IQWiG Reports – Commission No. A21-120

Vericiguat (cardiac failure) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Vericiguat (Herzinsuffizienz) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 December 2021). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

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

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

List of abbreviations

Abbreviation	Meaning
ACE	angiotensin converting enzyme
ACT	appropriate comparator therapy
AE	adverse event
ARB	angiotensin receptor blockers
ARNI	angiotensin receptor neprilysin inhibitors
BNP	brain natriuretic peptide
EPAR	European Public Assessment Report
EQ-5D	European Quality of Life – 5 Dimensions
ESC	European Society of Cardiology
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HbA1c	glycated haemoglobin
HF	heart failure
ICD	Implantable cardioverter-defibrillator
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IV	intravenous
KCCQ	Kansas City Cardiomyopathy Questionnaire
LOCF	last observation carried forward
LVEF	left ventricular ejection fraction
MI	myocardial infarction
MRA	mineralocorticoid receptor antagonists
NT proBNP	N-terminal pro-brain natriuretic peptide
NYHA	New York Heart Association
OSS	overall summary score
PT	preferred term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SGLT-2	sodium dependent glucose transporter 2
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug vericiguat. 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 15 September 2021.

Research question

The aim of the present report was to assess the added benefit of vericiguat in comparison with optimized standard therapy as the appropriate comparator therapy (ACT) for the treatment of symptomatic chronic heart failure (HF) in adult patients with reduced ejection fraction who are stabilized after a recent decompensation event requiring intravenous (IV) therapy.

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 vericiguat

Therapeutic indication	ACT[a]
Symptomatic chronic HF in adult patients with reduced ejection fraction who are stabilized after a recent decompensation event requiring IV therapy	Optimized standard therapy for the treatment of symptomatic chronic HF and underlying medical conditions, e.g. hypertension, cardiac arrhythmia, coronary heart disease, diabetes mellitus, hypercholesterolaemia, and concomitant symptoms[b]

a. Presentation of the respective ACT specified by the G-BA.
b. The patients in both study arms are assumed to have received optimal treatment: guideline-compliant individualized treatment of HF and underlying medical conditions or risk factors such as hypertension, cardiac arrhythmia, or diabetes mellitus as well as the concomitant symptoms, e.g. oedema.
It should have been possible to adapt the baseline/concomitant medication to the patient's individual needs in both study arms.
Unchanged continuation of an inadequate therapy does not concur with the ACT. If there was no further possibility for optimization, it had to be documented and explained that any other existing treatment options were unsuitable or had been exhausted.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HF: heart failure; IV: intravenous

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

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

Results

The VICTORIA study was used to assess the added benefit of vericiguat in comparison with optimized standard therapy for the treatment of symptomatic chronic HF in patients with

reduced ejection fraction who are stabilized after a recent decompensation event requiring IV therapy.

Study design

The VICTORIA study is a placebo-controlled double-blind, randomized parallel-group study on vericiguat. It included patients with chronic HF of New York Heart Association (NYHA) class II through IV whose left ventricular ejection fraction (LVEF) was < 45%. In addition, patients had to exhibit both increased N-terminal pro-brain natriuretic peptide (NT proBNP) or brain natriuretic peptide (BNP) levels and a decompensation event. In the VICTORIA study, this was operationalized as previous hospitalization for HF within 6 months and/or IV diuretic treatment for HF (without hospitalization) within 3 months prior to treatment start.

Patients were to receive adequate drug therapy for HF in accordance with the locally relevant guidelines, at the investigator's discretion, and as tolerated. Therapy was to be individualized, consisting of a combination of the drug classes of angiotensin converting enzyme (ACE), angiotensin receptor blockers (ARB), beta-blockers, oral diuretics, mineralocorticoid receptor antagonists (MRA), and angiotensin receptor neprilysin inhibitors (ARNI). Patients with implantable cardioverter-defibrillators (ICD) or biventricular pacemakers were eligible for inclusion.

Overall, 5050 patients were included in the study and randomly allocated in a 1:1 ratio either to treatment with vericiguat (N = 2526) or to placebo (N = 2524).

With regard to the therapeutic indication of vericiguat, the study's inclusion criteria may diverge from the Summary of Product Characteristics (SPC). Vericiguat is approved for the treatment of symptomatic chronic HF in adult patients with reduced ejection fraction who are stabilized after a recent decompensation event requiring IV therapy. IV therapy was not an explicit inclusion criterion for patients hospitalized due to a decompensation event. However, it is generally safe to assume that patients hospitalized for HF receive IV therapy. The study addressed the requirement of patients having been stabilized after the decompensation event by specifying that the IV therapy had to have been completed for more than 24 hours. A time period of 24 hours seems too short to ensure that patients are stabilized. According to the European Public Assessment Report (EPAR), the company conceded in the approval procedure that not all patients had been clinically stable. Based on the available data, it is impossible to determine to how many patients this applied.

Aside from this issue, the dosage and application of vericiguat was in accordance with the SPC.

The study's primary outcome was the composite outcome of cardiovascular death and hospitalization for HF. Patient-relevant secondary outcomes were all-cause mortality, outcomes of the morbidity and health-related quality of life categories, and adverse events (AEs).

The approval of vericiguat comprises patients with symptomatic chronic HF with reduced LVEF. According to the National Disease Management Guideline, this is defined as LVEF < 40%. The VICTORIA study included patients with LVEF < 45%. The company's dossier presents the results of a subpopulation with LVEF < 40% at baseline (N = 2158 per study arm). This subpopulation is relevant for the benefit assessment and was used.

Implementation of the ACT

The VICTORIA study's implementation of the ACT is subject to some limitations. The main limitation is that, for a majority of patients, not all therapeutic options might have been exhausted or available.

In the VICTORIA study, all patients were to receive individualized therapy in accordance with locally applicable guidelines (e.g. the European Society of Cardiology [ESC] guideline). Modifications of HF therapy were possible at any time before and during the study. Regarding the treatment of underlying medical conditions or risk factors, neither recommendations nor limitations had been specified. The information available in the dossier does not clarify to what extent this resulted in optimal patient treatment. Data are missing on modifications made for the treatment of the underlying medical conditions.

In the study, optimization of standard HF therapy was not ensured for all patients. The data show that in about 40% of patients from either study arm, the dose of one of the drugs was increased or treatment with a drug from a new class was initiated. However, the company did not submit any information about the type of modification, e.g. the drug classes to which patients switched or the reasons for performing or foregoing treatment modifications during the study.

Furthermore, it is notable that a relatively high percentage of patients (about 60%) did not receive any treatment modifications over the course of the study.

Implementation of the recommendations for treatment modifications in case of persistent symptoms

According to the National Disease Management Guideline as well as the recently updated ESC guideline, patients with symptomatic HF and reduced ejection fraction should be treated with a combination of an ACE inhibitor or ARB, a beta-blocker, and an MRA. For patients who continue to be symptomatic despite guideline-compliant therapy, the National Disease Management Guideline, version 3 recommends a switch from ACE inhibitors / ARBs to the ARNI sacubitril/valsartan or add-on therapy with a sodium-glucose cotransporter 2 (SGLT-2) inhibitor.

