the results of the individual studies can be used to derive at most hints, e.g. of an added benefit, for all outcomes. For patients with heart failure as an additional comorbidity, it is also unclear to what extent effects on patient-relevant outcomes are impacted by the potentially insufficient percentage of patients who were switched to sacubitril/valsartan therapy (only from the comparator arm according to the new recommendations of the National Disease Management Guideline version 3 [23]) or the fact that SGLT-2 inhibitors were disallowed. Since all patients in the DAPA-HF study exhibited symptomatic, chronic heart failure, it is impossible to quantify the effects on the individual outcomes for the DAPA-HF study's CKD subpopulation. In the DAPA-CKD study, in contrast, only 11% of the study population exhibited heart failure. Therefore, potentially insufficient treatment with sacubitril/valsartan for patients with heart failure is unlikely to affect the overall results of the DAPA-CKD study to a meaningful extent. Due to their differing percentages of patients with symptomatic chronic heart failure, conclusions, e.g. on added benefit, are drawn separately for the DAPA-CKD participants and the DAPA-HF study's CKD subpopulation. Another argument in favour of separate analyses is provided by the fact that all patients in the DAPA-CKD study exhibited albuminuria (≥ 200 mg/g), with half of them having a UACR of >1000 mg/g. Since the DAPA-HF study did not survey UACR, the CKD subpopulation of the DAPA-HF study was selected based on eGFR (eGFR < 60 mL/min/1.73 m^2). Consequently, subgroup analyses by albuminuria category (e.g. microalbuminuria or macroalbuminuria) cannot be conducted for the DAPA-HF study's CKD subpopulation.

This departs from the company's assessment, which, based primarily on the DAPA-CKD study, derived proof of major added benefit of dapagliflozin in comparison with the optimized standard therapy for CKD patients. Results from the IPD metaanalysis of the DAPA-CKD, DAPA-HF, and DECLARE-TIMI 58 studies are used as supplementary information in the company's derivation of added benefit. The company justifies the derivation of proof by claiming that the DAPA-CKD study fulfils the requirements stipulated in General Methods version 6.0 for inferring proof on the basis of only 1 study. Inferring proof on the basis of only 1 study is permissible only in exceptional cases and is subject to specific conditions [1]: The study must be multicentric, including ≥ 10 centres and at least 1000 patients in each study arm. The effect estimates observed must have very small p-values (p <0.001). Further, the results must be consistent within the study. The analysis of relevant subpopulations must in each case provide evaluable and sufficiently homogeneous effect estimates. The analyses for subpopulations must be available for all relevant outcomes. It is unclear whether DAPA-CKD fulfils all criteria. Firstly, the company did not submit adequate data for sufficiently

substantiating the consistency of effect estimates for the different subpopulations in all relevant outcomes. Secondly, the results on health-related quality of life (KDQOL-36) are unusable. In the present situation, no conclusions can therefore be drawn on the consistency of results.

2.4.3 Results

Table 13 and Table 14 summarize the results for the comparison of dapagliflozin + optimized standard therapy versus placebo + standard therapy in CKD patients. The results of the DAPA-CKD study and those of the DAPA-HF study's CKD subpopulation are used separately for deriving conclusions, e.g. regarding added benefit (for the reasoning, see Section 2.4.2). Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier. Kaplan-Meier curves for the included outcomes are presented in Appendix B of the full dossier assessment, and results on common AEs, SAEs, and discontinuation due to AEs are presented in Appendix C of the full dossier assessment.

Table 13: Results (mortality, morbidity, health-related quality of life, time to event) – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Outcome category Outcome Study	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]
Mortality					
All-cause mortality					
DAPA-CKD	2152	ND 101 (4.7)	2152	ND 146 (6.8)	0.69 [0.53; 0.89]; 0.003[a]
DAPA-HF[b]	962	ND 143 (14.9)	964	ND 168 (17.4)	0.85 [0.68; 1.07]; 0.162[c]
Morbidity					
ESRD[d]					
DAPA-CKD	2152	ND 109 (5.1)	2152	ND 161 (7.5)	0.64 [0.51; 0.82] < 0.001[a]
DAPA-HF[b]	962	ND 13 (1.4)	964	ND 8 (0.8)	1.64 [0.68; 3.97]; 0.264[c]
Confirmed sustained eGFR < 15 mL/min/1.73 m^2 as an individual component of ESRD					
DAPA-CKD	2152	ND 84 (3.9)	2152	ND 120 (5.6)	0.67 [0.51; 0.88]; 0.004[a]
DAPA-HF[b]	962	ND 1 (0.1)	964	ND 0 (0)	NC
Chronic dialysis treatment as an individual component of ESRD					
DAPA-CKD	2152	ND 68 (3.2)	2152	ND 99 (4.6)	0.66 [0.49; 0.90]; 0.008[a]
DAPA-HF[b]	962	ND 13 (1.4)	964	ND 8 (0.8)	1.64 [0.68; 3.96]; 0.265[c]
Receipt of a renal transplant as an individual component of ESRD					
DAPA-CKD	2152	ND 3 (0.1)	2152	ND 8 (0.4)	0.35 [0.09; 1.32]; 0.105[a]
DAPA-HF[b]	962	ND 0 (0)	964	ND 0 (0)	–

