Dapagliflozin
(heart failure with LVEF > 40%)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

- Bernd Niemann, German Society for Thoracic and Cardiovascular Surgery, University Hospital of Giessen and Marburg, Justus Liebig University of Giessen, Clinic for Cardiac, Paediatric Cardiac and Vascular Surgery, Giessen, Germany.

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Patient and family involvement

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

IQWiG employees involved in the dossier assessment

- Caroline Wöhl
- Nadia Abu Rajab
- Katharina Frangen
- Tatjana Hermanns
- Lisa Junge
- Michaela Florina Kerekes
- Jona Lilienthal
- Daniela Preukschat

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CHD	coronary heart disease
CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLP-1	glucagon-like peptide
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KCCQ	Kansas City Cardiomyopathy Questionnaire
LOCF	last observation carried forward
LVEF	left ventricular ejection fraction
NT-proBNP	N-terminal pro-brain natriuretic peptides
NVL	National Care Guideline
NYHA	New York Heart Association
OSS	overall summary score
PGIS	Patient Global Impression of Severity
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGLT	sodium-glucose cotransporter
SPC	System Organ Class
SPC	Summary of Product Characteristics
T2DM	type 2 diabetes mellitus
TSS	total symptom score
VAS	visual analogue scale

I 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 February 2023.

Research question

The aim of the present report is to assess the added benefit of dapagliflozin in comparison with optimized standard therapy as appropriate comparator therapy (ACT) in patients with symptomatic chronic heart failure with left ventricular ejection fraction (LVEF) > 40%.

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

Table 2: Research question of the benefit assessment of dapagliflozin

Therapeutic indication	**ACT**[a]
Adults with symptomatic chronic heart failure with LVEF > 40%[b]	Optimized standard therapy for the treatment of symptomatic chronic heart failure with LVEF > 40% and underlying medical conditions, e.g. hypertension, cardiac arrhythmias, coronary heart disease, diabetes mellitus, chronic kidney disease, dyslipoproteinaemias, and concomitant symptoms[c]
a. Presented is the ACT specified by the G-BA. b. This includes HFpEF, defined as heart failure with LVEF > 50%, and HFmrEF, defined as heart failure with LVEF > 40 to 49%. c. It is assumed that dapagliflozin is administered in addition to standard therapy for the treatment of symptomatic chronic heart failure with HFpEF and HFmrEF, and that patients in both study arms receive optimal treatment: Guideline-compliant individualized treatment of heart failure and underlying conditions or risk factors such as hypertension, cardiac arrhythmias, renal disorder, dyslipoproteinaemias, or diabetes mellitus, as well as of concomitant symptoms, e.g. oedema, is assumed. It should be possible to adapt the foundational/concomitant medication to the patient's individual needs in both study arms. Unchanged continuation of an inadequate therapy does not concur with the ACT. If there is no further possibility for optimization, it has to be documented and explained that any other existing treatment options are unsuitable or have been exhausted. G-BA: Federal Joint Committee; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction	

As ACT, the company named optimized standard therapy for the treatment of the underlying medical conditions, e.g. hypertension, cardiac arrhythmias, coronary heart disease (CHD), diabetes mellitus, hypercholesterolaemia and concomitant symptoms, to reduce cardiovascular risk. This wording corresponds to the original specification of the ACT by the

G-BA from 2019. The G-BA adjusted the wording of the ACT in 2023. The assessment of the added benefit is conducted in comparison with the updated ACT of the G-BA from 2023.

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

Study pool and study design

The DELIVER study is used to assess the added benefit of dapagliflozin in comparison with optimized standard therapy for the treatment of patients with symptomatic chronic heart failure with LVEF > 40%.

The DELIVER study is a double-blind, placebo-controlled RCT. It included adult patients with symptomatic heart failure of New York Heart Association (NYHA) classes II through IV with LVEF > 40%. Patients could be ambulatory or hospitalized, had to have predefined elevation in N-terminal pro-brain natriuretic peptides (NT-proBNP) and structural heart disease (left atrial enlargement and/or left ventricular hypertrophy).

A total of 6263 patients were included in the DELIVER study and randomly allocated in a 1:1 ratio either to treatment with dapagliflozin (N = 3131) or to placebo (N = 3132). Treatment with dapagliflozin was in compliance with the specifications of the Summary of Product Characteristics (SPC).

Primary outcome of the study was the composite outcome of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit. Furthermore, patient-relevant outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Inclusion criteria led to limited study population

In addition to LVEF > 40% and structural heart disease, an inclusion criterion for patients in the DELIVER study was elevated NT-proBNP at screening:

- ≥ 300 pg/mL for patients without ongoing atrial fibrillation or flutter
- ≥ 600 pg/mL for patients with ongoing atrial fibrillation or flutter

However, according to the current National Care Guideline (NVL) on chronic heart failure, the threshold required to meet the diagnostic criteria for heart failure with LVEF > 40% is already exceeded at an NT-proBNP level > 125 pg/mL. Patients in the present therapeutic indication with NT-proBNP levels between 125 pg/mL and 300 pg/mL were therefore not included in the DELIVER study. The higher threshold values of the NT-proBNP in the inclusion criteria led to a selection of the study population: About 32% of all patients who participated in the screening

were not included because the NT-proBNP values were too low. It is therefore unclear whether the observed effects in the DELIVER study can be transferred to all patients with heart failure with LVEF > 40%, and whether the study population fully represents the target population in the German health care context.

Implementation of the appropriate comparator therapy

With empagliflozin, a sodium-glucose cotransporter 2 (SGLT 2) inhibitor, an effective specific therapy has been approved for the treatment of symptomatic chronic heart failure with LVEF > 40%, and the G-BA has derived an added benefit for this drug. Also, the use of SGLT-2 inhibitors has gained importance in the treatment of the underlying conditions type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD).

With regard to the underlying conditions, such as hypertension, T2DM and CKD, the study population of the DELIVER study is a heterogeneous population. The drug treatment of the underlying conditions carried out as background therapy is of particular importance in the assessment of the implementation of the ACT. Uncertainties remain regarding the extent to which an optimal control of blood pressure and lipid levels could be achieved in the patients during the course of the study. In addition, the G-BA's ACT was not implemented for all subpopulations that could be delineated on the basis of the underlying diseases T2DM and CKD:

Patients without T2DM and without CKD

According to the 2022 update of the American College of Cardiology and American Heart Association guideline, SGLT-2 inhibitors should be considered for the treatment of heart failure in patients in the present therapeutic indication. This recommendation is based on the RCT EMPEROR-Preserved, which was used by the G-BA in September 2022 to determine a hint of minor added benefit for empagliflozin. However, empagliflozin is not yet included as a treatment option for patients with chronic heart failure with LVEF > 40% in the current versions of the NVL on chronic heart failure and the European Society of Cardiology (ESC) guideline on acute and chronic heart failure. It is unclear to what extent the use of SGLT-2 inhibitors (empagliflozin) for the treatment of chronic heart failure with LVEF > 40% has already found its way into the German health care context. Uncertainties therefore exist with regard to the implementation of the ACT in patients of subpopulation 1.

Patients without T2DM and with CKD

Half of the patients enrolled in the EMPEROR-Preserved study on empagliflozin, based on which the G-BA derived an added benefit (see above), were patients with CKD, defined as estimated glomerular filtration rate (eGFR) of < 60 mL/min/1.73 m². Therefore, due to the prohibition of SGLT-2 inhibitors – except for the study drug (dapagliflozin) in the intervention arm – the same uncertainties with regard to the implementation of the ACT exist as for

patients of subpopulation 1, as the heart failure could not be optimally treated according to new findings.

Patients with T2DM and with CKD

The NVL for T2DM recommends treatment with metformin in combination with an SGLT-2 inhibitor or a glucagon-like peptide (GLP-1) receptor agonist (e.g. liraglutide) for patients with T2DM and clinically relevant cardiovascular disease if drug therapy is indicated. However, as described in dossier assessment A21-109, there is only limited evidence for the treatment of T2DM with SGLT-2 inhibitors or GLP-1 receptor agonists in patients with concomitant CKD. This is due to the fact that the studies underlying these recommendations included mainly patients without CKD. However, the EMPEROR-Preserved study on empagliflozin (see above) included patients with and without T2DM as well as patients with and without CKD. The same uncertainties exist in the implementation of the ACT in subpopulation 3 as for subpopulations 1 and 2 due to the general prohibition of SGLT-2 inhibitors in the comparator arm.

Patients with T2DM and without CKD

The NVL for T2DM recommends treatment with metformin in combination with an SGLT-2 inhibitor or a GLP-1 receptor agonist for patients with T2DM and clinically relevant cardiovascular disease if drug therapy is indicated. For patients with T2DM and without concomitant CKD, there is thus a clear therapeutic indication for SGLT-2 inhibitors or GLP-1 receptor agonists. However, therapy with SGLT-2 inhibitors, with the exception of the study drug dapagliflozin in the intervention arm, was generally not allowed. Although therapy with GLP-1 receptor agonists was possible, it was hardly carried out. Thus, the ACT for subpopulation 4 was not implemented in the DELIVER study.

Summary on the appropriate comparator therapy

In summary, the implementation of the ACT specified by the G-BA in the DELIVER study is unclear for subpopulations 1 to 3 described above, as uncertainties exist due to the lack of use of SGLT-2 inhibitors for the treatment of heart failure. Due to this uncertainty, no more than hints, e.g. of an added benefit, can be derived for subpopulations 1 to 3. As the ACT was not implemented for subpopulation 4 (lack of use of SGLT-2 inhibitors for the treatment of T2DM), it is not possible to derive an added benefit for this subpopulation.

