IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Sacubitril/valsartan – Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Sacubitril/Valsartan – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 30 March 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

List of abbreviations

Abbreviation	Meaning
ACE	angiotensin converting enzyme
ACT	appropriate comparator therapy
AE	adverse event
ARB	angiotensin receptor blocker
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
KCCQ	Kansas City Cardiomyopathy Questionnaire
KCCQ OSS	Kansas City Cardiomyopathy Questionnaire overall summary score
MRA	mineralocorticoid receptor antagonist
MedDRA	Medical Dictionary for Regulatory Activities
NMQ	Novartis MedDRA Query
NYHA	New York Heart Association
OR	odds ratio
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TIA	transient ischaemic attack
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 sacubitril/valsartan. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 23 December 2015.

Research question

The aim of the present report was to assess the added benefit of sacubitril/valsartan in comparison with angiotensin converting enzyme (ACE) inhibitors (each in combination with a beta-blocker) as appropriate comparator therapy (ACT) in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

Table 2 shows the research question resulting under consideration of the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of sacubitril/valsartan + beta-blocker

Intervention	**Therapeutic indication**	**ACT**[a]
Sacubitril/valsartan	Treatment of symptomatic chronic heart failure with reduced ejection fraction in adult patients	ACE inhibitor (**enalapril**) and, if indicated, beta-blocker under consideration of the approval status Guideline-conforming treatment of the underlying diseases such as hypertension, cardiac arrhythmias or diabetes mellitus, as well as of the concomitant symptoms such as cardiac oedema, is presumed.
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACE: angiotensin converting enzyme; ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The company concurred with the G-BA's specifications and chose enalapril as option for the component of the ACE inhibitor.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Only randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used. This concurs with the company's inclusion criteria.

Results

Study pool and patient population

The study PARADIGM-HF was included in the benefit assessment. This study was a completed, randomized, active-controlled, double-blind approval study on the comparison of sacubitril/valsartan versus enalapril (each in combination with a beta-blocker). Adult patients with symptomatic chronic heart failure (New York Heart Association [NYHA] severity classes II to IV) and reduced ejection fraction (≤ 35%) were enrolled in the study. In addition, patients had to have received stable guideline-conforming treatment of their cardiac failure for at least 4 weeks before enrolment. This treatment had to include the use of ACE inhibitors or angiotensin receptor blockers (ARBs) together with beta-blockers and, if applicable, mineralocorticoid receptor antagonists (MRAs).

In the PARADIGM-HF study, a 5- to 10-week sequential, single-blind run-in phase with administration of enalapril, followed by administration of sacubitril/valsartan was planned for all patients included after the screening to ensure that patients tolerated the daily target dose of 20 mg enalapril and 400 mg sacubitril/valsartan. Subsequently, 8442 patients were randomly assigned in a ratio of 1:1. The daily target dose for patients in the control arm was 20 mg enalapril, and for patients in the intervention arm 400 mg sacubitril/valsartan. A prespecified analysis based on 1744 events of the primary outcome and 1027 cardiovascular deaths was conducted in March 2014. Following this analysis, the study was stopped prematurely (after 51 months) due to the early proof of superiority.

Risk of bias and certainty of conclusions

The risk of bias at study level was rated as low for the PARADIGM-HF study. The risk of bias at outcome level was rated as low for most outcomes. Exceptions were the following outcomes: health status (measured with the visual analogue scale [VAS] of the European Quality of Life-5 Dimensions [EQ-5D] questionnaire), health-related quality of life recorded with the overall summary score of the Kansas City Cardiomyopathy Questionnaire (KCCQ OSS) and the Novartis Medical Dictionary for Regulatory Activities (MedDRA) Query (NMQ) hypotension. The risk of bias for these outcomes was rated as high. The risk of bias was not assessed for the outcomes “serious adverse events (SAES)” and “discontinuation due to adverse events (AEs)” because conclusively interpretable data were missing.

Irrespective of the risk of bias, the certainty of conclusions of the PARADIGM-HF study was impaired by the sequential run-in phase. This possibly led to an underestimation of the AEs, particularly regarding sacubitril/valsartan. Furthermore, the approval of sacubitril/valsartan also includes treatment-naive patients and patients with reduced renal function. These patient groups were not included in the PARADIGM-HF study, however.