Table 13: Results (mortality, morbidity, health-related quality of life, time to event) – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Outcome category Outcome Study	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]
Renal morbidity (composite outcome)[e] (presented as supplementary information)					
DAPA-CKD	2152	ND 142 (6.6)	2152	ND 243 (11.3)	0.56 [0.45; 0.68]; < 0.001[a]
DAPA-HF[b]	962	ND 18 (1.9)	964	ND 19 (2.0)	0.96 [0.50; 1.82]; 0.893[c]
Confirmed ≥ 50% sustained decline in eGFR					
DAPA-CKD	2152	ND 112 (5.2)	2152	ND 201 (9.3)	0.53 [0.42; 0.67]; < 0.001[a]
DAPA-HF[b]	962	ND 7 (0.7)	964	ND 10 (1.0)	0.70 [0.27; 1.85]; 0.476[c]
Renal death					
DAPA-CKD	2152	ND 2 (0.1)	2152	ND 6 (0.3)	0.34 [0.07; 1.70]; 0.170[a]
DAPA-HF[b]	962	ND 0 (0)	964	ND 1 (0.1)	NC
Hospitalization for heart failure					
DAPA-CKD	2152	ND 37 (1.7)	2152	ND 71 (3.3)	0.51 [0.34; 0.76]; < 0.001[a]
DAPA-HF[b]	962	ND 118 (12.3)	964	ND 168 (17.4)	0.68 [0.54; 0.86]; 0.001[c]
Myocardial infarction[g]					
DAPA-CKD	2152	ND 40 (1.9)	2152	ND 37 (1.7)	1.07 [0.69; 1.68]; 0.761[a]
DAPA-HF[b]	962	ND 22 (2.3)	964	ND 21 (2.2)	1.06 [0.58; 1.93]; 0.842[c]
Stroke[g]					
DAPA-CKD	2152	ND 43 (2.0)	2152	ND 43 (2.0)	0.99 [0.65; 1.51]; 0.967[a]
DAPA-HF[b]	962	ND 22 (2.3)	964	ND 23 (2.4)	0.95 [0.53; 1.70]; 0.860[c]

Table 13: Results (mortality, morbidity, health-related quality of life, time to event) – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Outcome category Outcome Study	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]
Health-related quality of life					
KDQOL-36					
DAPA-CKD	No usable data[h]				
DAPA-HF[b]	Outcome not surveyed				

a. HR, CI, and p-value: Cox proportional hazards model with the randomization strata T2DM at baseline (yes vs. no) and UACR (≤ 1000 mg/g vs. > 1000 mg/g) as factors and baseline eGFR as covariable.
b. CKD subpopulation of patients with eGFR< 60 mL/min/1.73 m^2.
c. HR, CI, and p-value: Cox proportional hazards model taking into account treatment arm, stratified by T2DM at randomization (yes vs. no) and adjusted using baseline eGFR.
d. Defined as confirmed sustained eGFR < 15 mL/min/1.73 m^2 or chronic dialysis treatment, or receipt of a renal transplant.
e. The composite outcome includes confirmed ≥ 50% sustained decline in eGFR and renal death.
f. Both studies classified deaths for unknown causes as cardiovascular deaths, but not as renal deaths.
g. Fatal and nonfatal events.
h. It is unclear how many patients were actually being followed up at Month 36 and included in Month 36 analyses.

CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; HR: hazard ratio; KDQOL: Kidney Disease Quality of Life; N: number of analysed patients; n: number of patients with (at least 1) event; ND: no data; NR: not reached; RCT: randomized controlled trial; T2DM: type 2 diabetes mellitus

Table 14: Results (morbidity, side effects, dichotomous) – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Outcome category Outcome Study	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
Morbidity					
Health status (EQ-5D VAS)[a]					
DAPA-CKD	2152	523 (24.3)	2152	595 (27.6)	0.88 [0.79; 0.97]; 0.012[b]
DAPA-HF[c]	No usable data[d]				
Side effects					
AEs (supplementary information)					
DAPA-CKD	Outcome not surveyed[e]				
DAPA-HF[c]	Outcome not surveyed[e]				
SAEs					
DAPA-CKD	No usable data[f]				
DAPA-HF[c]					
Discontinuation due to AEs					
DAPA-CKD	No usable data[f]				
DAPA-HF[c]					
Genital infections (AEs)					
DAPA-CKD	No usable data[e]				
DAPA-HF[c]					
Urinary tract infections (PT, AEs)					
DAPA-CKD	No usable data[e]				
DAPA-HF[c]					
Diabetic ketoacidosis (AEs)[g]					
DAPA-CKD	2149	0 (0)	2149	2 (0.1)	0.20 [0.01; 4.16][h]; 0.212[i]
DAPA-HF[c]	960	0 (0)	962	0 (0)	–

Table 14: Results (morbidity, side effects, dichotomous) – RCT, direct comparison: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Outcome category Outcome Study	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. Percentage of patients with a score decrease by ≥ 15 points from baseline, given a scale range of 0 to 100. Lower (decreasing) values indicate a deterioration of symptoms. b. Effect estimate and p-value from its logistic regression; adjusted for baseline value. c. CKD subpopulation of patients with eGFR< 60 mL/min/1.73 m^2. d. No information available for the relevant subpopulation. e. Non-serious AEs were surveyed only if they led to treatment discontinuation or dose modification or if they belonged to a selection of AEs predefined by the company. f. High percentage of disease-related events (see Section 2.4.1). Disease-related events were excluded only if listed in a predefined PT list on the AESI renal events. g. Probable and definite diabetic ketoacidosis adjudicated by an outcome committee were analysed. h. For the calculation of effect estimates, a correction factor of 0.5 was used because there were 0 events in 1 study arm. i. IQWiG calculation, unconditional exact test (CSZ method according to [26]). AE: adverse event; CI: confidence interval; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; n: number of patients with (at least 1) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale					

Based on the available information, at most hints, e.g. of an added benefit, can be derived for all outcomes.

Mortality

The outcome of all-cause mortality represents mortality irrespective of cause of death and therefore provides a more comprehensive picture than the outcomes of cardiovascular death or renal death. Therefore, the outcome of all-cause mortality was relied on to derive added benefit.

All-cause mortality

The DAPA-CKD study shows a statistically significant effect in favour of dapagliflozin + optimized standard therapy for the outcome of all-cause mortality. No statistically significant difference between treatment groups was found for the DAPA-HF study's CKD subpopulation. For the DAPA-CKD study population, this results in a hint of added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. Added benefit has not been proven for the DAPA-HF study's CKD subpopulation.

Morbidity

ESRD

For the composite outcome of ESRD, defined as sustained eGFR < 15 mL/min/1.73 m^2, chronic dialysis treatment, or receipt of a renal transplant, a statistically significant effect in favour of dapagliflozin + optimized standard therapy was found. No statistically significant difference between treatment groups was found for the DAPA-HF study's CKD subpopulation. For the DAPA-CKD study population, this results in a hint of added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. Added benefit has not been proven for the DAPA-HF study's CKD subpopulation.

Hospitalization for heart failure

Both for the DAPA-CKD study and for the DAPA-HF study's CKD subpopulation, a statistically significant effect in favour of dapagliflozin + optimized standard therapy was found for the outcome of hospitalization for heart failure. For both the DAPA-CKD study population and the DAPA-HF study's CKD subpopulation, this results in a hint of added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Myocardial infarction, stroke

Neither the DAPA-CKD study nor the DAPA-HF study's CKD subpopulation showed any statistically significant difference between treatment groups for the outcomes of myocardial infarction or stroke. For these outcomes, this results in no hint of added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for these outcomes.

Health status (EQ-5D VAS)

For the outcome of health status, operationalized as deterioration of EQ-5D VAS by 15 points, the company presented data only from the DAPA-CKD study, despite the fact that this outcome was also surveyed in the DAPA-HF study. Regarding this outcome, the DAPA-CKD study showed a statistically significant advantage in favour of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. However, the effect for this outcome of the non-serious/non-severe symptoms / late complications category is no more than marginal. An added benefit is therefore not proven. Similarly, added benefit has not been proven for the DAPA-HF study's CKD subpopulation.