Furthermore, it is not clear from the presented analyses of the company how large the subpopulations 1 to 4 are, so that the proportion of patients in the total population with unclear implementation of the ACT is unknown. Despite this limitation, the total population of the DELIVER study is used for the benefit assessment. The consideration of the total population is justified below, and the consequences for the certainty of conclusions of the study are described.

Rationale for considering the total population of the DELIVER study

It is unclear how large the 4 subpopulations described above are in comparison with the total population, as no corresponding analyses of the subpopulations are available. It is therefore not possible to determine the exact proportion of the total population of the DELIVER study for which the ACT was implemented unclearly or not implemented.

Due to the pathogenesis of CKD, a relevant overlap of patients with T2DM and CKD can be assumed. This means that subpopulation 4 (T2DM without CKD), in which the ACT was not implemented, represents with sufficient certainty only a relatively small proportion of the total population of the DELIVER study. In addition, a subgroup analysis for patients with and without T2DM is available in the company's dossier. This shows that the results of the subgroup analysis for the characteristic of T2DM are sufficiently consistent with the results of the total population. Thus, the observed effects in the total population cannot be caused to an important degree by the only small proportion of patients from subpopulation 4 in whom the ACT was not implemented. Since this subgroup analysis does not call into question the observed effects in the total population for the assessment of the relevant subpopulations 1 to 3, the total population is used to derive the added benefit despite the uncertainties described. However, the extent of the observed effects in the total population cannot be quantified due to the unclear size of the subpopulations.

Risk of bias

The risk of bias across outcomes for the DELIVER study is rated as low. The outcome-specific risk of bias is rated as low, with the exception of the following outcomes: health status (recorded using the EQ-5D visual analogue scale [VAS] and Patient Global Impression of Severity [PGIS]) and health-related quality of life (recorded using the Kansas City Cardiomyopathy Questionnaire [KCCQ] overall summary score [OSS]).

Summary assessment of the certainty of conclusions

In the present benefit assessment, no more than indications, e.g. of an added benefit, can initially be derived on the basis of the single DELIVER study. However, there are various aspects that reduce the certainty of conclusions of the DELIVER study.

For subpopulations 1 to 3 (without T2DM and without CKD as well as with/without T2DM and with CKD), at most hints, e.g. of an added benefit, can be derived from the results of the total population due to the described uncertainties in the implementation of the ACT in these subpopulations.

Although the sizes of the individual subpopulations with unclear or missing implementation of the ACT are unknown, the total population of the DELIVER study is used to derive the added benefit. However, the extent of the observed effects in the total population cannot be

quantified due to the unclear size of the subpopulations. No suitable data are available for subpopulation 4 (T2DM without CKD) due to the lack of implementation of the ACT in this subpopulation. On the basis of the DELIVER study, no added benefit can therefore be derived for patients in subpopulation 4.

Results

Mortality

All-cause mortality

No statistically significant difference between treatment groups was shown for the outcome of all-cause mortality. There is no hint of added benefit of dapagliflozin + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

Morbidity

Severe heart failure events

A statistically significant difference in favour of dapagliflozin + optimized standard therapy was shown for the outcome of severe heart failure events (operationalized as hospitalization for heart failure). There is a hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Myocardial infarction

For the composite outcome of myocardial infarction, consisting of nonfatal myocardial infarction and fatal myocardial infarction, as well as for the individual component of fatal myocardial infarction, there was no statistically significant difference between the treatment groups. No results are available for the individual component of nonfatal myocardial infarction. There is no hint of added benefit of dapagliflozin + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

Stroke

For the composite outcome of stroke, consisting of nonfatal stroke and fatal stroke, as well as for the individual component of fatal stroke, there was no statistically significant difference between the treatment groups. No results are available for the individual component of nonfatal stroke. There is no hint of added benefit of dapagliflozin + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

Renal morbidity

No suitable data are available for the outcome of renal morbidity. There is no hint of added benefit of dapagliflozin + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

Health status

EQ-5D VAS

For the outcome of health status (surveyed using the EQ-5D VAS), no statistically significant difference between treatment groups was found. There is no hint of added benefit of dapagliflozin + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

PGIS

For the outcome of health status (surveyed using the PGIS), a statistically significant difference was found in favour of dapagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy. This difference was no more than marginal, however. There is no hint of added benefit of dapagliflozin + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

Health-related quality of life

KCCQ OSS

For the outcome of health-related quality of life (surveyed using the KCCQ OSS), a statistically significant difference was found in favour of dapagliflozin + optimized standard therapy. There is a hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Side effects

SAEs

For the outcome of serious adverse events (SAEs), no statistically significant difference between treatment groups was found. There is no hint of greater or lesser harm from dapagliflozin + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

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

Specific AEs

Urinary tract infection (AEs), genital infection (AEs)

No suitable data are available for the outcomes of urinary tract infection (AEs) and genital infection (AEs), as non-serious AEs were not systematically recorded in the study and it is known that the majority of these events belong to the category of non-serious side effects.

There is no hint of greater or lesser harm from dapagliflozin + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

Diabetic ketoacidosis

No statistically significant difference between treatment groups was shown for the outcome of diabetic ketoacidosis. There is no hint of greater or lesser harm from dapagliflozin + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

Gastrointestinal disorders (SAEs)

For the outcome of gastrointestinal disorders (SAEs), a statistically significant difference was found in favour of dapagliflozin + optimized standard therapy. There is a hint of lesser harm from dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

COVID-19 (SAEs)

For the outcome of COVID-19 (SAEs), a statistically significant difference was found to the disadvantage of dapagliflozin + optimized standard therapy. There is a hint of greater harm from dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

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

As explained in the sections above, the DELIVER study included patients who differed in terms of their underlying conditions. In some of the patients, the ACT was not implemented. The added benefit is therefore derived separately for the subpopulations with unclear or missing implementation of the ACT, in each case on the basis of the results of the total population of the DELIVER study.

Based on the results presented, probability and extent of the added benefit of the drug dapagliflozin in comparison with the ACT are assessed as follows:

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

Patients with heart failure with LVEF > 40% without T2DM and without CKD as well as with/without T2DM and with CKD

For patients with symptomatic chronic heart failure with LVEF > 40% without T2DM and without CKD as well as with/without T2DM and with CKD, several positive effects and one negative effect were shown for dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

On the positive effects side, there are hints of a non-quantifiable added benefit in the category of serious/severe symptoms/late complications for the outcome of severe heart failure events (operationalized as hospitalization for heart failure) and in the outcome category of health-related quality of life of health-related quality of life. In addition, there is a hint of lesser harm of non-quantifiable extent in the outcome category of serious/severe side effects on the basis of specific AEs (gastrointestinal disorders).

These positive effects are accompanied by a side effects outcome (COVID-19, extent non-quantifiable) on the side of negative effects. Overall, the positive effects outweigh the negative ones.

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

Patients with heart failure with LVEF > 40% with T2DM without CKD

There is no hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with the ACT in the form of optimized standard therapy for patients with symptomatic chronic heart failure with LVEF > 40% with T2DM, but without CKD. An added benefit for these patients is therefore not proven.

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

Table 3: Dapagliflozin – probability and extent of added benefit

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

a. Presented is the ACT specified by the G-BA.
b. This includes HFpEF, defined as heart failure with LVEF > 50%, and HFmrEF, defined as heart failure with LVEF > 40 to 49%.
c. The conclusion on added benefit is based on the results of the DELIVER study. For study inclusion, patients had to exceed certain NT-proBNP thresholds: ≥ 300 pg/mL for patients without ongoing atrial fibrillation/flutter or ≥ 600 pg/mL for patients with ongoing atrial fibrillation/flutter. It remains unclear whether the observed effects can be transferred to other patients in the target population.

CKD: chronic kidney disease; G-BA: Federal Joint Committee; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal prohormone B-type natriuretic peptide; T2DM: type 2 diabetes mellitus

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

I 2 Research question

The aim of the present report is to assess the added benefit of dapagliflozin in comparison with optimized standard therapy as ACT in patients with symptomatic chronic heart failure with LVEF > 40%.

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

Table 4: Research question of the benefit assessment of dapagliflozin

Therapeutic indication	**ACT**[a]
Adults with symptomatic chronic heart failure with LVEF > 40%[b]	Optimized standard therapy for the treatment of symptomatic chronic heart failure with LVEF > 40% and underlying medical conditions, e.g. hypertension, cardiac arrhythmias, coronary heart disease, diabetes mellitus, chronic kidney disease, dyslipoproteinaemias, and concomitant symptoms[c]
a. Presented is the ACT specified by the G-BA. b. This includes HFpEF, defined as heart failure with LVEF > 50%, and HFmrEF, defined as heart failure with LVEF > 40 to 49%. c. It is assumed that dapagliflozin is administered in addition to standard therapy for the treatment of symptomatic chronic heart failure with HFpEF and HFmrEF, and that patients in both study arms receive optimal treatment: Guideline-compliant individualized treatment of heart failure and underlying conditions or risk factors such as hypertension, cardiac arrhythmias, renal disorder, dyslipoproteinaemias, or diabetes mellitus, as well as of concomitant symptoms, e.g. oedema, is assumed. It should be possible to adapt the foundational/concomitant medication to the patient's individual needs in both study arms. Unchanged continuation of an inadequate therapy does not concur with the ACT. If there is no further possibility for optimization, it has to be documented and explained that any other existing treatment options are unsuitable or have been exhausted. G-BA: Federal Joint Committee; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction	

As ACT, the company named optimized standard therapy for the treatment of the underlying medical conditions, e.g. hypertension, cardiac arrhythmias, CHD, diabetes mellitus, hypercholesterolaemia and concomitant symptoms, to reduce cardiovascular risk. This wording corresponds to the original specification of the ACT by the G-BA from 2019. The G-BA adjusted the wording of the ACT in 2023. The assessment of the added benefit is conducted in comparison with the updated ACT of the G-BA from 2023 [3]. A detailed discussion of the implementation of the ACT is provided in Section I 3.2.