Although patients in the VICTORIA study exhibited classII through IV HF and had experienced a recent decompensation event, at 15%, only a small percentage of them received sacubitril/valsartan at baseline. By the later treatment phase (Weeks 113 through 128), the percentage of patients on sacubitril/valsartan rose to 19% in the intervention arm and 22% in

the comparator arm. Reasons for not treating with sacubitril/valsartan at baseline include the treatment not being indicated according to the treatment guidelines (20%) and treatment being unavailable (19%). This demonstrates that not all recommended treatment options were available to all patients.

SGLT-2 inhibitors, which are likewise recommended by guidelines for the VICTORIA patient population, were not available, neither at study start nor over the course of the study, except for patients who were treated with dapagliflozin (0.9%) or empagliflozin (3.5%) as part of their diabetes therapy.

In summary, the treatment options in the VICTORIA study do not fully represent the German standard of care, and the ACT was implemented only to a limited extent. Despite these limitations, the VICTORIA study was used for the benefit assessment.

Risk of bias

The study-level risk of bias for the VICTORIA study was rated as low. The risk of bias on the outcome level is deemed low, except for the following outcomes: health status (surveyed using visual analogue scale [VAS] of European Quality of Life – 5 Dimensions [EQ-5D]), health-related quality of life (surveyed using the overall summary score [OSS] of the Kansas City Cardiomyopathy Questionnaire [KCCQ]), serious adverse events (SAEs), hypotension (SAEs), and further specific AEs.

Assessment of the certainty of conclusions

Various aspects limit the certainty of conclusions of the present VICTORIA study for the benefit assessment.

Firstly, the percentage of patients who had not been clinically stabilized at baseline is unclear. Secondly, it is safe to assume in the present benefit assessment that the VICTORIA study implemented the ACT of optimized standard therapy for HF only to a limited extent. This was concluded, firstly, because relevant therapy options such as sacubitril/valsartan or SGLT-2 inhibitors were available only to a limited extent or not at all. Secondly, it is notable that relatively few patients received a modification of their pharmacological HF therapy during the study.

Particularly due to these limitations, overall, at most hints, e.g. of an added benefit, can be determined for all outcomes. In addition, it is unclear to what extent the potentially insufficient percentage of patients who switched to sacubitril/valsartan therapy or the lack of administration of SGLT-2 inhibitors impacted the effects on patient-relevant outcomes in the VICTORIA study. Therefore, the effects on the individual outcomes cannot be quantified.

Results

Mortality

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

Morbidity

Hospitalization for HF

A statistically significant difference between treatment groups in favour of vericiguat + optimized standard therapy was shown for the outcome of hospitalization for HF. However, there was a statistically significant interaction for the attribute of age. This resulted in a hint of an added benefit of vericiguat + optimized standard therapy versus optimized standard therapy for patients < 75 years of age. For patients ≥ 75 years of age, there is no hint of an added benefit of vericiguat + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven for this patient group.

Myocardial infarction (MI)

There was no statistically significant difference between treatment groups for the outcome of MI. This results in no hint of added benefit of vericiguat + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

Stroke

There was no statistically significant difference between treatment groups for the outcome of stroke. This results in no hint of added benefit of vericiguat + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

Health status

There was no statistically significant difference between treatment groups for the outcome of health status, surveyed with the EQ-5D VAS. This results in no hint of added benefit of vericiguat + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

Health-related quality of life

For the outcome of health-related quality of life as measured using KCCQ-OSS, no statistically significant difference between treatment groups was found. This results in no hint of added benefit of vericiguat + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

Side effects

SAEs

No statistically significant difference between treatment groups was shown for the outcome of SAEs. This resulted in no hint of greater or lesser harm from vericiguat + optimized standard therapy versus optimized standard therapy; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

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

Hypotension (SAEs)

No statistically significant difference between treatment groups was shown for the outcome of hypotension (SAEs). This resulted in no hint of greater or lesser harm from vericiguat + optimized standard therapy versus optimized standard therapy; greater or lesser harm is therefore not proven.

Blood and lymphatic system disorders (SAEs)

A statistically significant difference between treatment groups to the disadvantage of vericiguat + optimized standard therapy was shown for the outcome of disorders of the blood and lymphatic system (SAEs). This resulted in a hint of greater harm from vericiguat + optimized standard therapy in comparison with optimized standard therapy.

Atrial fibrillation (SAEs)

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

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

Overall, a hint of non-quantifiable added benefit of vericiguat in the outcome category of serious/severe symptoms / late complications was found only for patients < 75 years of age. In the outcome category of serious/severe side effects, both a favourable and an unfavourable

[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].

effect were found. However, it is questionable whether the favourable effect for the outcome of atrial fibrillation is actually to be allocated to the outcome category of side effects or whether it rather reflects the symptoms of the disease. A clear demarcation is not possible on the basis of the available information.

In summary, for the treatment of symptomatic chronic HF in adult patients < 75 years of age with reduced ejection fraction who are stabilized after a recent decompensation event requiring IV therapy, there is a hint of non-quantifiable added benefit of vericiguat in comparison with optimized standard therapy. For the treatment of symptomatic chronic HF in adult patients ≥ 75 years of age with reduced ejection fraction who are stabilized after a recent decompensation event requiring IV therapy, there is no hint of added benefit of vericiguat; added benefit is therefore not proven.

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

Table 3: Vericiguat – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Symptomatic chronic HF in adult patients with reduced ejection fraction who are stabilized after a recent decompensation event requiring IV therapy	Optimized standard therapy for the treatment of symptomatic chronic HF and underlying medical conditions, e.g. hypertension, cardiac arrhythmia, coronary heart disease, diabetes mellitus, hypercholesterolaemia and the concomitant symptoms	▪ Age < 75 years: hint of a non-quantifiable added benefit. ▪ Age ≥ 75 years: added benefit not proven.
a. Presented is respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HF: heart failure; IV: intravenous		

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

2.2 Research question

The aim of the present report was to assess the added benefit of vericiguat in comparison with optimized standard therapy as the ACT for the treatment of symptomatic chronic HF in adult patients with reduced ejection fraction who are stabilized after a recent decompensation event requiring IV therapy.

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 vericiguat

Therapeutic indication	**ACT**[a]
Symptomatic chronic HF in adult patients with reduced ejection fraction who are stabilized after a recent decompensation event requiring IV therapy	Optimized standard therapy for the treatment of symptomatic chronic HF and underlying medical conditions, e.g. hypertension, cardiac arrhythmia, coronary heart disease, diabetes mellitus, hypercholesterolaemia, and the concomitant symptoms[b]
a. Presentation of the respective ACT specified by the G-BA. b. The patients in both study arms are assumed to have received optimal treatment: guideline-compliant individualized treatment of HF and underlying medical conditions or risk factors such as hypertension, cardiac arrhythmia, or diabetes mellitus as well as the concomitant symptoms, e.g. oedema. It should have been possible to adapt the baseline/concomitant medication to the patient's individual needs in both study arms. Unchanged continuation of an inadequate therapy does not concur with the ACT. If there was no further possibility for optimization, it had to be documented and explained that any other existing treatment options were unsuitable or had been exhausted. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HF: heart failure; IV: intravenous	

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

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

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on vericiguat (status: 17 June 2021)
- bibliographical literature search on vericiguat (last search on 17 June 2021)
- search in trial registries / trial results databases for studies on vericiguat (last search on 17 June 2021)
- search on the G-BA website for vericiguat (last search on 17 June 2021)

To check the completeness of the study pool:

- search in trial registries for studies on vericiguat (last search on 7 October 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: vericiguat + 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)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
MK-1242-001 (VICTORIA[c])	Yes	Yes	Yes[d]	Yes [3,4]	Yes [5-7]	Yes [8-13]

a. Study for which the company was the sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.
d. The development programme for vericiguat is managed jointly by Bayer and Merck Sharp & Dohme Corp (MSD). The VICTORIA study was carried out by MSD.