All-cause mortality

A statistically significant difference in favour of sacubitril/valsartan was shown for the outcome “all-cause mortality”. This difference was mainly caused by a difference in

cardiovascular mortality. This resulted in an indication of an added benefit of sacubitril/ valsartan in comparison with enalapril (each in combination with a beta-blocker) for this outcome.

Morbidity

Hospitalization due to cardiac failure

A statistically significant difference in favour of sacubitril/valsartan (in combination with a beta-blocker) was shown for the outcome "hospitalization due to cardiac failure". Moreover, there was proof of an effect modification by the characteristic "severity grade (NYHA class)". This resulted in an indication of an added benefit for patients with severity grade of NYHA class I/II. No hint of an added benefit was shown for patients with severity grade of NYHA class III/IV. An added benefit for these patients is therefore not proven.

Health-related quality of life clinical summary score of the KCCQ (KCCQ OSS; responder for clinically relevant deterioration)

A statistically significant difference in favour of sacubitril/valsartan (in combination with a beta-blocker) was shown for the outcome "KCCQ OSS". This resulted in a hint of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker) for this outcome.

Hypotension

There was a statistically significant disadvantage of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker) for the outcome "hypotension". This resulted in a hint of greater harm of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker) for the outcome "hypotension".

Further outcomes

No statistically significant difference between the treatment groups was shown for further investigated outcomes. This included the following outcomes: myocardial infarction, nonfatal myocardial infarction, fatal myocardial infarction, stroke, nonfatal stroke, fatal stroke, terminal renal insufficiency, health status (EQ-5D VAS), health-related quality of life clinical summary score of the KCCQ (KCCQ OSS; responder for clinically relevant improvement) and angioedema.

Due to the recorded high proportion of events representing the late complications and symptoms of the underlying disease, no conclusively interpretable data were available for the outcomes "SAEs" and "discontinuation due to AEs". However, there were no signs of greater harm of sacubitril/valsartan in these outcomes.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug sacubitril/valsartan compared with the ACT is assessed as follows:

Overall, positive effects of sacubitril/valsartan (in combination with a beta-blocker) remain in the outcome categories "mortality", "morbidity" and "health-related quality of life", and a negative effect for the outcome category "side effects".

On the side of positive effects, there was an indication of considerable added benefit in comparison with the ACT for the outcome "all-cause mortality". This added benefit was mainly caused by cardiovascular mortality. Moreover, there was a hint of a minor added benefit for health-related quality of life. In addition, there was an indication of considerable added benefit for the outcome "hospitalization due to cardiac failure" for the patient population with severity grade of NYHA class I and II. This subgroup result did not lead to a different assessment of the added benefit for this patient population in comparison with the total population, however.

The positive effects are in contrast to a negative effect in the category of non-serious/non-severe side effects. There was a hint of greater harm with non-quantifiable extent for the outcome "hypotension". This did not challenge the positive effects of sacubitril/valsartan.

There were no conclusively interpretable data for the outcomes "SAEs" and "discontinuation due to AEs", but there were no signs of greater harm under sacubitril/valsartan.

In summary, there is an indication of considerable added benefit of sacubitril/valsartan in comparison with the ACT ACE inhibitor (enalapril) (each in combination with a beta-blocker) for adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

The result of the assessment of the added benefit of sacubitril/valsartan in comparison with an ACE inhibitor (each in combination with a beta-blocker) is summarized in Table 3.

[4] 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, no added benefit, or less benefit). For further details see [1,2].