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

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on dapagliflozin (status: 16 December 2022)
- bibliographical literature search on dapagliflozin (last search on 16 December 2022)
- search in trial registries/trial results databases for studies on dapagliflozin (last search on 16 December 2022)
- search on the G-BA website for dapagliflozin (last search on 21 December 2022)

To check the completeness of the study pool:

- search in trial registries for studies on dapagliflozin (last search on 20 March 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

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

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

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
D169CC00001 (DELIVER[c])	Yes	Yes	No	Yes [4]	Yes [5-7]	Yes [8-10]

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. 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 concurs with that of the company.

I 3.2 Study characteristics

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
DELIVER	RCT, double-blind, parallel	Adult patients (≥ 40 years) with symptomatic heart failure (NYHA classes II–IV) and LVEF > 40%[b]	Dapagliflozin + optimized standard therapy (N = 3131) Placebo + optimized standard therapy (N = 3132)	▪ Screening: up to 21 days ▪ Treatment/ observation: event-driven study: study closure visit up to 6 weeks after 1117 events in the primary outcome	353 study centres in: Argentina, Belgium, Brazil, Bulgaria, Canada, China, Czech Republic, Hungary, Japan, Mexico, Netherlands, Peru, Poland, Romania, Russia, Saudi Arabia, Spain, Taiwan, USA, Vietnam 8/2018–3/2022	Primary: composite outcome of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit Secondary: overall survival, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Heart failure with a history of typical symptoms and/or signs ≥ 6 weeks before enrolment, with at least intermittent treatment with diuretics, and fulfilling the following criteria:
- evidence of structural heart disease (left atrial enlargement and/or left ventricular hypertrophy) documented by the most recent imaging assessment (echocardiogram or cardiac MRI) within the last 12 months prior to enrolment; for patients with prior acute cardiac events or procedures that may reduce LVEF (e.g. myocardial infarction, unstable angina pectoris, coronary revascularization), imaging assessment ≥ 12 weeks following the event or procedure was required
- elevated NT-proBNP levels at enrolment: ≥ 300 pg/mL for patients without atrial fibrillation/flutter, ≥ 600 pg/mL for patients with atrial fibrillation/flutter

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

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

Study	Intervention	Comparison
DELIVER	Dapagliflozin 10 mg once daily, orally + optimized standard therapy	Placebo once daily, orally + optimized standard therapy
	Dose adjustments ▪ dose interruptions were allowed in case of risk or actual occurrence of volume depletion, hypotension, unexpected deterioration of renal functioning or suspected diabetic ketoacidosis[a] **Allowed prior and concomitant treatment** ▪ treatment of heart failure and comorbidities (e.g. hypertension, ischaemic heart disease, atrial fibrillation, diabetes, hyperlipidaemia) according to local guidelines ▪ adjustment of concomitant antidiabetic medication, e.g. to achieve glycaemic targets of the ADA and EASD joint position paper [11,12], individually for each patient as required by the investigator or the treating physician ▪ other drugs at the discretion of the investigator, if clinically indicated **Prohibited prior and concomitant treatment** ▪ drug infusion therapy (including diuretics) for heart failure within 12 hours before enrolment and 24 hours before randomization ▪ any SGLT-2 inhibitors or fixed combinations with SGLT-2 inhibitors (other than the blinded study medication) ≤ 4 weeks before enrolment and during the study[b] ▪ coronary revascularization, ablation of atrial fibrillation/flutter, valve repair/replacement within 12 weeks before enrolment or during the study ▪ elective CRT implant during the study ▪ previous cardiac transplantation	

a. If a diagnosis of diabetic ketoacidosis was confirmed by the investigator, the study medication was to be discontinued.
b. If treatment with an SGLT-2 inhibitor as monotherapy/combination therapy was deemed necessary, the study medication had to have been interrupted or discontinued before the start of treatment.

ADA: American Diabetes Association; CRT: cardiac resynchronization therapy; EASD: European Association for the Study of Diabetes; RCT: randomized controlled trial; SGLT: sodium-glucose cotransporter

The DELIVER study is a double-blind, placebo-controlled RCT. It included adult patients with symptomatic heart failure of NYHA classes II through IV with LVEF > 40%. Patients could be ambulatory or hospitalized, had to have predefined elevation in NT-proBNP (see below for a detailed description of this inclusion criterion) and structural heart disease (left atrial enlargement and/or left ventricular hypertrophy). Patients with heart failure due to cardiomyopathy (infiltrative, genetic hypertrophic, or obstructive hypertrophic), arrhythmogenic right ventricular cardiomyopathy/dysplasia, active myocarditis, constrictive pericarditis, cardiac tamponade, or uncorrected primary valvular disease were excluded. In addition, patients with type 1 diabetes mellitus or eGFR < 25 mL/min/1.73 m² at the time of randomization were excluded from the study.

A total of 6263 patients were included in the DELIVER study and randomly allocated in a 1:1 ratio either to treatment with dapagliflozin (N = 3131) or to placebo (N = 3132). Randomization was stratified by T2DM (yes versus no).

Treatment with dapagliflozin was in compliance with the recommendations of the SPC [13]. According to the study protocol, all patients had to be treated according to local guideline-recommended therapy for heart failure and comorbidities. Adjustments to the therapy were possible in the course of the study.

The DELIVER study was event-driven and was ended after 1117 events of the primary outcome. After the required number of events was reached, patients were invited to a study closure visit within 6 weeks. Treatment with the study medication was continued until this visit. Patients who discontinued the study medication prematurely had a visit as soon as possible after the last dose and were asked to continue attending all scheduled visits, including the study closure visit, until the end of the study, if possible.

Primary outcome of the study was the composite outcome of cardiovascular death, hospitalization for heart failure, and urgent heart failure visit. Furthermore, patient-relevant outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Inclusion criteria led to limited study population

In addition to LVEF > 40% and structural heart disease, an inclusion criterion for patients in the DELIVER study was elevated NT-proBNP at screening:

- ≥ 300 pg/mL for patients without ongoing atrial fibrillation or flutter
- ≥ 600 pg/mL for patients with ongoing atrial fibrillation or flutter

However, according to the current NVL on chronic heart failure, the threshold required to meet the diagnostic criteria for heart failure with LVEF > 40% is already exceeded at an NT-proBNP level > 125 pg/mL [14]. Patients in the present therapeutic indication with NT-proBNP levels between 125 pg/mL and 300 pg/mL were therefore not included in the DELIVER study. The higher threshold values of the NT-proBNP in the inclusion criteria led to a selection of the study population: About 32% of all patients who participated in the screening were not included because the NT-proBNP values were too low. It is therefore unclear whether the observed effects in the DELIVER study can be transferred to all patients with heart failure with LVEF > 40%, and whether the study population fully represents the target population in the German health care context.

Table 8 shows the patient characteristics of the included study.

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

Study Characteristic Category	**Dapagliflozin + optimized standard therapy N[a] = 3131**	**Placebo + optimized standard therapy N[a] = 3132**
DELIVER		
Age [years], mean (SD)	72 (10)	72 (10)
Sex [F/M], %	44/56	44/56
Family origin, n (%)		
White	2214 (71)	2225 (71)
Black/African American	81 (3)	78 (3)
Asian	630 (20)	644 (21)
Indo-Americans or native Alaskans	93 (3)	96 (3)
Other	113 (4)	89 (3)
Region, n (%)		
Asia	607 (19)	619 (20)
Europe/Saudi Arabia	1494 (48)	1511 (48)
North America	428 (14)	423 (14)
Latin America	602 (19)	579 (19)
LVEF [%]		
Mean (SD)	54.0 (8.6)	54.3 (8.9)
≤ 40, n (%)	3 (< 1)	1 (< 1)
≥ 41 to 49, n (%)	1064 (34)	1048 (34)
≥ 50 to 59, n (%)	1133 (36)	1123 (36)
≥ 60, n (%)	931 (30)	960 (31)
NT-proBNP[b] [pg/mL], median [Q1; Q3]	1021 [625; 1777]	1005 [620; 1735]
NYHA class[b], n (%)		
I	0	1 (< 1)
II	2314 (74)	2399 (77)
III	807 (26)	724 (23)
IV	10 (< 1)	8 (< 1)
History of hospitalization for heart failure, n (%)	1270 (41)	1269 (41)
Systolic blood pressure[b] [mmHg]		
Mean (SD)	128.2 (15.4)	128.2 (15.3)
Median [min; max]	128.0 [91; 207]	128.0 [90; 179]
Diastolic blood pressure[b] [mmHg]		
Mean (SD)	73.9 (10.3)	74.0 (10.4)
Median [min; max]	74.0 [35; 113]	74.0 [35; 123]
Atrial fibrillation or flutter[c], n (%)	1327 (42)	1317 (42)

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

Study Characteristic Category	**Dapagliflozin + optimized standard therapy N[a] = 3131**	**Placebo + optimized standard therapy N[a] = 3132**
eGFR (CKD-EPI)[b] [mL/min/1.73 m^2]		
Mean (SD)	61.2 (19.0)	60.9 (19.3)
Median [Q1; Q3]	60.0 [47.0; 75.0]	60.0 [46.0; 75.0]
≥ 60, n (%)	1615 (52)	1577 (50)
45 to < 60, n (%)	826 (26)	831 (27)
30 to < 45, n (%)	599 (19)	622 (20)
25 to < 30, n (%)	89 (3)	99 (3)
< 25, n (%)	2 (< 1)	2 (< 1)
Serum creatinine[b] [µmol/L]		
Mean (SD)	102.3 (31.2)	102.7 (30.9)
Median [min; max]	96.4 [29; 251]	97.2 [34; 253]
Type 2 diabetes mellitus, n (%)	1401 (45)	1405 (45)
HbA1c[b] [%]		
Mean (SD)	6.59 (1.42)	6.58 (1.39)
Median [min; max]	6.20 [4.2; 17.2]	6.10 [4.2; 15.3]
Dyslipidaemia, n (%)	ND	ND
Treatment discontinuation, n (%)[d]	444 (14)	442 (14)
Study discontinuation, n (%)	ND	ND

a. Number of randomized patients.
b. Last measurement before first dose of study medication.
c. According to ECG at enrolment.
d. Common reasons for treatment discontinuation in the intervention vs. control arm were: patient decision (7.7% vs. 7.7%), AEs (5.8% vs. 5.7%).