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

2.3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: vericiguat + 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]
VICTORIA	RCT, double-blind, parallel-group	Adult patients with chronic HF[b] NYHA classes II–IV and ejection fraction with LVEF < 45%[c] and decompensation event[d]	Vericiguat (N = 2526) Placebo (N = 2524) Relevant subpopulation (patients with LVEF < 40%): Vericiguat (n = 2158) Placebo (n = 2158)	Screening: Until 30 days before randomization / treatment start Treatment: Event-driven study: primary data cut-off after 782 adjudicated cardiovascular deaths Follow-up observation[e]: outcome-specific, 14 days after final visit	Total of 694 centres in Argentina, Australia, Austria, Belgium, Canada, Chile, China, Columbia, Czech Republic, Denmark, Finland, France, Germany, Greece, Guatemala, Hong Kong, Hungary, Ireland, Israel, Italy, Japan, Malaysia, Mexico, Netherlands, New Zealand, Norway, Peru, Philippines, Poland, Puerto Rico, Republic of Korea, Russian Federation, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Turkey, Ukraine, United Kingdom, United States 09/2016–09/2019 Primary data cut-off: 18 June 2019	Primary: composite outcome consisting of cardiovascular death and hospitalization for HF Secondary: all-cause mortality, morbidity, health status, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. Patients had to exhibit a prior history of chronic HF under standard therapy.
c. LVEF < 45% had to have been measured within 12 months before randomization. In addition, within 30 days before randomization, the following NT-proBNP or BNP levels had to be measured: in sinus rhythm NT-proBNP ≥ 1000 pg/mL or BNP ≥ 300 pg/mL; with atrial fibrillation, NT-proBNP ≥ 1600 pg/mL or BNP ≥ 500 pg/mL. At randomization, the patients had to be clinically stable (IV treatment completed more than 24 hours ago and systolic blood pressure ≥ 100 mmHg).
d. The decompensation event was defined as hospitalization for HF within 6 months prior to randomization or HF treatment with IV diuretics (without hospitalization) within 3 months prior to randomization.
e. Outcome-specific information is described in Table 10.

AE: adverse event; BNP: brain natriuretic peptide; HF: heart failure; IV: intravenous; LVEF: left-ventricular ejection fraction; n: relevant subpopulation; N: number of randomized patients; NT-proBNP: N-terminal pro-brain natriuretic peptide; NYHA: New York Heart Association; RCT: randomized controlled trial

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

Study	Intervention	Comparison
VICTORIA	Vericiguat once daily, orally, starting dose 2.5 mg, dose doubling every 2 weeks until the maintenance dose of 10 mg has been reached[a] + optimized standard therapy	Placebo once daily, orally, proper placebo for 2.5 mg, 5 mg, and 10 mg; treatment course analogous to vericiguat arm[a] + optimized standard therapy
	Dose adjustments ▪ Depending on systolic blood pressure while sitting and only in the absence of symptoms suggesting hypotension ▫ SBP ≥ 100 mmHg and target value of 10 mg not yet reached – dose increased ▫ SBP ≥ 100 mmHg and target value of 10 mg reached – dose maintained ▫ SBP ≥ 90 mmHg and < 100 mg – dose maintained ▫ SBP < 90 mmHg (asymptomatic) – dose reduced (at 5 mg or 10 mg) or interrupted (at 2.5 mg) ▫ SBP < 90 mmHg (symptomatic) – dose interrupted ▪ Reduction of the 5 mg or 10 mg dose was possible at any time if deemed justified for safety reasons **Prior and concomitant treatment** ▪ HF treatment should be administered in accordance with locally recognized guidelines (e.g. ACCF/AHA and ESC), at the investigator's discretion, and as tolerated: ▫ ACE inhibitors or ARBs ▫ Beta-blockers ▫ Oral diuretics ▫ MRAs ▫ ARNIs ▫ Therapies with ICD and biventricular pacemakers ▪ Short-acting nitrates (e.g. sublingual nitroglycerin spray for the treatment of angina episodes) ▪ Any dose modifications, add-ons, changes in administration route, discontinuations, or terminations of concomitant therapy are possible upon the investigator's discretion **Prohibited prior and concomitant treatment** ▪ Other soluble guanylate cyclase stimulators (e.g. riociguat) ▪ PDE4 inhibitors (vardenafil, tadalafil, or sildenafil) ▪ Long-acting nitrates or NO donors that are longer acting than sublingual nitroglycerin, e.g. isosorbide dinitrate, isosorbide 5-mononitate, pentaerythritol tetranitrate, nicorandil or transdermal nitroglycerin patch, or molsidomine ▪ Continuous IV administration of an inotrope ▪ Ventricular assist device or awaiting heart transplantation ▪ Valvular heart disease, with surgery or intervention within ≤ 3 months or planned	

a. The study medication should be taken with food at approximately the same time each day. If the dose of 10 mg had not been reached by the end of the uptitration phase (duration of 4 weeks), uptitration was to be considered at each subsequent visit, taking into account systolic blood pressure.

ACCF: American College of Cardiology Foundation; ACE: angiotensin converting enzyme; AHA: American Heart Association; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; ESC: European Society of Cardiology; ICD: implantable cardioverter-defibrillator; MRA: mineralocorticoid receptor antagonist; NO: nitrogen monoxide; PDE5: phosphodiesterase-5; RCT: randomized controlled trial; SBP: systolic blood pressure

The VICTORIA study is a placebo-controlled double-blind, randomized parallel-group study on vericiguat. It included patients with chronic HF of New York Heart Association (NYHA) classes II through IV whose LVEF was < 45%. In addition, patients had to exhibit both increased NT proBNP or BNP levels and a decompensation event. In the VICTORIA study, this was operationalized as previous hospitalization for HF within 6 months and/or IV diuretic treatment for HF (without hospitalization) within 3 months prior to treatment start.

Patients were to receive adequate drug therapy for HF in accordance with the locally relevant guidelines, at the investigator's discretion, and as tolerated. The therapy was to be individualized, consisting of combinations of the drug classes of ACE inhibitors, ARB, beta-blockers, oral diuretics, MRA, and ARNI. Patients with ICDs or biventricular pacemakers were eligible for inclusion. A detailed discussion of the implementation of the ACT in the course of the study can be found below.

A total of 5050 patients were included in the study and randomly allocated in a 1:1 ratio either to treatment with vericiguat (N = 2526) or to placebo (N = 2524). Randomization was stratified by geographic region (Eastern Europe [plus Israel and South Africa] versus Western Europe versus North America [Black] versus North America [Non-Black] versus Central and South America versus Asia [including Australia]). The percentage of included patients whose qualifying decompensation event was more than 3 months in the past was limited to 20%.