Health-related quality of life

For the outcome category of health-related quality of life, no usable data are available (see Section 2.4.1). This results in no hint of added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy. An added benefit is therefore not proven for this outcome.

Side effects

SAEs, discontinuation due to AEs

The studies included a large number of disease-related events in their recording of SAEs and discontinuation due to AEs (see Section 2.4.1). While the company also calculated SAEs and discontinuation due to AEs excluding renal events, AEs representing symptoms of the underlying illness or comorbidities are still included in the overall rates. The results for individual common AEs (e.g. myocardial infarction and heart failure in DAPA-CKD; heart failure in DAPA-HF) therefore show similar advantages of dapagliflozin as the morbidity results. Consequently, the total rates of SAEs and discontinuation due to AEs are unusable for assessing the side effects of dapagliflozin. Based on the results on common SAEs and discontinuation due to AEs (see Appendix C of the full dossier assessment), however, no unfavourable effects of dapagliflozin of an extent that might call into question the added benefit of dapagliflozin are expected. Consequently, for the outcomes of SAEs and discontinuation due to AEs, there is no hint of greater or lesser harm of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

Genital infection, urinary tract infection

No usable data are available on the outcomes of genital infection and urinary tract infection because the studies did not systematically identify non-serious AEs, and the events of interest are known to largely belong to the category of non-serious side effects (see Section 2.4.1).

Diabetic ketoacidosis

For the outcome of diabetic ketoacidosis, neither the DAPA-CKD study nor the DAPA-HF study's CKD subpopulation exhibit any statistically significant differences between treatment groups. Consequently, there is no hint of greater or lesser harm of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

2.4.4 Subgroups and other effect modifiers

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

- Age (≤ 65 versus > 65)
- Sex (male versus female)
- Baseline type 2 diabetes mellitus (yes versus no)
- Severity of kidney disease (GFR < 45 versus ≥ 45)

Further subgroup characteristics of interest would be albuminuria (e.g. with a cutoff UACR: 30 mg/g or 300 mg/g) and heart failure at baseline (yes versus no). However, the company submitted only subgroup analyses with a UACR cutoff of 1000 mg/g for the DAPA-CKD study. UACR levels were not surveyed in the DAPA-HF study. The potential influence of the attribute of heart failure on study results is analysed by the separate consideration of the DAPA-CKD study and the DAPA-HF study's CKD subpopulation.

Interaction tests were performed whenever at least 10 patients per subgroup were included in the analysis. For binary data, there must also be 10 events in at least 1 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.

To perform subgroup analyses with binary operationalizations, the company uses the Breslow-Day Test for homogeneity of the odds ratios (ORs). However, a test for subgroup effects regarding the effect measure of relative risk (RR) would be required instead. The subgroup analyses for the binary outcomes are not usable because, depending on what the effect measure is used for, the results regarding an effect modification can be interpreted differently. The statistical method employed for event-time analyses has not been described. Hence, no usable subgroup analyses are available for any relevant outcomes in the dossier.

2.5 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are presented below. The various outcome categories and the effect sizes have been taken into account. The methods used for this purpose are explained in the IQWiG General Methods [1].

The approach for deriving an overall conclusion on any added benefit by aggregating the conclusions reached at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.1 Assessment of added benefit at outcome level

On the basis of the results presented in Section 2.4, the extent of the respective added benefit at outcome level was estimated (see Table 15).

Determination of the outcome category for symptom outcomes

For the symptoms outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. The allocation of these outcomes is explained below.

ESRD, hospitalization for heart failure

Outcomes which are fatal or require hospitalization are deemed severe/serious. Therefore, the outcomes of ESRD and hospitalization for heart failure are allocated to the outcome category of serious/severe symptoms / late complications.

Health status (EQ-5D VAS)

For the outcome of health status as measured using EQ-5D VAS, none of the data available for the allocation of severity would justify rating it as serious. Therefore, this outcome is allocated to the outcome category of non-serious/non-severe symptoms / late complications.