AE: adverse event; CKD-EPI: chronic kidney disease epidemiology collaboration equation; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; F: female; HbA1c: glycosylated haemoglobin; LVEF: left ventricular ejection fraction; M: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized patients; ND: no data; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

Patient characteristics were sufficiently balanced between the treatment groups. The mean age of the patients was 72 years; the majority of them were male (56%), and most were from Europe or Saudi Arabia (48%). About 1 third of the patients had an LVEF < 50%, about 2 thirds had an LVEF ≥ 50%. 45% of patients had T2DM at enrolment, and about half had CKD, defined as an eGFR of < 60 mL/min/1.73 m². The extent to which the subpopulations with T2DM and CKD overlap is unclear. 75% of the patients showed mild limitation of physical activity due to

heart failure (NYHA class II), 24% showed moderate limitation (NYHA class III) and < 1% showed severe limitation (NYHA class IV). In both study arms, about 14% of the patients discontinued treatment prematurely.

Implementation of the appropriate comparator therapy

With empagliflozin, an effective specific therapy has been approved for the treatment of symptomatic chronic heart failure with LVEF > 40%, and the G-BA has derived an added benefit for this drug [15] on the basis of dossier assessment A22-39 [16]. Also, the use of SGLT-2 inhibitors has gained importance in the treatment of the underlying conditions T2DM and CKD [17-21].

In terms of the underlying conditions, such as hypertension, T2DM and CKD, the study population is heterogeneous. In the following, the data submitted by the company on concomitant treatments are presented, the patients are characterized with regard to their underlying conditions, and any deficiencies in the implementation of the ACT in the subpopulations that can be delineated on the basis of the underlying conditions are identified and discussed.

Concomitant treatments in the DELIVER study

In the DELIVER study, all patients had to be treated according to local guideline-recommended therapy for heart failure and comorbidities. Adjustments to therapy were possible during the course of the study, but the use of SGLT-2 inhibitors or fixed combinations with an SGLT-2 inhibitor – with the exception of the study medication dapagliflozin in the intervention arm – was generally not permitted (see Table 7). Their use (in the form of monotherapy/ combination therapy) could only be considered at the discretion of the investigator in the event of a temporary interruption or after discontinuation of the study medication if all other treatment options had been considered and the use was clinically indicated. A total of 62 patients in the intervention arm and 78 patients in the comparator arm received an SGLT-2 inhibitor during the course of the study (see Table 9), of which 20 and 32, respectively, received treatment concurrently with the study medication. Since the use of SGLT-2 inhibitors (empagliflozin) has meanwhile gained importance in the treatment of heart failure, the fundamental lack of the possibility of using this drug class in the implementation of the ACT leads to uncertainties (for further explanations see below). There were no further restrictions in the study regarding concomitant drug treatment.

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

Study Therapy Category	At study start		Dose adjustment after study start		Initiated after study start	
	Dapagliflozin + optimized standard therapy	Placebo + optimized standard therapy	Dapagliflozin + optimized standard therapy	Placebo + optimized standard therapy	Dapagliflozin + optimized standard therapy	Placebo + optimized standard therapy
	N = 3131	N = 3132	N = 3131	N = 3132	N = 3131	N = 3132
DELIVER						
ACE inhibitors/ARBs	2262 (72.2)	2281 (72.8)	335 (14.8)[a]	344 (15.1)[a]	132 (15.2)[b]	170 (20.0)[b]
ARNIs	165 (5.3)	136 (4.3)	38 (23.0)[a]	18 (13.2)[a]	83 (2.8)[b]	126 (4.2)[b]
Beta-blockers	2592 (82.8)	2585 (82.5)	439 (16.9)[a]	465 (18.0)[a]	126 (23.4)[b]	140 (25.6)[b]
Diuretics	2793 (89.2)	2787 (89.0)	688 (24.6)[a]	759 (27.2)[a]	92 (27.2)[b]	136 (39.4)[b]
MRAs	1340 (42.8)	1327 (42.4)	182 (13.6)[a]	181 (13.6)[a]	220 (12.3)[b]	297 (16.5)[b]
Antithrombotics	2708 (86.5)	2731 (87.2)	ND	ND	ND	ND
Vitamin K antagonists	606 (19.4)	608 (19.4)	ND	ND	68 (2.7)[b, c]	64 (2.5)[b, c]
Acetylsalicylic acid	1077 (34.4)	1102 (35.2)	ND	ND	106 (5.2)[b, c]	142 (7.0)[b, c]
Antidiabetics	1194 (38.1)[c]	1208 (38.6)[c]	ND	ND	ND	ND
Insulins	407 (13.0)[c]	436 (13.9)[c]	ND	ND	ND	ND
DPP-4 inhibitors	245 (7.8)[c]	226 (7.2)[c]	ND	ND	66 (2.3)[b, c]	70 (2.4)[b, c]
GLP-1 receptor agonists	34 (1.1)[c]	27 (0.9)[c]	ND	ND	37 (1.2)[b, c]	63 (2.0)[b, c]
SGLT-2 inhibitors[d]	0	0	ND	ND	62 (2.0)	78 (2.5)
Lipid-lowering drugs	2061 (65.8)	2096 (66.9)	ND	ND	ND	ND
Statins	2004 (64.0)	2035 (65.0)	ND	ND	127 (11.3)[b, c]	129 (11.8)[b, c]

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

Study	At study start		Dose adjustment after study start		Initiated after study start	
Therapy Category	Dapagliflozin + optimized standard therapy	Placebo + optimized standard therapy	Dapagliflozin + optimized standard therapy	Placebo + optimized standard therapy	Dapagliflozin + optimized standard therapy	Placebo + optimized standard therapy
	N = 3131	N = 3132	N = 3131	N = 3132	N = 3131	N = 3132

a. The proportion refers to the patients who were treated with a drug of the respective drug class at the start of the study.
b. The proportion refers to the patients who were treated with no drug of the respective drug class at the start of the study.
c. Institute's calculation.
d. The use of SGLT-2 inhibitors, with the exception of the study drug (dapagliflozin) in the intervention arm, was generally not allowed in the DELIVER study. The use of SGLT-2 inhibitors at the discretion of the investigator was only an option in the event of a temporary interruption or after discontinuation of the study medication if all other treatment options had been considered and the use was clinically indicated. However, 20 (0.6%) patients in the intervention arm and 32 (1.0%) patients in the comparator arm received an SGLT-2 inhibitor concurrently with the study medication.

ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; DPP-4: dipeptidyl peptidase 4; GLP-1: glucagon-like peptide 1; MRA: mineralocorticoid receptor antagonist; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SGLT: sodium-glucose cotransporter

In Module 4 A, the company only provided information on the 5 drug classes of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, angiotensin receptor neprilysin inhibitors, beta-blockers, diuretics, and mineralocorticoid receptor antagonists. The data include the number or proportion of patients who received these drug classes at the start of the study and during the course of the study. The company further differentiated between dose adjustment (total, dose increase/reduction) and treatment initiation during the course of the study (see Table 9).

In defining arterial hypertension, the NVL Hypertension guideline group follows the ESC/European Society of Hypertension guideline [22], which specifies a blood pressure target under drug treatment of < 140/90 mmHg. With readings of ≥ 140 mmHg, the systolic blood pressure at the start of the study was thus inadequately controlled in about 22% of the patients. During the course of the study, the systolic blood pressure in both study arms only changed slightly in the third quartile. It can therefore be assumed that the systolic blood pressure of some of the patients was inadequately controlled also during the course of the study.

According to information provided in Module 4 A, dose adjustments and treatment initiations in the drug classes of diuretics and mineral corticoid receptor antagonists were made in both study arms, whereby a larger proportion of patients in the comparator arm started diuretic treatment in the course of the study (see Table 9). In addition, there were slightly more dose adjustments for diuretics in the comparator arm. However, at month 12, when a large proportion of patients were still receiving treatment with the study medication, the mean reduction in body weight was greater in the intervention arm than in the comparator arm (1.11 kg versus 0.04 kg). This was also evident at later time points in the course of the study. It therefore remains unclear whether existing optimization options for diuretic therapy in the comparator arm may not have been exhausted.

With regard to concomitant treatment with drugs that influence lipid metabolism, data are only available for statins both at the start of the study and during the course of the study, which can be used to determine the number or proportion of patients with treatment initiation (see Table 9). The company did not provide any values for lipid parameters at the start of the study or during the course of the study. Overall, it is therefore not possible to conclusively assess whether all patients actually received individually optimized treatment for dyslipidaemias within the framework of the therapy carried out in the study.