With regard to the therapeutic indication of vericiguat, the study's inclusion criteria may diverge from the SPC [14]. Vericiguat is approved for the treatment of symptomatic chronic HF in adult patients with reduced ejection fraction who are stabilized after a recent decompensation event requiring IV therapy. IV therapy was not an explicit inclusion criterion for patients hospitalized due to a decompensation event. However, it is generally safe to assume that patients hospitalized for HF receive IV therapy. The study addressed the requirement of patients having been stabilized after the decompensation event by specifying that the IV therapy had to have been completed for more than 24 hours. A time period of 24 hours seems too short to ensure that patients are stabilized. According to the EPAR, the company itself conceded in the approval procedure that not all patients were clinically stable [15]. Based on the available data, it is impossible to determine to how many patients this applied. Consequences for the certainty of conclusions of the study are described in Section 2.4.2.

Aside from the above issue, the vericiguat dosage and administration were in line with SPC specifications [14]. In addition, patients in both study arms continued to receive individualized HF therapy after randomization.

The study's primary outcome was the composite outcome of cardiovascular death and hospitalisation for HF. Patient-relevant secondary outcomes were all-cause mortality, outcomes of the morbidity and health-related quality of life categories, and AEs.

The predefined data cut-off of the VICTORIA study was event controlled, to occur after 782 events of cardiovascular death. After the required number of events was reached, patients were invited to a final visit. A final call for another survey of outcomes was made 14 days after the final visit. Patients who discontinued the study medication early had a visit at the time of permanent treatment discontinuation and another one within 14 days after the last dose and were to continue participating in all planned visits until the end of the study as if they had continued treatment.

The approval of vericiguat comprises patients with symptomatic chronic HF with reduced LVEF. According to the National Disease Management Guideline, this corresponds to LVEF < 40% [16]. The VICTORIA study included patients with LVEF < 45%. The company's dossier presents the results of a subpopulation with LVEF < 40% at baseline (N = 2158 per study arm). This subpopulation is relevant for the benefit assessment and was used.

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

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

Study Characteristic Category	Vericiguat + optimized standard therapy N[a] = 2158	Placebo + optimized standard therapy N[a] = 2158
VICTORIA		
Age [years], mean (SD)	67 (12)	67 (12)
Sex [F/M], %	23/77	23/77
Ancestry, n (%)		
White	1350 (63)	1359 (63)
Asian	500 (23)	475 (22)
Black	111 (5)	118 (5)
Other	196 (9)	206 (10)
Missing	1 (0)	0 (0)
Geographical region, n (%)		
Asia-Pacific	511 (24)	503 (23)
Eastern Europe	722 (33)	718 (33)
Central and South America	316 (15)	324 (15)
North America	243 (11)	244 (11)
Western Europe	366 (17)	369 (17)
Decompensation event, n (%)		
Hospitalization for HF within 3–6 months	390 (18)	365 (17)
Hospitalization for HF within 3 months	1441 (67)	1478 (68)
IV diuretics within 3 months (without hospitalization)	327 (15)	315 (15)
Time since primary diagnosis of HF with reduced ejection fraction [years]		
Median [Q1; Q3]	3.0 [0.8; 7.1]	3.0 [0.9; 7.1]
Mean (SD)	4.8 (5.6)	4.9 (5.4)
LVEF, n (%)		
< 35	1725 (80)	1741 (81)
≥ 35	433 (20)	417 (19)
NT-proBNP level [pg/mL], median [Q1; Q3]	2932.0 [1610.5; 5506.5]	2913.0 [1575.0; 5425.0]
BMI [kg/m²], mean (SD)	27.6 (5.8)	27.8 (6.1)
eGFR [mL/min/1.73 m³], mean (SD)	62.0 (27.2)	62.2 (27.2)
NYHA class, n (%)		
I	0 (0)	1 (0)
II	1241 (58)	1270 (59)
III	885 (41)	861 (40)
IV	30 (1)	26 (1)
Missing	2 (0)	0 (0)
Diabetes mellitus, n (%)	1051 (49)	985 (46)

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

Study Characteristic Category	Vericiguat + optimized standard therapy N[a] = 2158	Placebo + optimized standard therapy N[a] = 2158
Treatment discontinuation[b], n (%)	506 (23)	490 (23)
Study discontinuation[c], n (%)	17 (1)	18 (1)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Excluding deaths; common reasons for discontinuation of therapy in the intervention versus control arms: patient wish (7.4% vs. 7.7%), AEs (6.9% vs. 6.3%), investigator's decision (6.6% vs. 6.4%).
c. Excluding deaths; reasons for study dropout in the intervention vs. control arms: loss to follow-up (0.4% vs. 0.2%) or patient wish (0.4% vs. 0.6%).

AE: adverse event; BMI: body mass index; eGFR: estimated glomerular filtration rate; f: female; HF: heart failure; LVEF: left ventricular ejection fraction; m: male; n: number of patients in the category; N: number of randomized (or included) patients; NT-proBNP: N-terminal pro B type natriuretic peptide; NYHA: New York Heart Association; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation

Patient characteristics were sufficiently balanced between the treatment arms. Patients had a mean age of 67 years; most were male (77%), and half were from Eastern Europe (33%) or Western Europe (17%). About 59% of patients exhibited mild limitations from the disease (NYHA class II), while about 40% of patients already exhibited moderate limitations (NYHA III). As the most common consequence of the decompensation event, 68% of patients had been hospitalized for HF within the previous 3 months. The high rate of treatment discontinuations (23%) is notable but balanced between treatment arms.

Implementation of the ACT

The VICTORIA study implemented the ACT only with limitations. The main limitation is that, for a majority of patients, not all therapeutic options might have been exhausted or available.

In the VICTORIA study, all patients were to receive individualized therapy in accordance with locally applicable guidelines (e.g. the ESC guideline). Modifications of HF therapy were possible at any time before and during the study.

The G-BA's notes on the ACT specify that patients in both study arms are assumed to receive optimal treatment. This includes not only a modification of HF therapy, but also guideline-compliant individualized treatment of the underlying medical condition or risk factors such as hypertension, arrhythmia, or diabetes mellitus as well as accompanying symptoms, such as oedema. Regarding the treatment of the underlying medical condition or risk factors, the VICTORIA study specified neither recommendations nor limitations. The information available in the dossier does not clarify to what extent this resulted in optimal patient treatment. In Module 4 A, the company presents only the change in mean glycated haemoglobin (HbA1c) over the course of the study for patients with a diabetes mellitus diagnosis at baseline as well as the change in mean systolic blood pressure over the course of the study for patients with

hypertension at baseline. On the basis of the HbA1c levels remaining constant and the recommended systolic blood pressure thresholds not being exceeded by patients with hypertension, the company assumed therapy in the study to be adequate. No further data are available on modifications made for the treatment of these or other underlying medical conditions.

In the study, optimization of standard HF therapy was not ensured for all patients. In Module 4 A, the company clarifies which HF standard therapy patients received at baseline as well as in the course of the study. These data were each aggregated for various time periods. Table 9 shows the data available on HF standard therapy at baseline as well as the proportions of patients for whom treatment was modified during the study.