Table 3: Sacubitril/valsartan – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Treatment of symptomatic chronic heart failure with reduced ejection fraction in adult patients	ACE inhibitor (**enalapril**) and, if indicated, beta-blocker under consideration of the approval status Guideline-conforming treatment of the underlying diseases such as hypertension, cardiac arrhythmias or diabetes mellitus, as well as of the concomitant symptoms such as cardiac oedema, is presumed.	Indication of considerable added benefit
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACE: angiotensin converting enzyme; ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

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

2.2 Research question

The aim of the present report was to assess the added benefit of sacubitril/valsartan in comparison with ACE inhibitors (each in combination with a beta-blocker) as ACT in adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

Table 4 shows the research question resulting under consideration of the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of sacubitril/valsartan + beta-blocker

Intervention	**Therapeutic indication**	**ACT**[a]
Sacubitril/valsartan	Treatment of symptomatic chronic heart failure with reduced ejection fraction in adult patients	ACE inhibitor (**enalapril**) and, if indicated, beta-blocker under consideration of the approval status Guideline-conforming treatment of the underlying diseases such as hypertension, cardiac arrhythmias or diabetes mellitus, as well as of the concomitant symptoms such as cardiac oedema, is presumed.
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACE: angiotensin converting enzyme; ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The company concurred with the G-BA's specifications and chose enalapril as option for the component of the ACE inhibitor.

The assessment was conducted based on patient-relevant outcomes and on the data provided by the company in the dossier. Only RCTs with a minimum duration of 24 weeks were used. 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 sacubitril/valsartan (status: 19 October 2015)
- bibliographical literature search on sacubitril/valsartan (last search on 20 October 2015)
- search in trial registries for studies on sacubitril/valsartan (last search on 9 October 2015)

To check the completeness of the study pool:

- search in trial registries for studies on sacubitril/valsartan (last search on 15 January 2016)

No additional relevant study was identified from the check.

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
CLCZ696B2314 (PARADIGM-HF)[b]	Yes	Yes	No

a: Study for which the company was sponsor.
b: In the following tables, the study is referred to with the abbreviated form (PARADIGM-HF).
RCT: randomized controlled trial; vs.: versus

Section 2.6 contains a reference list for the study included.

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: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PARADIGM-HF	RCT, double-blind, parallel	Adult patients with chronic cardiac failure of NYHA classes II-IV and reduced ejection fraction with: ▪ LVEF ≤ 35%[b] ▪ BNP ≥ 150 pg/mL ▪ BNP ≥ 100 pg/mL in case of hospitalization due to cardiac failure within the last 12 months prior to enrolment stable guideline-conforming treatment of their cardiac failure for at least 4 weeks (ARB or ACE inhibitor plus beta-blocker, if applicable MRA)	Sacubitril/valsartan + beta-blocker (N = 4209) enalapril + beta-blocker (N = 4233)	Sequential, single-blind run-in phase: 5-10 weeks Treatment phase: event-driven study duration end of study for all patients after 2410 events in the primary outcome	948 centres in 47 countries in North America, Latin America, Asia, Western Europe, Central Europe and South Africa 8/2009–5/2014[c]	Primary: composite outcome of hospitalization due to cardiac failure and cardiovascular mortality Secondary: all-cause mortality composite outcome of mortality and morbidity outcomes hospitalization myocardial infarction stroke terminal renal insufficiency health-related quality of life AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on the relevant available outcomes for this benefit assessment.
b: Reduction of the allowed LVEF from ≤ 40% to ≤ 35% following Amendment 1.
c: Study was stopped prematurely after 51 months due to early proof of superiority.

ACE: angiotensin converting enzyme; AE: adverse event; ARB: angiotensin receptor blocker; BNP: brain natriuretic peptide; LVEF: left-ventricular ejection fraction; MRA: mineralocorticoid receptor antagonist; N: number of randomized (enrolled) patients; NYHA: New York Heart Association; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker

Study	Intervention	Comparison	Pretreatment and concomitant treatment
PARADIGM-HF	Sequential, single-blind run-in phase:		Pretreatment: stable guideline-conforming treatment of their cardiac failure for at least 4 weeks (ARB or ACE inhibitor plus beta-blocker, if applicable MRA) Concomitant treatment permitted: ▪ calcium channel blockers ▪ diuretics ▪ β- and α-blockers ▪ nitrates ▪ MRAs Non-permitted concomitant treatment ▪ ACE inhibitors ▪ ARBs ▪ bile acid sequestrants
	First period enalapril 10 mg bid, oral (2 weeks)[a] + placebo		
	Second period sacubitril/valsartan 100 mg bid, oral (1–2 weeks), followed by titration to 200 mg bid, oral (2 weeks) + placebo		
	Double-blind phase (randomized):		
	sacubitril/valsartan 200 mg bid, oral + placebo	enalapril 10 mg bid, oral + placebo	
	background medication: beta-blockers, MRAs	background medication: beta-blockers, MRAs	
	temporary dose reduction to 50 or 100 mg bid or short-term interruption of treatment in case of intolerance	temporary dose reduction to 5 or 2.5 mg bid or short-term interruption of treatment in case of intolerance	