It is not clear from the study documents to what extent treatment adjustments were made in drug classes other than those listed in Table 9, as only information according to anatomical-therapeutic-chemical classification is available for all drugs taken during the course of the study, and the company did not summarize this information into drug classes. In addition, with regard to the therapy of the underlying conditions or comorbidities, no information is

available on the drug classes the patients switched to during the course of the study and on the reasons for treatment adjustments.

The following section discusses in detail the partly inadequate therapy of T2DM and CKD in individual subpopulations.

Patient population separated according to the underlying conditions T2DM and CKD

In addition to heart failure with LVEF > 40%, 45% of patients had T2DM at baseline and 49% had CKD, defined as eGFR < 60 mL/min/1.73 m² (see Table 8). Based on these patient characteristics, there are a total of 4 subpopulations in the DELIVER study, which are decisive for the assessment of the implementation of the ACT:

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

Subpopulation 1: patients without T2DM and without CKD

According to the 2022 update of the American College of Cardiology and American Heart Association guideline, SGLT-2 inhibitors should be considered for the treatment of heart failure in patients in the present therapeutic indication [23]. This recommendation is based on the EMPEROR-Preserved study, which was used by the G-BA in September 2022 to determine a hint of minor added benefit for empagliflozin [15]. However, empagliflozin is not yet included as a treatment option for patients with chronic heart failure with LVEF > 40% in the current versions of the NVL on chronic heart failure [14] and the ESC guideline on acute and chronic heart failure [24]. It is unclear to what extent the use of SGLT-2 inhibitors (empagliflozin) for the treatment of chronic heart failure with LVEF > 40% has already found its way into the German health care context. As SGLT-2 inhibitors were prohibited in the DELIVER study – with the exception of the study drug (dapagliflozin) in the intervention arm – there are uncertainties for patients in subpopulation 1 regarding the implementation of the ACT, which are addressed in the certainty of conclusions in Section I 4.2.

Subpopulation 2: patients without T2DM and with CKD

Due to the prohibition of SGLT-2 inhibitors – except for the study drug (dapagliflozin) in the intervention arm – the same uncertainties with regard to the implementation of the ACT exist for patients of subpopulation 2 as for patients of subpopulation 1, since the heart failure (in patients with CKD) could not be optimally treated according to new findings. This is due to the fact that half of the patients enrolled in the EMPEROR-Preserved study on empagliflozin,

based on which the G-BA derived an added benefit (see above), were patients with CKD, defined as eGFR < 60 mL/min/1.73 m².

Subpopulation 3: patients with T2DM and with CKD

The NVL for T2DM recommends treatment with metformin in combination with an SGLT-2 inhibitor or a GLP-1 receptor agonist (e.g. liraglutide) for patients with T2DM and clinically relevant cardiovascular disease if drug therapy is indicated [17]. However, as described in dossier assessment A21-109 [25], there is only limited evidence for the treatment of T2DM with SGLT-2 inhibitors or GLP-1 receptor agonists in patients with concomitant CKD. This is due to the fact that the studies underlying these recommendations (LEADER on liraglutide, EMPA-REG on empagliflozin, DECLARE-TIMI 58 on dapagliflozin) included mainly patients without CKD. The EMPEROR-Preserved study on empagliflozin (see above) included patients with and without T2DM as well as patients with and without CKD. Thus, the same uncertainties exist regarding the implementation of the ACT in subpopulation 3 as for subpopulations 1 and 2 due to the general prohibition of SGLT-2 inhibitors in the comparator arm.

Subpopulation 4: patients with T2DM and without CKD

As described for subpopulation 3, the NVL for T2DM recommends treatment with metformin in combination with an SGLT-2 inhibitor or a GLP-1 receptor agonist for patients with T2DM and clinically relevant cardiovascular disease if drug therapy is indicated [17]. For patients with T2DM and without concomitant CKD, there is thus a clear therapeutic indication for SGLT-2 inhibitors or GLP-1 receptor agonists. However, therapy with SGLT-2 inhibitors, with the exception of the study drug dapagliflozin in the intervention arm, was generally not allowed. Although therapy with GLP-1 receptor agonists was possible, it was hardly carried out. The proportion of patients treated with a GLP-1 receptor agonist (e.g. liraglutide) was less than 3% in both study arms, both at baseline and during the course of the study (see Table 9). Thus, the ACT was not implemented for subpopulation 4 in the DELIVER study.

Summary on the appropriate comparator therapy

In summary, the implementation of the ACT specified by the G-BA in the DELIVER study is unclear for subpopulations 1 to 3 described above, as uncertainties exist due to the lack of use of SGLT-2 inhibitors for the treatment of heart failure. Due to this uncertainty, no more than hints, e.g. of an added benefit, can be derived for subpopulations 1 to 3. As the ACT was not implemented for subpopulation 4 (lack of use of SGLT-2 inhibitors for the treatment of T2DM), it is not possible to derive an added benefit for this subpopulation.

It is not clear from the presented analyses of the company how large the subpopulations 1 to 4 are, so that the proportion of patients in the total population with unclear implementation of the ACT is unknown. Despite this limitation, the total population of the DELIVER study is used for the benefit assessment. The consideration of the total population is justified below,

and the consequences for the certainty of conclusions of the study are described. A summary of the certainty of conclusions can be found in Section I 4.2.

Rationale for considering the total population of the DELIVER study

It is unclear how large the 4 subpopulations described above are in comparison with the total population, as no corresponding analyses of the subpopulations are available. It is therefore not possible to determine the exact proportion of the total population of the DELIVER study for which the ACT was implemented unclearly or not implemented.

As explained in dossier assessment A22-39 [16], a relevant overlap of patients with T2DM and CKD can be assumed due to the pathogenesis of CKD. This means that subpopulation 4 (T2DM without CKD), in which the ACT was not implemented, represents with sufficient certainty only a relatively small proportion of the total population of the DELIVER study. In addition, a subgroup analysis for patients with and without T2DM is available in the company's dossier. This shows that the results of the subgroup analysis for the characteristic of T2DM are sufficiently consistent with the results of the total population (see I Appendix E of the full dossier assessment). Thus, the observed effects in the total population cannot be caused to an important degree by the only small proportion of patients from subpopulation 4 in whom the ACT was not implemented. Since this subgroup analysis does not call into question the observed effects in the total population for the assessment of the relevant subpopulations 1 to 3, the total population is used to derive the added benefit despite the uncertainties described. However, the extent of the observed effects in the total population cannot be quantified due to the unclear size of the subpopulations.

Duration of treatment and follow-up observation

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

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

Study **Duration of the study phase** **Outcome category**	**Dapagliflozin + optimized standard therapy** **N = 3131**	**Placebo + optimized standard therapy** **N = 3132**
DELIVER[a]		
Treatment duration [months]		
Median [Q1; Q3]	26.9 [17.5; 33.2]	27.0 [17.5; 33.2]
Mean (SD)	24.7 (10.6)	24.7 (10.4)
Observation period [months][b]		
Mortality, morbidity, health-related quality of life, side effects		
Median [min; max]	28.5 [0.5; 42.2]	28.4 [0.1; 42.0]
Mean (SD)	27.3 (ND)	27.2 (ND)

a. Data at the study closure visit.
b. The observation period is calculated on the basis of the observed time until death, withdrawal of consent, or the last examination of all patients.

max: maximum; min: minimum; N: number of patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation

Treatment duration and observation period are comparable between the 2 study arms. The median treatment duration was 26.9 months in the intervention arm and 27.0 months in the comparator arm. The median observation period for all outcomes was 28.5 versus 28.4 months.

Risk of bias across outcomes (study level)

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

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

Study	**Adequate random sequence generation**	**Allocation concealment**	**Blinding**		**Reporting independent of the results**	**No additional aspects**	**Risk of bias at study level**
			Patients	**Treating staff**			
DELIVER	Yes	Yes	Yes	Yes	Yes	Yes	Low

RCT: randomized controlled trial

The risk of bias across outcomes for the DELIVER study is rated as low.

Transferability of the study results to the German health care context

The company explained that according to a commissioned health insurance data analysis, the mean age of approx. 71 years of patients with heart failure corresponded quite well to the age of the study population of the DELIVER study. With 44%, the proportion of women in the DELIVER study was very similar the proportion of women in the target population of the health insurance data analysis (42%). Moreover, the company pointed out that about 71% of the patients included in the DELIVER study were of Caucasian origin and that a proportion of 48% came from European countries. Subgroup analyses on the characteristics of age, sex, religion, and family origin had not shown any effect modifications relevant for the conclusion, the company added.