Table 9: Data on HF therapies – RCT, direct comparison: vericiguat + optimized standard therapy vs. placebo + optimized standard therapy

Study Characteristic Category	Vericiguat + optimized standard therapy N[a] = 2158	Placebo + optimized standard therapy N[a] = 2158
VICTORIA		
At baseline		
HF therapies, n (%)	2150 (100)	2154 (100)
ACE inhibitors or ARB or sacubitril/valsartan	1880 (87)	1895 (88)
ACE inhibitors or ARBs	1562 (72)	1578 (73)
Sacubitril/valsartan	330 (15)	330 (15)
Beta-blockers	2008 (93)	2009 (93)
MRAs	1531 (71)	1584 (73)
Device therapies, n (%)		
ICD	644 (30)	654 (30)
Biventricular pacemaker	325 (15)	339 (16)
During the study		
Dose modification of standard therapy or new initiation[b], n (%)	843 (39)	893 (41)
Dose reduction or discontinuation of standard therapy at one or several visits[c], n (%)	944 (44)	959 (44)

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Comprises dose increases for one of the drugs included in standard therapy and treatment with a new drug class from the drugs included in standard therapy in comparison with baseline.
c. The most common reason was patient or investigator preference (34.2% vs. 34.8%).

ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; HF: heart failure; ICD: implantable cardioverter-defibrillator; MRA: mineralocorticoid receptor antagonist; n: number of patients with event; N: number of randomized (or included) patients; RCT: randomized controlled trial

The data show that in about 40% of patients in both study arms, the dosage of one of the drugs was increased, or treatment with a new drug class was initiated. However, the company did not

submit any information about the type of modification, e.g. the drug classes to which patients switched or the reasons for performing or foregoing treatment modifications during the study.

Furthermore, it is notable that a relatively high percentage of patients (about 60%) did not receive any treatment modifications over the course of the study.

Implementation of the recommendations for treatment modifications in case of persistent symptoms

According to the National Disease Management Guideline [16,17] as well as the recently updated ESC guideline [18], patients with symptomatic HF and reduced ejection fraction should be treated with a combination of an ACE inhibitor or ARB, a beta-blocker, and an MRA. For patients who continue to be symptomatic despite guideline-compliant therapy, the National Disease Management Guideline version 3 recommends a switch from ACE inhibitors / ARBs to the ARNI sacubitril/valsartan or add-on SGLT-2 inhibitor treatment [16]. However, due to the current uncertainties regarding the long-term tolerability and side effect profile of sacubitril/valsartan, attention should be paid to contraindications and intolerances [17]. The G-BA refers to this treatment switch to sacubitril/valsartan in its comments on the ACT.

Although the patients of the VICTORIA study had HF classes II to IV and recently experienced a decompensation event, only a small percentage of them, 15%, received sacubitril/valsartan at baseline. In contrast, at study start, 73% of patients were treated with ACE inhibitors / ARB, 93% with beta-blockers, and 72% with MRAs. Over the course of the study, the percentage of patients who received sacubitril/valsartan increased. While at the start of treatment (Days 2 to 21), 16% of patients in both the intervention arm and the comparator arm received sacubitril/valsartan, this percentage increased over the course of treatment to 20% and 21%, respectively (Weeks 17 through 32). By the later treatment (Week 113 through 128), the percentage of patients who received sacubitril/valsartan had changed only slightly, to 19% and 22%, respectively. Module 4 A of the company's dossier lists reasons for patients not receiving sacubitril/valsartan at baseline. In addition to patient or investigator preference (36%), this includes the treatment not being indicated according to treatment guidelines (20%) or being unavailable (19%). These data confirm that not all recommended treatment options were available to all patients.

SGLT-2 inhibitors, which are likewise recommended by guidelines for the VICTORIA patient population, were not available, neither at study start nor over the course of the study, except to patients who were treated with dapagliflozin (0.9%) or empagliflozin (3.5%) as part of their diabetes therapy.

In summary, the treatment options in the VICTORIA study do not fully represent the German standard of care, and the ACT was implemented only to a limited extent. Despite these limitations, the VICTORIA study was used for the benefit assessment. Consequences for the certainty of conclusions of the study are described in Section 2.4.2.

Duration of treatment and follow-up observation

Table 10 shows the mean/median treatment duration of patients and the mean/median observation period for individual outcomes.

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

Study **Duration of the study phase** **Outcome category**	**Vericiguat + optimized standard therapy** **N = 2158**	**Placebo + optimized standard therapy** **N = 2158**
VICTORIA		
Treatment duration [months][a]		
Median [Q1; Q3]	11.8 [7.0; 20.0]	11.5 [7.2; 19.8]
Mean (SD)	13.3 (8.6)	13.2 (8.3)
Observation period [months]		
All-cause mortality[b]		
Median [Q1; Q3]	13.8 [8.4; 21.9]	13.4 [8.3; 21.7]
Mean (SD)	15.2 (8.0)	15.0 (7.9)
Hospitalization for HF		
Median [Q1; Q3]	11.0 [6.4; 19.1]	10.2 [5.8; 18.3]
Mean (SD)	12.6 (8.4)	12.0 (8.3)
Myocardial infarction		
Median [Q1; Q3]	13.5 [8.3; 21.6]	13.1 [8.2; 21.5]
Mean (SD)	14.9 (8.1)	14.7 (7.9)
Stroke		
Median [Q1; Q3]	13.6 [8.3; 21.8]	13.2 [8.3; 21.6]
Mean (SD)	15.0 (8.1)	14.8 (7.9)
Health status (EQ-5D VAS)[c]		
Median [Q1; Q3]	10.3 [4.1; 11.3]	10.3 [4.1; 11.3]
Mean (SD)	9.8 (6.6)	9.8 (6.5)
Health-related quality of life – (KCCQ-C)[c]		
Median [Q1; Q3]	10.4 [4.1; 11.3]	10.4 [4.1; 11.3]
Mean (SD)	9.8 (6.6)	9.8 (6.5)
Side effects[a, d]		
Median [Q1; Q3]	11.4 [6.7; 19.7]	11.3 [6.8; 19.5]
Mean (SD)	13.1 (8.4)	12.9 (8.1)

a. These figures refer to the study's safety population (2152 vs. 2151 patients).
b. The observation duration is calculated based on the observed period up to death, last available information on the outcome, or, if no event was observed, the data-cut off date.
c. Data are based on the safety population with at least one questionnaire survey (EQ-5D VAS: 2115 vs. 2117 patients; KCCQ: 2115 vs. 2119 patients).
d. The observation duration for side effects is defined as the time from the first dose until 14 days after treatment end, until death, or until the data cut-off date.

KCCQ: Kansas City Cardiomyopathy Questionnaire; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

Treatment duration was comparable between the two study arms. The observation periods for the individual outcome categories or outcomes were also comparable between both study arms.

Risk of bias across outcomes (study level)

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

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: vericiguat + 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			
VICTORIA	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The study-level risk of bias for the VICTORIA study was rated as low.

Transferability to the German health care context

For presenting the transferability of the results of the VICTORIA study to the German healthcare context, the company compares characteristics of the VICTORIA study population with the patient characteristics from publications on various cohort and registry studies [19-23]. According to the company, patient characteristics are similar, taking into account the decompensation event or treatment intensification. Furthermore, all described factors (age, sex, body mass index, NT-proBNP) were reportedly examined for impact in subgroup analyses, which showed no effect modifications relevant for the conclusion. Furthermore, the company reports that the optimized standard therapy was in line with the recommendations by German guidelines [17],had been modifiable at any time, and led to no relevant limitations. Overall, the company believes that the study population largely reflects the actual situation in German healthcare and that the study results can be extrapolated to the German healthcare context.