a: A starting dose of 5 mg bid for 1 or 2 weeks before up-titration to 10 mg bid was allowed for patients currently treated with ARBs or low-dose ACE inhibitors.

ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; bid: twice daily; MRA: mineralocorticoid receptor antagonist; RCT: randomized controlled trial; vs.: versus

The included study PARADIGM-HF was a completed randomized active-controlled double-blind approval study. The multicentre study was conducted in countries in North and Latin America, Western and Central Europe, Asia, and the Pacific region.

Adult patients with symptomatic chronic heart failure (NYHA severity classes II to IV) and reduced ejection fraction (≤ 35%) were enrolled. In addition, patients had to have received stable guideline-conforming treatment of their cardiac failure for at least 4 weeks before enrolment. This treatment had to include the use of ACE inhibitors or ARBs together with beta-blockers and, if applicable, MRAs.

In the PARADIGM-HF study, a 5- to 10-week sequential, single-blind run-in phase with administration of enalapril, followed by administration of sacubitril/valsartan, was planned for all patients included after the screening. The aim of the run-in phase was to ensure that patients tolerated the daily target dose of 20 mg enalapril and 400 mg sacubitril/valsartan. Patients who did not tolerate the target doses of enalapril or sacubitril/valsartan left the study and were not randomized.

8442 patients were randomized in a ratio of 1:1, 4209 patients to the sacubitril/valsartan arm and 4233 patients to the enalapril arm. The daily target dose for patients in the control arm was 20 mg enalapril, and for patients in the intervention arm 400 mg sacubitril/valsartan. Dose reduction or short-term interruption of treatment in case of intolerance was envisaged in both treatment groups.

Besides the study medications (sacubitril/valsartan and enalapril) and the background medication (beta-blocker and, if applicable, MRA), the randomized patients were to receive optimum cardiac failure treatment. This could consist of calcium channel blockers, diuretics and nitrates. ACE inhibitors, ARBs and bile acid sequestrants were not allowed.

Primary outcome of the study was a composite outcome of hospitalization due to cardiac failure and cardiovascular mortality. Further patient-relevant outcomes were all-cause mortality, a composite outcome (with components from the categories of mortality and morbidity), hospitalization, myocardial infarction, stroke, terminal renal insufficiency, health-related quality of life and AEs.

Three formal event-driven interim analyses were conducted in the study. The end of the study was planned after reaching 2410 events of the primary composite outcome consisting of the 2 components hospitalization due to cardiac failure and cardiovascular mortality. The final prespecified interim analysis based on 1744 events of the primary outcome and 1027 cardiovascular deaths was conducted in March 2014, and the study was stopped prematurely (after 51 months) due to the early proof of superiority.

Assessment of the study design

Run-in phase

The 5- to 10-week sequential, single-blind run-in phase with administration of enalapril, followed by administration of sacubitril/valsartan, used in the PARADIGM-HF study resulted in a selected patient population at the time point of randomization. 2079 (19.8%) of the 10513 patients included after screening had discontinued the study during the run-in phase already before randomization because of side effects or abnormal laboratory findings (and other things) (see Section 2.7.2.4.1 of the full dossier assessment). It was therefore ensured for the patient population included in the randomized phase that they tolerated the approved maintenance doses of both drugs. Correspondingly, the side effects or other reasons for discontinuation that occur in the initial or in the titration phase of sacubitril/valsartan and enalapril were not recorded in the randomized phase of the study. This may lead to an underestimation of the AEs for sacubitril/valsartan and enalapril in the randomized study phase.