The optimized standard therapy used in both study arms to treat the underlying conditions, such as hypertension, cardiac arrhythmias, CHD, diabetes mellitus, hypercholesterolaemia, as well as the accompanying symptoms to reduce cardiovascular risk, were in line with the recommendations of the current guidelines [14,24], according to the company. The company did not provide any further information on the transferability of the study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - all-cause mortality
- Morbidity
  - severe heart failure events
  - myocardial infarction
  - stroke
  - renal morbidity
  - health status
    - PGIS
    - EQ-5D VAS
- Health-related quality of life
  - KCCQ OSS
- Side effects
  - SAEs
  - discontinuation due to AEs
  - urinary tract infection (PT, AEs)
  - genital infection (PT, AEs)
  - diabetic ketoacidosis
  - further specific AEs, if any

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

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

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

Study	Outcomes												
	All-cause mortality	Severe heart failure events[a]	Myocardial infarction[b]	Stroke[c]	Renal morbidity[d]	Health status (PGIS, EQ-5D VAS)	Health-related quality of life (KCCQ OSS)	SAEs[e]	Discontinuation due to AEs[f]	Urinary tract infection (PT, AEs)	Genital infection (PT, AEs)	Diabetic ketoacidosis[g]	Further specific AEs[h]
DELIVER	Yes	Yes	Yes	Yes	No[i]	Yes	Yes	Yes	Yes	No[j]	No[j]	Yes	Yes

a. Operationalized as hospitalization for heart failure.
b. The composite outcomes comprises nonfatal myocardial infarctions and fatal myocardial infarctions adjudicated by an outcome committee. Myocardial infarctions were recorded as AEs in the DELIVER study.
c. The composite outcomes comprises nonfatal myocardial strokes and fatal strokes adjudicated by an outcome committee. Strokes were recorded as AEs in the DELIVER study.
d. In Module 4 A, the company presented analyses for the following operationalizations for the outcome of renal morbidity:
- confirmed ≥ 50% sustained decline in eGFR
- doubling of serum creatinine level accompanied by an eGFR ≤ 45 mL/min/1.73m^2

e. Without taking into account the following events, defined by the company in Module 4 A as late complications: death from any cause, hospitalization for heart failure, myocardial infarction, stroke, transient ischaemic attack, atrial fibrillation, acute renal failure, and unstable angina pectoris.
f. Including events defined by the company as late complications; in the present data situation, however, the analysis is usable because the disease-related events included in the analysis are not assumed to have a relevant influence on the study results.
g. Analysis of probable and definite diabetic ketoacidoses, adjudicated by an outcome committee.
h. The following events (MedDRA coding) are considered: gastrointestinal disorders (SOC, AEs) and COVID-19 (PT, SAEs).
i. No suitable data; for reasoning, see text below.
j. No suitable data because of incomplete recording; only non-serious AEs were recorded that led to dose reduction/discontinuation/interruption of the study medication, that were potentially also recorded as efficacy outcomes or belonged to a selection of AEs predefined by the company. Urinary tract infections and genital infections were excluded from the selection of AEs predefined by the company; they are primarily relevant as non-serious AEs.

AE: adverse event; COVID-19: coronavirus disease 2019; eGFR: estimated glomerular filtration rate; KCCQ: Kansas City Cardiomyopathy Questionnaire; MedDRA: Medical Dictionary for Regulatory Activities; OSS: overall summary score; PGIS: Patient Global Impression of Severity; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Primary composite outcome

In its present operationalization, the composite outcome on cardiovascular morbidity is not used for the benefit assessment. The composite outcome comprises the components of cardiovascular mortality, hospitalization for heart failure, and urgent heart failure visit. This operationalization is only a limited representation of cardiovascular morbidity, as nonfatal myocardial infarctions and strokes are not covered by this outcome. In contrast, fatal myocardial infarctions and strokes are covered by cardiovascular mortality. Therefore, the primary composite outcome on cardiovascular morbidity is not used for the benefit assessment.

Renal morbidity

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

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

None of the 2 operationalizations is used for the benefit assessment. The company did not specify how "confirmed sustained decline" was defined. Furthermore, a relative decline in eGFR of ≥ 50% is not necessarily patient-relevant due to the high baseline eGFR values in the DELIVER study (see Table 8). Similarly, taking into account the baseline serum creatinine levels (see Table 8), it is not ensured that a doubling of the serum creatinine level accompanied by an eGFR of ≤ 45 mL/min/1.73 m² reflects a tangible deterioration in renal function for all affected patients.

Health status and health-related quality of life

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

- EQ-5D VAS: improvement and deterioration by ≥ 15 points, each at month 8 and at the study closure visit (scale range of EQ-5D VAS: 0 to 100 points)
- KCCQ OSS: improvement and deterioration by ≥ 5 and ≥ 15 points, each at month 8 and at the study closure visit (scale range of KCCQ OSS: 0 to 100 points)
- To analyse improvement or deterioration by ≥ 15 points in the KCCQ OSS, analyses were also carried out in which patients with ≥ 85 points or ≤ 15 points at baseline were considered responders if their scores at the time of the analysis was at least as high or at least as low as at baseline ("ceiling correction").

Since the patients included in the DELIVER study were symptomatic (NYHA class ≥ II) at baseline and additional treatment with dapagliflozin could therefore in principle improve symptoms, the analysis of improvement is considered for both the EQ-5D VAS and the KCCQ OSS. Due to the longer observation period, the data of the study closure visit are used instead of those at the prespecified time point at month 8. In addition, the analyses for the study closure visit show a larger proportion of patients included in the analyses than the analyses at month 8. As explained in the IQWiG *General Methods* [1], for a response criterion to reflect with sufficient certainty a patient-noticeable change, it should correspond to at least 15% of the scale range of an instrument if prespecified (and exactly 15% of the scale range in post-hoc analyses). Accordingly, the results for the improvement by ≥ 15 points (in each case exactly 15% of the scale range) at the study closure visit are used for the derivation of the added benefit for the outcomes of EQ-5D VAS and KCCQ OSS.

It is not clear from the information provided by the company in Module 4 A whether patients were only rated as responders if they showed a score increase of ≥ 15 points at month 8 or at the study closure visit compared with baseline, or if they fulfilled the response criterion at at least one visit up to month 8 or up to the study closure visit. Since the company stated in Appendix 4-G to Module 4 A, in accordance with information in the study documents on predefined responder analyses for the KCCQ total symptom score (KCCQ TSS), that this was an analysis at month 8 or at the study closure visit, it is assumed that this also applies to the responder analyses in Module 4 A, i.e. that patients were only rated as responders if there was a score increase of ≥ 15 points at the study closure visit compared with baseline. Therefore, the responder analyses from Module 4 A are used for the present assessment.

In post-hoc sensitivity analyses for the KCCQ OSS, in addition to patients with a score increase of ≥ 15 points, patients with a sustained high score of ≥ 85 points at baseline and month 8 or at the study closure visit were also considered responders. Since, for example, patients with a score of 90 points at baseline and at the study closure visit were thus considered responders, it is not ensured that this represents a tangible change for all patients included in the analysis. Therefore, the present benefit assessment considers the responder analysis in which only patients with a score increase of ≥ 15 points were taken into account to be an adequate analysis.

Side effects

AEs (independent of severity) were not systematically recorded in the DELIVER study. Only those non-serious AEs were recorded that led to dose reduction or discontinuation/ interruption of the study medication, that were potentially also recorded as efficacy outcomes or belonged to a selection of AEs predefined by the company. The approach of the company is not appropriate. This approach does not enable systematic identification of common, patient-relevant non-serious AEs.

In the dossier, the company did not present an additional analysis for the overall rate of discontinuations due to AEs, which do not take into account the disease-related events defined by the company in Module 4 A (see Table 12). The total rate of discontinuations due to AEs including disease-related events are used in the present benefit assessment because in the present data situation, these events included in the analysis presumably do not have any relevant impact on the study results.

I 4.2 Risk of bias

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

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

Study		Outcomes													
	Study level	All-cause mortality	Severe heart failure events[a]	Myocardial infarction[b]	Stroke[c]	Renal morbidity[d]	Health status (EQ-5D VAS)	Health status (PGIS)	Health-related quality of life (KCCQ OSS)	SAEs[e]	Discontinuation due to AEs[f]	Urinary tract infection (PT, AEs)	Genital infection (PT, AEs)	Diabetic ketoacidosis[g]	Further specific AEs[h]
DELIVER	L	L	L	L	L	–[i]	H[j, k]	H[j]	H[j]	L	L	–[j]	–[j]	L	L

a. Operationalized as hospitalization for heart failure.
b. The composite outcomes comprises nonfatal myocardial infarctions and fatal myocardial infarctions adjudicated by an outcome committee. Myocardial infarctions were recorded as AEs in the DELIVER study.
c. The composite outcomes comprises nonfatal myocardial strokes and fatal strokes adjudicated by an outcome committee. Strokes were recorded as AEs in the DELIVER study.
d. In Module 4 A, the company presented analyses for the following operationalizations for the outcome of renal morbidity:
- confirmed ≥ 50% sustained decline in eGFR
- doubling of serum creatinine level accompanied by an eGFR ≤ 45 mL/min/1.73m^2

e. Without taking into account the following events, defined by the company in Module 4 A as late complications: death from any cause, hospitalization for heart failure, myocardial infarction, stroke, transient ischaemic attack, atrial fibrillation, acute renal failure, and unstable angina pectoris.
f. Including events defined by the company as late complications; in the present data situation, however, the analysis is usable because the disease-related events included in the analysis are not assumed to have a relevant influence on the study results.
g. Analysis of probable and definite diabetic ketoacidoses, adjudicated by an outcome committee.
h. The following events (MedDRA coding) are considered: gastrointestinal disorders (SOC, AEs) and COVID-19 (PT, SAEs).
i. No suitable data; for reasoning, see text below.
j. No suitable data because of incomplete recording; only non-serious AEs were recorded that led to dose reduction/discontinuation/interruption of the study medication, that were potentially also recorded as efficacy outcomes or belonged to a selection of AEs predefined by the company. Urinary tract infections and genital infections were excluded from the selection of AEs predefined by the company; they are primarily relevant as non-serious AEs.