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

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality

- All-cause mortality

- Morbidity
  - Hospitalization for HF
  - MI
  - Stroke
  - Health status, surveyed using the EQ-5D VAS
- Health-related quality of life
  - KCCQ OSS
- Side effects
  - SAEs
  - Discontinuation due to AEs
  - Hypotension (preferred term [PT], SAEs)
  - Further specific AEs, if any

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

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

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

Study	Outcomes									
	All-cause mortality	Hospitalization for HF	MI	Stroke	Health status (EQ-5D VAS)	Health-related quality of life (KCCQ OSS)	SAEs[a]	Discontinuation due to AEs[a]	Hypotension (PT, SAEs)[a]	Further specific AEs[b]
VICTORIA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. No data available as to whether disease-related events were included in the total rate.
b. The following events (MedDRA coding) were considered: blood and lymphatic system disorders (SOC, SAEs) and atrial fibrillation (PT, AEs).

AE: adverse event; KCCQ: Kansas City Cardiomyopathy Questionnaire; MedDRA: Medical Dictionary for Regulatory Activities; OSS: overall summary score; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

- Primary composite outcome: In its present operationalization, the primary composite outcome on cardiovascular morbidity was not used for the benefit assessment. The composite outcome comprises the components of cardiovascular mortality and hospitalization for HF. This operationalization represents cardiovascular morbidity only to a limited extent, Firstly, nonfatal MIs and strokes are not covered by this outcome, despite the fact that these events represent relevant components of cardiovascular morbidity. Secondly, fatal MIs and strokes are covered by cardiovascular mortality. Therefore, the primary composite outcome on cardiovascular morbidity was excluded from the benefit assessment.
- MI and stroke: The VICTORIA study operationalizes these outcomes as hospitalization for MI and hospitalization for stroke. This is generally not appropriate because in order to reflect all relevant components, outcomes on MIs and strokes should include all fatal and nonfatal events. The employed operationalization of hospitalization comprises only nonfatal events. However, the data submitted in Module 4 A show that in the vericiguat arm, all patients with fatal MIs and strokes had been previously hospitalized. In the comparator arm, there is a minor, irrelevant deviation in patients who died of MI or stroke without prior hospitalization. In this particular constellation, fatal events have already been included in the outcome due to the prior hospitalization, and the submitted operationalization adequately represents the outcomes of MI and stroke and can be used for the benefit assessment.
- Health status (EQ-5D VAS) and health-related quality of life (KCCQ OSS):

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

  - EQ-5D VAS: improvement and deterioration of the baseline value by ≥ 7 or ≥ 10 points at Week 32 (scale range of EQ-5D VAS: 0 to 100 points)
  - KCCQ OSS: improvement and deterioration of the baseline value by ≥ 5 points at Week 32 (scale range of KCCQ OSS: 0 to 100 points)
  - As supplementary analyses (EQ-5D VAS, KCCQ-OSS): improvement and deterioration by 15 points of the scale range at Week 32

  Given the course of disease to be expected in the present therapeutic indication and the distribution of absolute values of the scales at baseline, it is the analysis of the improvement of health status which is of primary relevance for the present benefit assessment.

  As explained in the IQWiG General Methods [1,24], for a response criterion to reflect with sufficient certainty a change noticeable for the patient, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post hoc analyses, exactly 15% of the scale range). To derive added benefit, therefore, the supplementary analyses performed by the company on improvement by ≥ 15 points each (exactly 15% of

the scale range) at Week 32 were used. The analyses of improvement of EQ-5D VAS by ≥ 7 or ≥ 10 points and KCCQ-OSS by ≥ 5 points are presented as supplementary information in Appendix D of the full dossier assessment.

2.4.2 Risk of bias

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

Table 13: Risk of bias at study level and outcome-specific risk of bias – RCT, direct comparison: vericiguat + optimized standard therapy vs. placebo + optimized standard therapy

Study	Study level	Outcomes									
		All-cause mortality	Hospitalization for HF	MI	Stroke	Health status (EQ-5D VAS)	Health-related quality of life (KCCQ OSS)	SAEs[a]	Discontinuation due to AEs[a]	Hypotension (PT, SAEs)[a]	Further specific AEs[b]
VICTORIA	L	L	L	L	L	H[c]	H[c]	H[d]	L	H[d]	H[d]

a. It is unclear whether disease-related events were included in the total rate.
b. The following events (MedDRA coding) were considered: blood and lymphatic system disorders (SOC, SAEs) and atrial fibrillation (PT, AEs).
c. High percentage of LOCF-replaced values (EQ-5D VAS: 18% vs. 19%, KCCQ-OSS: 21% vs. 22%); furthermore, a high percentage of patients (> 10%) were excluded from the analysis.
d. Incomplete observations for potentially informative reasons.

AE: adverse event; H: high; KCCQ: Kansas City Cardiomyopathy Questionnaire; L: low; LOCF: last observation carried forward; MedDRA: Medical Dictionary for Regulatory Activities; OSS: overall summary score; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

The 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 (as measured using EQ-5D VAS) and health-related quality of life (surveyed using KCCQ-OSS) is deemed high due to the high percentage of values replaced by last observation carried forward (LOCF) and additionally the high percentage (> 10%) of patients disregarded in the analysis. Furthermore, the risk of bias of the results on SAEs, hypotension (SAEs), and further specific AEs is deemed high due to incomplete follow-up duration, which ended 14 days after treatment discontinuation as well as the high number of treatment discontinuations (23% versus 23%).

Overall assessment of the certainty of conclusions

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

Firstly, the percentage of patients who had not been clinically stabilized at baseline is unclear. Secondly, it is safe to assume in the present benefit assessment that the VICTORIA study implemented the ACT of optimized standard therapy for HF only to a limited extent. This was concluded, for one thing, because relevant therapy options such as sacubitril/valsartan or SGLT-2 inhibitors were available only to a limited extent or not at all. In addition, it is notable that relatively few patients received a modification of their pharmacological HF therapy during the study.

Particularly due to these limitations, overall, at most hints, e.g. of an added benefit, can be determined for all outcomes. Further, it is unclear to what extent the potentially insufficient percentage of patients who switched to sacubitril/valsartan therapy or the lack of administration of SGLT-2 inhibitors impacted the effects on patient-relevant outcomes in the VICTORIA study. Therefore, the effects on the individual outcomes cannot be quantified.

This deviates from the assessment by the company, which derived proof of minor added benefit of vericiguat versus optimized standard therapy for patients with symptomatic chronic HF with reduced ejection fraction. The company justifies the derivation of proof by stating that the VICTORIA study fulfils the requirements for the derivation of proof based on 1 study which are described in the General Methods, Version 6.0 [1]. The derivation of proof on the basis of 1 study is subject to certain conditions and is possible only in exceptional cases [1]: For example, the present study must be multicentric, with ≥ 10 study centres and at least 1000 patients in each study arm. The p-values for the observed effect estimates must be very small (< 0.001). Moreover, the results must be consistent within the study. Thus, the analysis of relevant subpopulations must each yield assessable and sufficiently homogeneous effect estimates. The analyses for subpopulations must be available for all relevant outcomes. However, the p-values for the observed effect estimators are > 0.001 in all outcomes of the VICTORIA study; therefore, this criterion was not met, and no proof can be derived.