Table 15: Extent of added benefit at outcome level: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Outcome category **Outcome** **Study** **Effect modifier** **Subgroup**	**Dapagliflozin + optimized standard therapy vs. optimized standard therapy** **or event rate (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality		
DAPA-CKD	ND vs. ND HR: 0.69 [0.53; 0.89] p = 0.003 Probability: hint	Outcome category: mortality $0.85 \leq CI_u < 0.95$ Added benefit; extent: considerable
DAPA-HF	ND vs. ND HR: 0.85 [0.68; 1.07] p = 0.162	Lesser/added benefit not proven
Morbidity		
ESRD[c]		
DAPA-CKD	ND vs. ND HR: 0.64 [0.51; 0.82] p < 0.001 Probability: hint	Outcome category: serious/severe symptoms / late complications $0.75 \leq CI_u < 0.90$ Added benefit; extent: considerable
DAPA-HF	ND vs. ND HR: 1.64 [0.68; 3.97] p = 0.264	Lesser/added benefit not proven
Hospitalization for heart failure		
DAPA-CKD	ND vs. ND HR: 0.51 [0.34; 0.76] p < 0.001 Probability: hint	Outcome category: serious/severe symptoms / late complications $0.75 \leq CI_u < 0.90$ Added benefit; extent: considerable
DAPA-HF	ND vs. ND HR: 0.68 [0.54; 0.86] p = 0.001 Probability: hint	Outcome category: serious/severe symptoms / late complications Added benefit, extent: nonquantifiable
Myocardial infarction		
DAPA-CKD	ND vs. ND HR: 1.07 [0.69; 1.68] p = 0.761	Lesser/added benefit not proven
DAPA-HF	ND vs. ND HR: 1.06 [0.58; 1.93]; p = 0.842	Lesser/added benefit not proven

Table 15: Extent of added benefit at outcome level: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Outcome category **Outcome** **Study** **Effect modifier** **Subgroup**	**Dapagliflozin + optimized standard therapy vs. optimized standard therapy** **or event rate (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Stroke		
DAPA-CKD	ND vs. ND HR: 0.99 [0.65; 1.51] p = 0.967	Lesser/added benefit not proven
DAPA-HF	ND vs. ND HR: 0.95 [0.53; 1.70] p = 0.860	Lesser/added benefit not proven
Health status (EQ-5D VAS)		
DAPA-CKD	24.3% vs. 27.6% RR: 0.88 [0.79; 0.97] p = 0.012	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[d]
DAPA-HF	No usable data[e]	Lesser/added benefit not proven
Health-related quality of life		
Health-related quality of life (KDQOL-36)		
DAPA-CKD	No usable data[f]	Lesser/added benefit not proven
DAPA-HF	Outcome not surveyed	Lesser/added benefit not proven
Side effects		
SAEs		
DAPA-CKD	No usable data[g]	Greater/lesser harm not proven
DAPA-HF		
Discontinuation due to AEs		
DAPA-CKD	No usable data[g]	Greater/lesser harm not proven
DAPA-HF		
Genital infections (AEs)		
DAPA-CKD	No usable data[h]	Greater/lesser harm not proven
DAPA-HF		

Table 15: Extent of added benefit at outcome level: dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy (multipage table)

Outcome category **Outcome** **Study** **Effect modifier** **Subgroup**	**Dapagliflozin + optimized standard therapy vs. optimized standard therapy** **or event rate (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Urinary tract infections (PT, AEs)		
DAPA-CKD	No usable data[h]	Greater/lesser harm not proven
DAPA-HF		
Diabetic ketoacidoses (AEs)		
DAPA-CKD	0.0% vs. 0.1% RR: 0.20 [0.01; 4.16] p = 0.212	Greater/lesser harm not proven
DAPA-HF	0.0% vs. 0.0% -	

a. Probability is stated whenever a statistically significant and relevant effect is present.
b. For the DAPA-CKD study, estimations of effect size are made depending on the outcome category, with different limits based on the upper confidence limit (CI_u). No quantifiable assessments of effect size are possible on the basis of the DAPA-HF study's CDK subpopulation (see Section 2.4.2).
c. Defined as confirmed sustained eGFR < 15 mL/min/1.73 m^2, chronic dialysis treatment, or receipt of a renal transplant.
d. The extent of the effect is no more than marginal for this non-serious/non-severe outcome.
e. No information is available for the relevant subpopulation.
f. It is unclear how many patients were actually being followed up at Month 36 and included in Month 36 analyses.
g. High percentage of disease-related events (see Section 2.4.1).
h. Incomplete survey. Non-serious AEs were surveyed only if they led to treatment discontinuation or dose modification or were included in a selection of AEs predefined by the company. Genital infections and urinary tract infections were not included in the selection of AEs predefined by the company and are particularly relevant as non-serious AEs.