AE: adverse event; COVID-19: coronavirus disease 2019; eGFR: estimated glomerular filtration rate; H: high; KCCQ: Kansas City Cardiomyopathy Questionnaire; L: low; MedDRA: Medical Dictionary for Regulatory Activities; OSS: overall summary score; PGIS: Patient Global Impression of Severity; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias is rated as low, except for the following outcomes: The risk of bias of the results on the outcomes of health status (surveyed using EQ-5D VAS and PGIS) and health-related quality of life (surveyed using KCCQ OSS) is rated as high due to the large proportion of values imputed by last observation carried forward (LOCF). For health status (surveyed using EQ-5D

VAS), the risk bias of the results is also increased due to the large proportion (> 10%) of patients not included in the analysis.

Summary assessment of the certainty of conclusions

In the present benefit assessment, no more than indications, e.g. of an added benefit, can initially be derived on the basis of the single DELIVER study. However, there are various aspects that reduce the certainty of conclusions of the DELIVER study.

As explained in Section I 3.2, no suitable data are available for subpopulation 4 (T2DM without CKD) due to the lack of implementation of the ACT in this subpopulation. On the basis of the DELIVER study, no added benefit can therefore be derived for patients in subpopulation 4. An added benefit is not proven for this subpopulation.

For subpopulations 1 to 3 (without T2DM and without CKD as well as with/without T2DM and with CKD), at most hints, e.g. of an added benefit, can be derived from the results of the total population due to the uncertainties in the implementation of the ACT in these subpopulations described in Section I 3.2.

Although the sizes of the individual subpopulations with unclear or missing implementation of the ACT are unknown (see Section I 3.2), the total population of the DELIVER study is used to derive the added benefit. However, the extent of the observed effects in the total population cannot be quantified due to the existing uncertainties.

I 4.3 Results

Table 14 and Table 15 summarize the results of the comparison of dapagliflozin + optimized standard therapy with placebo + optimized standard therapy in patients with symptomatic chronic heart failure with LVEF > 40%. The present benefit assessment uses the estimate of the effects for the entire treatment strategy, regardless of treatment discontinuation, for all outcomes. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

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

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

Study **Outcome category** **Outcome**	**Dapagliflozin + optimized standard therapy**		**Placebo + optimized standard therapy**		**Dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
DELIVER					
Mortality[b]					
All-cause mortality	3131	ND 497 (15.9)	3132	ND 526 (16.8)	0.94 [0.83; 1.07]; 0.343
Cardiovascular death	3131	ND 231 (7.4)	3132	ND 261 (8.3)	0.88 [0.74; 1.05]; 0.168
Morbidity[b]					
Severe heart failure events (operationalized as hospitalization for heart failure)					
First event	3131	ND 329 (10.5)	3132	ND 418 (13.3)	0.77 [0.67; 0.89]; < 0.001
		Number of events		*Number of events*	*Rate ratio [95% CI]; p-value[c]*
Including repeat events (presented as supplementary information)	*3131*	*508*	*3132*	*707*	*0.72 [0.60; 0.85]; < 0.001*
Myocardial infarction (composite outcome)	3131	ND 83 (2.7)	3132	ND 81 (2.6)	1.02 [0.75; 1.39]; 0.890
Nonfatal	3131	ND	3132	ND	ND
Fatal[d]	3131	ND 12 (0.4)	3132	ND 15 (0.5)	0.80 [0.37; 1.70]; 0.560
Stroke (composite outcome)	3131	ND 115 (3.7)	3132	ND 109 (3.5)	1.05 [0.81; 1.37]; 0.706
Nonfatal	3131	ND	3132	ND	ND
Fatal[d]	3131	ND 28 (0.9)	3132	ND 25 (0.8)	1.12 [0.65; 1.92]; 0.682
Renal morbidity	No suitable data[e]				

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

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

a. Effect, CI and p-value: Cox proportional hazards model stratified by T2DM status at randomization.
b. Includes all events from the first dose of the study medication, regardless of whether the patient was under treatment with the study medication or not when the event occurred.
c. Effect, CI and p-value: Lin-Wei-Yang-Ying proportional rates model, stratified by T2DM status at randomization.
d. Adjudicated by an outcome committee.
e. See Section I 4.1 of the present dossier assessment for the reasoning.

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; T2DM: type 2 diabetes mellitus

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

Study Outcome category Outcome	Dapagliflozin + optimized standard therapy		Placebo + optimized standard therapy		Dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value[b]
DELIVER					
Morbidity[c]					
Health status					
EQ-5D VAS[d]	2498	682 (27.3)	2536	633 (25.0)	1.09 [1.00; 1.20]; 0.059[e]
PGIS[f]	2842	2154 (75.8)	2841	2088 (73.5)	1.03 [1.00; 1.06]; 0.047[e]
Health-related quality of life[c]					
KCCQ OSS[d]	2842	855 (30.1)	2837	769 (27.1)	1.11 [1.02; 1.21]; 0.013[e]
Domains					
Physical limitation	2792	843 (30.2)	2792	747 (26.8)	1.13 [1.04; 1.23]
Psychological quality of life	2842	1147 (40.4)	2837	1053 (37.1)	1.02 [0.99; 1.04]
Social limitation	2669	884 (33.1)	2664	845 (31.7)	1.03 [0.98; 1.09]
Symptoms (KCCQ TSS)	2842	920 (32.4)	2837	857 (30.2)	1.07 [0.99; 1.16]
Side effects[c]					
AEs (supplementary information)	Outcome not recorded[g]				
SAEs[h]	3126	947 (30.3)	3127	975 (31.2)	0.97 [0.90; 1.05]; 0.443
Discontinuation due to AEs[i]	3126	183 (5.9)	3127	181 (5.8)	1.01 [0.83; 1.24]; 0.907
Urinary tract infection (PT, AEs)	No suitable data[g]				
Genital infection (PT, AEs)	No suitable data[g]				
Diabetic ketoacidosis[j] (AEs)	3126	2 (< 0.1)	3127	0	5.00 [0.24; 104.1]; 0.172[k]
Gastrointestinal disorders (SOC, SAEs)	3126	86 (2.8)	3127	147 (4.7)	0.59 [0.45; 0.76]; < 0.001[k]
COVID-19 (PT, SAEs)	3126	183 (5.9)	3127	144 (4.6)	1.27 [1.03; 1.57]; 0.027[k]

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

Study Outcome category Outcome	Dapagliflozin + optimized standard therapy		Placebo + optimized standard therapy		Dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy
	N[a]	Patients with event n (%)	N[a]	Patients with event n (%)	RR [95% CI]; p-value[b]

a. Outcomes in the categories of morbidity and health-related quality of life: number of patients for whom the value at baseline and at least one value after the start of the study were available. Missing values at the study closure visit were imputed using LOCF.
b. Effect, CI and p-value: logistic regression model with log link, adjusted for T2DM status at baseline.
c. Includes all events from the first dose of the study medication, regardless of whether the patient was under treatment with the study medication or not when the event occurred.
d. Improvement at study closure visit; proportion of patients with score increase by ≥ 15 points from baseline at the study closure visit within 6 weeks after the planned number of events of the primary outcome; scale range of 0 to 100, higher (increasing) values indicate an improvement of health status/health-related quality of life.
e. Unadjusted model, due to convergence problems.
f. Stability (no deterioration at the study closure visit); proportion of patients without score increase of ≥ 1 point on a 6-point scale (from 1 “no symptoms” to 6 “very severe symptoms”) between baseline and study closure visit.
g. Only non-serious AEs were recorded that led to dose reduction/discontinuation/interruption of the study medication, that were potentially also recorded as efficacy outcomes or belonged to a selection of AEs predefined by the company.
h. Without taking into account the following events, defined by the company in Module 4 A as late complications: death from any cause, hospitalization for heart failure, myocardial infarction, stroke, transient ischaemic attack, atrial fibrillation, acute renal failure, and unstable angina pectoris.
i. Including events defined by the company as late complications.
j. Analysis of probable and definite diabetic ketoacidoses, adjudicated by an outcome committee.
k. Institute’s calculation, 95% CI asymptotic; unconditional exact test, (CSZ method according to [26]).

AE: adverse event; CI: confidence interval; COVID-19: coronavirus disease 2019; KCCQ: Kansas City Cardiomyopathy Questionnaire; LOCF: last observation carried forward; n: number of patients with (at least one) event; N: number of analysed patients; OSS: overall summary score; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; T2DM: type 2 diabetes mellitus; TSS: total symptom score; VAS: visual analogue scale

Due to the uncertainties described above (see Sections I 3.2 and I 4.2), at most hints, e.g. of added benefit, can be derived on the basis of the available information.