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

2.4.3 Results

Table 14 and Table 15 summarize the results on the comparison of vericiguat + optimized standard therapy versus placebo + optimized standard therapy for symptomatic chronic HF in patients with reduced ejection fraction who are stabilized after a recent decompensation event requiring IV therapy. Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves on the included outcomes are presented in Appendix B of the full dossier assessment, and the results on common AEs, SAEs, and discontinuation due to AEs are presented in Appendix C of the full dossier assessment. Supplementary responder analyses on

the outcomes of of EQ-5D VAS (improvement by ≥ 7 or ≥ 10 points) and KCCQ-OSS (improvement by ≥ 5 points) are presented in Appendix D of the full dossier assessment.

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

Study **Outcome category** **Outcome**	**Vericiguat + optimized standard therapy**		**Placebo + optimized standard therapy**		**Vericiguat + 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]**
VICTORIA					
Mortality					
All-cause mortality	2158	NA 443 (20.5)	2158	NA 464 (21.5)	0.94 [0.83; 1.07]; 0.363
Cardiovascular death	2158	NA 358 (16.6)	2158	NA 384 (17.8)	0.92 [0.80; 1.06]; 0.256
Morbidity					
Hospitalization for HF					
1st event	2158	NA 602 (27.9)	2158	NA 659 (30.5)	0.88 [0.79; 0.99]; 0.029
Including repeat events (presented as supplementary information)	*2158*	*Number of events 1049*	*2158*	*Number of events 1203*	0.86 [0.79; 0.95]; 0.001[b]
MI	2158	NA 39 (1.8)	2158	NA 37 (1.7)	1.04 [0.66; 1.63]; 0.863
Stroke	2158	NA 32 (1.5)	2158	NA 31 (1.4)	1.02 [0.62; 1.68]; 0.930

a. Unless otherwise indicated, HR [95% CI] based on Cox regression model with treatment as a covariable, stratified by region and ancestry; p-value based on two-sided logrank test stratified by region and ancestry.
b. HR [95% CI] and p-value calculated using Andersen-Gill model, adjusted by region and ancestry; robust estimate of standard error for taking into account multiple HF-related hospitalizations of the same patient.

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial

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

Study Outcome category Outcome	Vericiguat + optimized standard therapy		Placebo + optimized standard therapy		Vericiguat + 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]
VICTORIA					
Morbidity					
Improvement ≥ 15 points[c]					
Health status (EQ-5D VAS)	1753	483 (27.6)	1739	460 (26.5)	1.04 [0.93; 1.16]; 0.457
Health-related quality of life					
Improvement ≥ 15 points[c]					
KCCQ OSS	1655	558 (33.7)	1628	563 (34.6)	0.98 [0.89; 1.07]; 0.606
Physical limitation	1726	588 (34.1)	1718	576 (33.5)	1.02 [0.93; 1.12]
Symptoms (KCCQ-TSS)	1760	581 (33.0)	1751	613 (35.0)	0.94 [0.86; 1.03]
Social limitation	1669	656 (39.3)	1642	610 (37.1)	1.06 [0.97; 1.15]
Psychological quality of life	1760	755 (42.9)	1751	738 (42.1)	1.02 [0.94; 1.10]
Side effects					
AEs (supplementary information)[d]	2152	1726 (80.2)	2151	1741 (80.9)	–
SAEs[d]	2152	702 (32.6)	2151	743 (34.5)	0.94 [0.87; 1.03]; 0.182[e]
Discontinuation due to AEs[d]	2152	139 (6.5)	2151	134 (6.2)	1.04 [0.82; 1.30]; 0.758[e]
Hypotension (PT, SAEs)[d]	2152	31 (1.4)	2151	38 (1.8)	0.82 [0.51; 1.31]; 0.530[f]
Blood and lymphatic system disorders (SOC, SAEs)	2152	39 (1.8)	2151	20 (0.9)	1.92 [1.15; 3.21]; 0.013[f]
Atrial fibrillation (SAEs)[d]	2152	9 (0.4)	2151	26 (1.2)	0.38 [0.19; 0.73]; 0.004[f]

a. Outcomes of the categories of morbidity and health-related quality of life: missing values were replaced using LOCF.
b. Unless otherwise indicated: RR [95% CI] according to Mantel-Haenszel method, stratified by region and ancestry; p-value of RR two-sided based on Wald test.
c. Percentage of patients with an increase by ≥ 15 points from baseline at Week 32, given a scale range of 0 to 100. Higher (increasing) values indicate an improvement of health-related quality of life / symptoms.
d. No data available as to whether disease-related events are included in the total rate; no distinction between side effects of the intervention and symptoms of the underlying medical condition.
e. RR [95% CI] based on log-binomial regression model with Wald CI; p-value two-sided based on Wald test.
f. RR [95% CI] based on log-binomial regression model with Wald CI. If the event rate in ≥ 1 group is ≤ 1%: Peto OR as estimator for the relative risk; p-value: IQWiG calculation, unconditional exact test (CSZ method according to [25]).

AE: adverse event; CI: confidence interval; KCCQ: Kansas City Cardiomyopathy Questionnaire; LOCF: last observation carried forward; n: number of patients with (at least 1) event; N: number of analysed patients; OSS: overall summary score; PT: preferred term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: system organ class; TSS: total symptom score; VAS: visual analogue scale

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

Mortality

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

All-cause mortality

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

Morbidity

Hospitalization for HF

A statistically significant difference between treatment groups in favour of vericiguat + optimized standard therapy was shown for the outcome of hospitalization for HF. However, there was a statistically significant interaction for the attribute of age. This results in a hint of added benefit of vericiguat + optimized standard therapy in comparison with placebo + optimized standard therapy for patients < 75 years of age. For patients ≥ 75 years of age, there is no hint of added benefit of vericiguat + optimized standard therapy in comparison with optimized standard therapy; an added benefit is therefore not proven (see Section 2.4.4).

MI

There was no statistically significant difference between treatment groups for the outcome of MI. This results in no hint of added benefit of vericiguat + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

Stroke

There was no statistically significant difference between treatment groups for the outcome of stroke. This results in no hint of added benefit of vericiguat + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

Health status

EQ-5D VAS

There was no statistically significant difference between treatment groups for the outcome of health status, surveyed with the EQ-5D VAS. This results in no hint of added benefit of vericiguat + 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 as measured using KCCQ-OSS, no statistically significant difference between treatment groups was found. This results in no hint of added benefit of vericiguat + optimized standard therapy versus optimized standard therapy; an added benefit is therefore not proven.

Side effects

SAEs

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

Discontinuation due to AEs

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

Hypotension (SAEs)

No statistically significant difference between treatment groups was shown for the outcome of hypotension (SAEs). This resulted in no hint of greater or lesser harm from vericiguat + optimized standard therapy versus optimized standard therapy; greater or lesser harm is therefore not proven.

Specific AEs

Blood and lymphatic system disorders (SAEs)

A statistically significant difference between treatment groups to the disadvantage of vericiguat + optimized standard therapy was shown for the outcome of disorders of the blood and lymphatic system (SAEs). This resulted in a hint of greater harm from vericiguat + optimized standard therapy in comparison with optimized standard therapy.

Atrial fibrillation (SAEs)

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

2.4.4 Subgroups and other effect modifiers

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

- age (< 75 years versus ≥ 75 years)
- sex (male versus female)
- severity of heart failure (NYHA classes I/II vs. III/IV)

The corresponding subgroup analyses had been predefined for the primary outcome (cardiovascular death and hospitalization for HF) and its individual components. However, the company presented post hoc subgroup analyses on the above-mentioned attributes for all analysed outcomes.