AE: adverse event; CI: confidence interval; CI_u: upper confidence limit; KDQOL: Kidney Disease Quality of Life 36; RR: relative risk; SAE: serious adverse event

2.5.2 Overall conclusion on added benefit

Table 16 summarizes the results which were factored into the overall conclusion on the extent of added benefit.

Table 16: Favourable and unfavourable effects from the assessment of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy

Favourable effects	Unfavourable effects
DAPA-CKD	
Mortality ▪ All-cause mortality ▫ Hint of added benefit – extent: considerable	–
Morbidity ▪ ESRD ▫ Hint of added benefit – extent: considerable ▪ Hospitalization for heart failure ▫ Hint of added benefit – extent: considerable	–
CKD subpopulation of DAPA-HF	
Morbidity ▪ Hospitalization for heart failure ▫ Hint of added benefit – extent: non-quantifiable	–
Neither of the included studies provides any usable data on health-related quality of life outcomes. Non-serious AEs were not systematically surveyed in DAPA-CKD or DAPA-HF. Data on SAEs and discontinuation due to AEs cannot be quantitatively interpreted.	
AE: adverse event; ESRD: end-stage renal disease; SAE: serious adverse event	

DAPA-CKD

Overall, for patients with CKD (eGFR ≥ 25 to ≤ 75 mL/min/1.73 m^2 and albuminuria [UACR ≥ 200 to ≤ 5000 mg/g]) without the comorbidity of symptomatic chronic heart failure, exclusively favourable effects of dapagliflozin were found in comparison with optimized standard therapy. The effects were found for all-cause mortality and the outcomes of ESRD and hospitalization for heart failure. The favourable effect for the outcome of ESRD is supported by the results of the renal morbidity outcome, which was presented as supplementary information. No usable data are available for outcomes on health-related quality of life and the overall rates of AEs. On the basis of the available information on side effects, however, no unfavourable effects of an extent which might call into question an added benefit are expected.

In summary, for patients with CKD without the comorbidity of symptomatic, chronic heart failure, there is a hint of considerable added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

CKD subpopulation of the DAPA-HF study

Overall, for patients with CKD (eGFR < 60 mL/min/1.73 m^2 irrespective of albuminuria since the study did not collect data on UACR) and the additional comorbidity of symptomatic, chronic heart failure, there is 1 favourable effect of dapagliflozin in comparison with optimized standard therapy. Regarding the outcome of hospitalization for heart failure, a hint of non-quantifiable added benefit of dapagliflozin + optimized standard therapy was found for the DAPA-HF study's CKD subpopulation. No usable data are available for outcomes on health-

related quality of life and the overall rates of AEs. On the basis of the available information on side effects, however, no unfavourable effects of an extent which might call into question an added benefit are expected.

In summary, for patients with CKD and the additional comorbidity of symptomatic, chronic heart failure, there is a hint of non-quantifiable added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Table 17 presents a summary of the results of the benefit assessment of dapagliflozin in comparison with the ACT.

Table 17: Dapagliflozin – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adults with CKD		
Without symptomatic chronic heart failure as a comorbidity	Optimized standard therapy for CKD taking into account the underlying illness and common comorbidities (such as diabetes mellitus, hypertension, dyslipoproteinaemia, anaemia) and sequelae	Hint of considerable added benefit[b]
With additional symptomatic chronic heart failure as a comorbidity		Hint of non-quantifiable added benefit[c]

a. Presented is the respective ACT specified by the G-BA.
b. The conclusion on added benefit is based on the results of the DAPA-CKD study. DAPA-CKD included patients with eGFR ≥ 25 to ≤ 75 mL/min/1.73 m^2 and albuminuria (UACR ≥ 200 to ≤ 5000 mg/g). It remains unclear whether the observed effects can be extrapolated to other patients in the target population. Only 11% of the patients showed heart failure at enrolment.
c. The conclusion on added benefit is based on the results of the DAPA-HF study's CKD subpopulation. The DAPA-HF study's CKD subpopulation included patients with symptomatic chronic heart failure involving reduced ejection fraction and an eGFR < 60 mL/min/1.73 m^2, irrespective of albuminuria (UACR data are not available from the study). It remains unclear whether the observed effects can be extrapolated to other patients in the target population.

ACT: appropriate comparator therapy; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; G-BA: Federal Joint Committee; UACR: urine albumin–creatinine ratio

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

The approach for deriving an overall conclusion on 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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