In addition, the potential underestimation of AEs may be greater for sacubitril/valsartan due to the sequential run-in phase. A comparable proportion of patients dropped out under enalapril and under the subsequent sacubitril/valsartan administration in the run-in phase (10.5% of the exposed patients under enalapril, and 10.4% of the exposed patients under sacubitril/

valsartan). No comparable tolerability profile of the drugs can be inferred from this, however. Instead it is unclear whether the patients who had dropped out already under enalapril would have also not tolerated sacubitril/valsartan, and would therefore have led to a higher AE rate. Further information can be found in Section 2.7.2.4.1 of the full dossier assessment.

The influence of the run-in phase on the results of the study in the present case was not considered to be so large as to raise doubts about the relevance of the study. However, the certainty of conclusions of the study was limited because of this.

Enalapril dosage

A maximum daily dose of 40 mg is approved for enalapril according to the information provided in the Summary of Product Characteristics (SPC) [3]. However, several studies with enalapril have shown that a dose of 20 mg enalapril daily is to be considered a conventional maintenance dose in the present disease [4,5]. The described deviation from the SPC therefore did not raise doubts about the relevance of the study.

Characteristics of the study population

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

Table 8: Characteristics of the study population – RCT, direct comparison: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker

Study Characteristics Category	**Sacubitril/valsartan + beta-blocker**	**Enalapril + beta-blocker**
PARADIGM-HF	N = 4209	N = 4233
Age [years], mean (SD)	63.78 (11.52)	63.82 (11.25)
Sex [F/M], %	21/79	23/77
Ethnicity, n (%)[a]		
Caucasian	2780 (66)	2799 (66)
Black	213 (5)	215 (5)
Asian	760 (18)	750 (18)
Other	456 (11)[a]	469 (11)[a]
Region, n (%)		
North America	310 (7)	292 (7)
Latin America	726 (17)	732 (17)
Western Europe	1029 (24)	1028 (24)
Central Europe	1398 (33)	1439 (34)
Asia/Pacific/other	746 (18)	742 (18)
LVEF (%), mean (SD)	29.55 (6.14)	29.41 (6.29)
NYHA class, n (%)		
NYHA I	183 (4)	213 (5)
NYHA II	3007 (71)	2930 (69)
NYHA III	979 (23)	1056 (25)
NYHA IV	33 (1)	27 (1)
Missing	7 (0)	7 (0)
BMI, mean (SD)	28.1 (5.5)	28.2 (5.5)
SBP (mmHg), mean (SD)	121.5 (15.2)	121.2 (15.4)
DBP (mmHg), mean (SD)	73.6 (10.0)	73.6 (10.1)
eGFR (mL/min/1.73 m^2), mean (SD)	67.6 (19.9)	67.7 (20.3)
BNP (pmol/L), mean (SD)	120.7 (155.0)	120.6 (156.6)
Hypertension, n (%)	2980 (71)	2990 (71)
Diabetes, n (%)	1462 (35)	1465 (35)
Treatment discontinuation, n (%)	1182 (28)	1353 (32)
Study discontinuation, n (%)	741 (18)	862 (20)
Cardiovascular events and treatments before enrolment		
Prior hospitalization due to cardiac failure; n (%)	2620 (62)	2679 (63)
Prior myocardial infarction, n (%)	1827 (43)	1822 (43)

(continued)

Table 8: Characteristics of the study population – RCT, direct comparison: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker (continued)

Study Characteristics Category	**Sacubitril/valsartan + beta-blocker**	**Enalapril + beta-blocker**
	N = 4209	N = 4233
Prior stroke, n (%)	359 (9)	370 (9)
Prior TIA, n (%)	126 (3)	148 (3)
Pretreatment with ACE inhibitor, n (%)	3279 (78)	3281 (78)
Pretreatment with ARB, n (%)	938 (22)	969 (23)
Pretreatment with MRA, n (%)	2404 (57)	2527 (60)
Pretreatment with beta-blocker, n (%)	3975 (94)	3984 (94)
Pretreatment with diuretics, n (%)	3495 (83)	3476 (82)

a: Institute's calculation.

ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; BMI: body mass index; BNP: brain natriuretic peptide; DBP: diastolic blood pressure, eGFR: estimated glomerular filtration rate; F: female; LVEF: left-ventricular ejection fraction; M: male; MRA: mineralocorticoid receptor antagonist; N: number of randomized patients; n: number of patients in the category; NYHA: New York Heart Association; RCT: randomized controlled trial; SBP: systolic blood pressure; SD: standard deviation; TIA: transient ischaemic attack; vs.: versus

The characteristics of the patients included in the PARADIGM-HF study were comparable between the treatment groups. The mean age of the patients was 64 years. About one fifth of the patients were women.

Before randomization, physical endurance of all patients was rated using the NYHA classification. The majority of the patients (about 70%) in both treatment groups were in severity class NYHA II and had slight limitation of physical activity. About 24% of the patients were in severity grade NYHA III and had marked limitation of physical activity. Only about 5% and 1% of the patients were in the lowest (NYHA I) and in the highest (NYHA IV) severity class.

Left-ventricular ejection fraction was comparable in both treatment groups (about 29%).

All patients enrolled had been pretreated with an ACE inhibitor or an ARB with 78% of the patients pretreated with an ACE inhibitor, and 22% with an ARB. Almost all patients (94%) had received prior beta-blocker (94%) or diuretic (about 83%) therapy in addition to the primary treatment.

The majority (62% to 63%) of the patients had already been hospitalized due to cardiac failure at least once before enrolment. 43% of the patients had prior myocardial infarction, 9% stroke and 3% prior transient ischaemic attack (TIA).

Two thirds of the patients in both treatment groups were Caucasians. These were recruited mainly in Central (33% to 34%) and Western Europe (24%).

The proportion of study discontinuations was about 18% in the sacubitril/valsartan arm and 20% in the enalapril arm. The proportion of treatment discontinuations was also lower in the sacubitril/valsartan arm (28%) than in the enalapril arm (32%).

Treatment duration and observation period

Table 9 shows the mean and median observation periods, treatment and exposure durations as well as the proportion of patients with treatment interruption or dose reduction.

Table 9: Information on the course of the study – RCT, direct comparison: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker

Study **Duration of the study phase**	**Sacubitril/valsartan + beta-blocker**	**Enalapril + beta-blocker**
PARADIGM-HF	N = 4203	N = 4229
Observation period [years]		
Median [Q1; Q3]	2.27 [1.61; 2.98]	2.25 [1.57; 2.97]
Mean (SD)	2.26 (0.87)	2.23 (0.90)
Treatment duration[a] [months]		
Median [Q1; Q3]	24.44 [17.02; 33.77]	23.46 [16.30; 33.48]
Mean (SD)	24.66 (11.40)	23.91 (11.76)
Exposure duration[b] [months]		
Median [Q1; Q3]	24.15 [16.82; 33.41]	23.11 [16.13; 33.17]
Mean (SD)	24.41 (11.37)	23.65 (11.72)
Patients with at least one treatment interruption, n (%)[c]	1428 (34)	1528 (36)
Patients with at least one dose reduction, n (%)	1758 (42)	1796 (43)

a: The time between the start of the medication in the double-blind study phase and the day of the last administration of the study medication including interruptions.
b: Time in which the patient actually received the study medication, i.e. treatment duration minus times of interruption.
c: Interruption of treatment was considered to be a non-administration of the study medication for > 7 days.
max: maximum; min: minimum; N: number of randomized patients; n: number of patients in the category; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The mean observation period and the treatment duration was comparable between the 2 treatment groups (median observation period: about 2.3 years; median treatment duration: about 24 months). The number of patients with treatment interruption or dose reduction also did not differ to a relevant degree between the 2 treatment groups. About 34% of the patients in the sacubitril/valsartan arm and 36% of the patients in the enalapril arm interrupted treatment. Slightly more than 40% of the patients in both treatment groups had at least one dose reduction.

Risk of bias and certainty of conclusions

Table 10 shows the risk of bias at study level.

Table 10: Risk of bias at study level – RCT, direct comparison: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
PARADIGM-HF	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for the PARADIGM-HF study. This concurs with the company's assessment.