For the attribute of age, an age limit of 75 years was used since HF is a disease of advanced age and because more advanced age – one of several demographic characteristics – is among the prognostic factors associated with an unfavourable course [16].

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

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least 1 subgroup.

Table 16 summarizes the subgroup results for the comparison of vericiguat + optimized standard therapy versus placebo + optimized standard therapy for symptomatic chronic HF in adult patients with reduced ejection fraction who are stabilized after a recent decompensation event requiring IV therapy.

Kaplan-Meier curves on the presented time-to-event analyses can be found in Appendix B of the full dossier assessment.

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

Study Outcome Characteristic Subgroup	Vericiguat + optimized standard therapy		Placebo + optimized standard therapy		Vericiguat + optimized standard therapy vs. placebo + optimized standard therapy	
	N	Median time to event in months [95 % CI] Patients with event n (%)	N	Median time to event in months [95 % CI] Patients with event n (%)	HR [95% CI][a]	p-value[b]
VICTORIA						
Hospitalization for HF						
Age						
< 75 years	1523	NA 393 (25.8)	1538	NA 470 (30.6)	0.81 [0.71; 0.92]	0.002
≥ 75 years	635	NA 209 (32.9)	620	NA 189 (30.5)	1.08 [0.89; 1.31]	0.477
Total					Interaction:	0.017[c]

a. HR [95% CI] based on Cox regression model with the covariables of treatment, region, ancestry, subgroup, and interaction between treatment and subgroup.
b. Unless otherwise indicated: p-value based on two-sided logrank test stratified by region and ancestry.
c. p-value of the likelihood ratio test of interaction between treatment and subgroup.

CI: confidence interval; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NA: not achieved; RCT: randomized controlled trial

Morbidity

Hospitalization for HF

For the outcome of hospitalization for HF, there was a statistically significant interaction for the attribute of age.

A statistically significant difference in favour of vericiguat + optimized standard therapy was shown for the age group < 75 years. For this outcome, this resulted in a hint of added benefit of vericiguat + optimized standard therapy in comparison with optimized standard therapy for patients < 75 years of age. There was no statistically significant difference between treatment groups for the age group ≥ 75 years. Consequently, there is no hint of added benefit of vericiguat + optimized standard therapy in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

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

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

2.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4 (see Table 17).

Determination of the outcome category for the outcomes on morbidity

It was not possible to glean from the dossier whether the following outcome is serious/severe or non-serious/non-severe. The classification for this outcome is justified.

Hospitalization for HF

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

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

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Vericiguat + 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	Median: NA vs. NA HR: 0.94 [0.83; 1.07] p = 0.363	Lesser benefit/added benefit not proven
Morbidity		
Hospitalization for HF Age < 75 years	Median: NA vs. NA HR: 0.81 [0.71; 0.92] p = 0.002 Probability: "hint"	Outcome category: serious/severe symptoms/late complications Added benefit, extent: “non-quantifiable”
≥ 75 years	Median: NA vs. NA HR: 1.08 [0.89; 1.31] p = 0.477	Lesser benefit/added benefit not proven
MI	Median: NA vs. NA HR: 1.04 [0.66; 1.63] p = 0.863	Lesser benefit/added benefit not proven
Stroke	Median: NA vs. NA HR: 1.02 [0.62; 1.68] p = 0.930	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS; improvement ≥ 15 points)	27.6 % vs. 26.5 % RR: 1.04 [0.93; 1.16] p = 0.457	Lesser benefit/added benefit not proven
Health-related quality of life		
KCCQ-OSS; improvement by ≥ 15 points	33.7% vs. 34.6% RR: 0.98 [0.89; 1.07] p = 0.606	Lesser benefit/added benefit not proven
Side effects		
SAEs	32.6% vs. 34.5% RR: 0.94 [0.87; 1.03] p = 0.182	Greater/lesser harm not proven
Discontinuation due to AEs	6.5% vs. 6.2% RR: 1.04 [0.82; 1.30] p = 0.758	Greater/lesser harm not proven

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

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Vericiguat + 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]
Hypotension (SAEs)	1.4% vs. 1.8% RR: 0.82 [0.51; 1.31] p = 0.530	Greater/lesser harm not proven
Blood and lymphatic system disorders (SAEs)	1.8% vs. 0.9% RR: 1.92 [1.15; 3.21] RR: 0.52 [0.31; 0.87][c] p = 0.013 Probability: "hint"	Outcome category: serious/severe side effects greater harm, extent: "non-quantifiable"
Atrial fibrillation (SAEs)	0.4% vs. 1.2% RR: 0.38 [0.19; 0.73] p = 0.004 Probability: "hint"	Outcome category: serious/severe side effects Lesser harm, extent: "non-quantifiable"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. IQWiG calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; HR: hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; NA: not achieved; OSS: overall summary score; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

2.5.2 Overall conclusion on added benefit

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

Table 18: Favourable and unfavourable effects from the assessment of vericiguat + optimized standard therapy in comparison with optimized standard therapy

Favourable effects	**Unfavourable effects**
Morbidity Serious/severe symptoms / late complications ▪ Hospitalization for HF ▫ < 75 years hint of an added benefit, extent: non-quantifiable	–
Serious/severe side effects ▪ Atrial fibrillation (SAEs): hint of lesser harm – extent: non-quantifiable	Serious/severe side effects ▪ Blood and lymphatic system disorders (SAEs): hint of greater harm – extent: non-quantifiable
HF: heart failure; SAE: serious adverse event	

Overall, concerning favourable effects, a hint of non-quantifiable added benefit of vericiguat in the outcome category of serious/severe symptoms / late complications was found only for patients < 75 years of age. In the outcome category of serious/severe side effects, there is both a favourable and an unfavourable effect. However, it is questionable whether the favourable effect regarding the outcome of atrial fibrillation is to be allocated to the outcome category of side effects or whether it rather reflects the symptoms of the disease. A clear demarcation is not possible on the basis of the available information.

In summary, for the treatment of symptomatic chronic HF in adult patients < 75 years of age with reduced ejection fraction who are stabilized after a recent decompensation event requiring IV therapy, there is a hint of non-quantifiable added benefit of vericiguat in comparison with optimized standard therapy. For the treatment of symptomatic chronic HF in adult patients ≥ 75 years of age with reduced ejection fraction who are stabilized after a recent decompensation event requiring IV therapy, there is no hint of added benefit of vericiguat; added benefit is therefore not proven.

Table 19 summarizes the result of the assessment of added benefit of vericiguat in comparison with the ACT.

Table 19: Vericiguat – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Symptomatic chronic HF in adult patients with reduced ejection fraction who are stabilized after a recent decompensation event requiring IV therapy	Optimized standard therapy for the treatment of symptomatic chronic HF and underlying medical conditions, e.g. hypertension, cardiac arrhythmia, coronary heart disease, diabetes mellitus, hypercholesterolaemia and the concomitant symptoms	▪ Age < 75 years: hint of a non-quantifiable added benefit. ▪ Age ≥ 75 years: added benefit not proven.
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HF: heart failure; IV: intravenous		

The assessment described above deviates from that of the company, which derived proof of minor added benefit.

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

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Please see full dossier assessment for full reference list.

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

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