Mortality

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

All-cause mortality

No statistically significant difference between treatment groups was shown for the outcome of all-cause mortality. There is no hint of added benefit of dapagliflozin + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

Morbidity

Severe heart failure events

A statistically significant difference in favour of dapagliflozin + optimized standard therapy was shown for the outcome of severe heart failure events (operationalized as hospitalization for heart failure). There is a hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Myocardial infarction

For the composite outcome of myocardial infarction, consisting of nonfatal myocardial infarction and fatal myocardial infarction, as well as for the individual component of fatal myocardial infarction, there was no statistically significant difference between the treatment groups. No results are available for the individual component of nonfatal myocardial infarction. There is no hint of added benefit of dapagliflozin + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

Stroke

For the composite outcome of stroke, consisting of nonfatal stroke and fatal stroke, as well as for the individual component of fatal stroke, there was no statistically significant difference between the treatment groups. No results are available for the individual component of nonfatal stroke. There is no hint of added benefit of dapagliflozin + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

Renal morbidity

No suitable data are available for the outcome of renal morbidity. See Section I 4.1 of the present dossier assessment for the reasoning. There is no hint of added benefit of dapagliflozin + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

Health status

EQ-5D VAS

For the outcome of health status (surveyed using the EQ-5D VAS), no statistically significant difference between treatment groups was found. There is no hint of added benefit of dapagliflozin + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

PGIS

For the outcome of health status (surveyed using the PGIS), a statistically significant difference was found in favour of dapagliflozin + optimized standard therapy in comparison with placebo + optimized standard therapy. This difference was no more than marginal, however (see Section I 5.1). There is no hint of added benefit of dapagliflozin + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

Health-related quality of life

KCCQ OSS

For the outcome of health-related quality of life (surveyed using the KCCQ OSS), a statistically significant difference was found in favour of dapagliflozin + optimized standard therapy. There is a hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

Side effects

SAEs

For the outcome of SAEs, no statistically significant difference between treatment groups was found. There is no hint of greater or lesser harm from dapagliflozin + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

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

Specific AEs

Urinary tract infection (AEs), genital infection (AEs)

No suitable data are available for the outcomes of urinary tract infection (AEs) and genital infection (AEs), as non-serious AEs were not systematically recorded in the study and it is known that the majority of these events belong to the category of non-serious side effects (see Section I 4.1). There is no hint of greater or lesser harm from dapagliflozin + optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

Diabetic ketoacidosis

No statistically significant difference between treatment groups was shown for the outcome of diabetic ketoacidosis. There is no hint of greater or lesser harm from dapagliflozin +

optimized standard therapy in comparison with optimized standard therapy; greater or lesser harm is therefore not proven.

Gastrointestinal disorders (SAEs)

For the outcome of gastrointestinal disorders (SAEs), a statistically significant difference was found in favour of dapagliflozin + optimized standard therapy. There is a hint of lesser harm from dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

COVID-19 (SAEs)

For the outcome of COVID-19 (SAEs), a statistically significant difference was found to the disadvantage of dapagliflozin + optimized standard therapy. There is a hint of greater harm from dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

I 4.4 Subgroups and other effect modifiers

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

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

The subgroup characteristic of age is not considered in the present benefit assessment, as in the DELIVER study only the median age of the included patients was prespecified as a cut-off value for this subgroup characteristic and is not substantiated in terms of content.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there had to be at least 10 events in at least 1 subgroup.

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

Using the methods described above, the available subgroup results did not show any effect modifications.

I 5 Probability and extent of added benefit

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

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

I 5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section I 4 (see Table 16).

Determination of the outcome category for the morbidity outcomes

For the morbidity outcomes below, it cannot be inferred from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Severe heart failure events

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

Health status (PGIS)

No information is available on the assignment of the severity grade for the outcome of health status (recorded using PGIS) that allows a classification as serious/severe. Therefore, this outcome is assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 16: Extent of added benefit at outcome level: dapagliflozin + optimized standard therapy vs. optimized standard therapy (multipage table)

Outcome category **Outcome**	**Dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	ND vs. ND HR: 0.94 [0.83; 1.07] p = 0.343	Lesser/added benefit not proven
Morbidity		
Severe heart failure events (hospitalization for heart failure)	ND vs. ND HR: 0.77 [0.67; 0.89] p < 0.001 Probability: "hint"	Outcome category: Serious/severe symptoms/late complications Added benefit, extent: "non-quantifiable"
Myocardial infarction	ND vs. ND HR: 1.02 [0.75; 1.39] p = 0.890	Lesser/added benefit not proven
Stroke	ND vs. ND HR: 1.05 [0.81; 1.37] p = 0.706	Lesser/added benefit not proven
Renal morbidity	No suitable data[c]	Lesser/added benefit not proven
Health status		
EQ-5D VAS (improvement by ≥ 15 points)	27.3% vs. 25.0% RR: 1.09 [1.00; 1.20] p = 0.059	Lesser/added benefit not proven
PGIS (no deterioration by ≥ 1 point)	75.8% vs. 73.5% RR: 1.03 [1.00; 1.06] RR: 0.97 [0.94; 1.00][d] p = 0.047	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[e]
Health-related quality of life		
KCCQ OSS (improvement by ≥ 15 points)	30.1% vs. 27.1% RR: 1.11 [1.02; 1.21] RR: 0.90 [0.83; 0.98][d] p = 0.013 Probability: "hint"	Outcome category: Health-related quality of life Added benefit, extent: "non-quantifiable"

Table 16: Extent of added benefit at outcome level: dapagliflozin + optimized standard therapy vs. optimized standard therapy (multipage table)

Outcome category **Outcome**	**Dapagliflozin + optimized standard therapy vs. placebo + optimized standard therapy** **Median time to event (months) or proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	30.3% vs. 31.2% RR: 0.97 [0.90; 1.05] p = 0.443	Greater/lesser harm not proven
Discontinuation due to AEs	5.9% vs. 5.8% RR: 1.01 [0.83; 1.24] p = 0.907	Greater/lesser harm not proven
Urinary tract infection (AEs)	No suitable data[f]	Greater/lesser harm not proven
Genital infection (AEs)	No suitable data[f]	Greater/lesser harm not proven
Diabetic ketoacidosis	< 0.1% vs. 0% RR: 5.00 [0.24; 104.1] p = 0.172	Greater/lesser harm not proven
Gastrointestinal disorders (SAEs)	2.8% vs. 4.7% RR: 0.59 [0.45; 0.76] p < 0.001 Probability: "hint"	Outcome category: serious/severe side effects Lesser harm, extent: "non-quantifiable"
COVID-19 (SAEs)	5.9% vs. 4.6% RR: 1.27 [1.03; 1.57] RR: 0.79 [0.64; 0.97][d] p = 0.027 Probability: "hint"	Outcome category: serious/severe side effects Greater harm, extent: "non-quantifiable"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. No suitable data; for the reasoning, see Section I 4.1 of the present benefit assessment.
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.
e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
f. Incomplete observation; only non-serious AEs were recorded that led to dose reduction/discontinuation/interruption of the study medication, that were potentially also recorded as efficacy outcomes or belonged to a selection of AEs predefined by the company.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; COVID-19: coronavirus disease 2019; HR: hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; ND: no data; OSS: overall summary score; PGIS: Patient Global Impression of Severity; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 17 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of dapagliflozin + optimized standard therapy in comparison with optimized standard therapy

Positive effects	Negative effects
Serious/severe symptoms/late complications ▪ Severe heart failure events (hospitalization for heart failure): hint of an added benefit – extent: "non-quantifiable"	–
Health-related quality of life ▪ KCCQ OSS (improvement by ≥ 15 points): hint of an added benefit – extent: "not quantifiable"	–
Serious/severe side effects ▪ Gastrointestinal disorders (SAEs): hint of lesser harm – extent: "not quantifiable"	Serious/severe side effects COVID-19 (SAEs); hint of greater harm – extent: "not quantifiable"
Non-serious AEs were not systematically recorded in the DELIVER study.	
AE: adverse event; COVID-19: coronavirus disease 2019; KCCQ: Kansas City Cardiomyopathy Questionnaire; OSS: overall summary score; SAE: serious adverse event	

As explained in Sections I 3.2 and I 4.2, the DELIVER study included patients who differed in terms of their underlying conditions. As the ACT was not implemented in some of the patients, the added benefit is derived separately for the subpopulations defined in Section I 3.2, in each case on the basis of the results of the overall population of the DELIVER study.

Patients with heart failure with LVEF > 40% without T2DM and without CKD as well as with/without T2DM and with CKD (concurs with subpopulations 1 to 3)

For patients with symptomatic chronic heart failure with LVEF > 40% without T2DM and without CKD as well as with/without T2DM and with CKD, several positive effects and one negative effect were shown for dapagliflozin + optimized standard therapy in comparison with optimized standard therapy.

On the positive effects side, there are hints of a non-quantifiable added benefit in the category of serious/severe symptoms/late complications for the outcome of severe heart failure events (operationalized as hospitalization for heart failure) and in the outcome category of health-related quality of life of health-related quality of life. In addition, there is a hint of lesser harm of non-quantifiable extent in the outcome category of serious/severe side effects on the basis of specific AEs (gastrointestinal disorders).

These positive effects are accompanied by a side effects outcome (COVID-19, extent non-quantifiable) on the side of negative effects. Overall, the positive effects outweigh the negative ones.

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

Patients with heart failure with LVEF > 40% with T2DM without CKD (concurs with subpopulation 4)

There is no hint of an added benefit of dapagliflozin + optimized standard therapy in comparison with the ACT in the form of optimized standard therapy for patients with symptomatic chronic heart failure with LVEF > 40% with T2DM, but without CKD. An added benefit for these patients is therefore not proven.

The result of the assessment of the added benefit of dapagliflozin in comparison with the ACT is summarized in Table 18.

Table 18: Dapagliflozin – probability and extent of added benefit

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

a. Presented is the ACT specified by the G-BA.
b. This includes HFpEF, defined as heart failure with LVEF > 50%, and HFmrEF, defined as heart failure with LVEF > 40 to 49%.
c. The conclusion on added benefit is based on the results of the DELIVER study. For study inclusion, patients had to exceed certain NT-proBNP thresholds: ≥ 300 pg/mL for patients without ongoing atrial fibrillation/flutter or ≥ 600 pg/mL for patients with ongoing atrial fibrillation/flutter. It remains unclear whether the observed effects can be transferred to other patients in the target population.

CKD: chronic kidney disease; G-BA: Federal Joint Committee; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; LVEF: left ventricular ejection fraction; NT-proBNP: N-terminal prohormone B-type natriuretic peptide; T2DM: type 2 diabetes mellitus

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

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

I 6 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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