Irrespective of the risk of bias, the certainty of conclusions of the PARADIGM-HF study was impaired by the sequential run-in phase. This possibly led to an underestimation of the AEs, particularly regarding sacubitril/valsartan. Furthermore, the approval of sacubitril/valsartan also includes treatment-naive patients and patients with reduced renal function. These patient groups were not included in the PARADIGM-HF study, however.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
  - cardiovascular mortality
- Morbidity
  - composite outcome consisting of cardiovascular mortality, hospitalization due to cardiac failure, nonfatal myocardial infarction, nonfatal stroke, nonfatal cardiac arrest
  - hospitalization due to cardiac failure
  - myocardial infarction
    - nonfatal myocardial infarction

    - fatal myocardial infarction
  - stroke
    - nonfatal stroke
    - fatal stroke
  - terminal renal insufficiency
  - health status measured with the EQ-5D VAS
- health-related quality of life
  - health-related quality of life recorded with the KCCQ OSS
- Side effects
  - overall rate of SAEs
  - discontinuation due to AEs
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in Module 4 A of the dossier (see Section 2.7.2.4.3 of the full dossier assessment). Deviating from the company, the following outcomes were additionally used for the assessment: myocardial infarction, fatal myocardial infarction, stroke, fatal stroke, and the composite outcome consisting of cardiovascular mortality, hospitalization due to cardiac failure, nonfatal myocardial infarction, nonfatal stroke and nonfatal cardiac arrest.

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

Table 11: Matrix of outcomes – RCT, direct comparison: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker

Study	Outcomes																
	All-cause mortality	Cardiovascular mortality	Cardiovascular mortality, hospitalization due to cardiac failure, nonfatal myocardial infarction, nonfatal stroke, nonfatal cardiac arrest	Hospitalization due to cardiac failure	Myocardial infarction	Nonfatal myocardial infarction	Fatal myocardial infarction	Stroke	Nonfatal stroke	Fatal stroke	Terminal renal insufficiency	Health status (EQ-5D VAS)	Health-related quality of life (KCCQ OSS)	Serious adverse events[a]	Discontinuation due to adverse events[a]	Hypotension (NMQ)	Angioedema
PARADIGM-HF	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	(Y)	(Y)	Y	Y

a: No conclusively interpretable data available.

EQ-5D: European Quality of Life-5 Dimensions; KCCQ: Kansas City Cardiomyopathy Questionnaire; MedDRA: Medical Dictionary for Regulatory Activities; NMQ: Novartis MedDRA Query; OSS: overall summary score; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus; Y: yes

Data were available for all outcomes. Data for the outcomes "SAEs" and "discontinuation due to AEs" were available, but these were not conclusively interpretable because the proportion of events representing the late complications and symptoms of the underlying disease was high for both outcomes. The outcomes could therefore not be used to conclusively determine the harm of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker).

2.4.2 Risk of bias

Table 12 shows the risk of bias for the relevant outcomes.

Table 12: Risk of bias at study and outcome level – RCT, direct comparison: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker

Study	Outcomes																		
	Study level	All-cause mortality	Cardiovascular mortality	Cardiovascular mortality, hospitalization due to cardiac failure, nonfatal myocardial infarction, nonfatal stroke, nonfatal cardiac arrest	Hospitalization due to cardiac failure	Myocardial infarction	Nonfatal myocardial infarction	Fatal myocardial infarction	Stroke	Nonfatal stroke	Fatal stroke	Terminal renal insufficiency	Health status (EQ-5D VAS)	Health-related quality of life (KCCQ OSS)	SAEs	Discontinuation due to AEs	Hypotension (NMQ)	Angioedema
PARADIGM-HF	L	L	L	L	L	L	L	L	L	L	L	L	H[a]	H[a]	-[b]	-[b]	H[c]	L

a: Total of > 10% missing values in the analysis.
b: No conclusively interpretable data available.
c: Due to the low certainty of measurement of the chosen operationalization of this outcome; for reasons see Section 2.7.2.4.3 of the full dossier assessment.
EQ-5D: European Quality of Life-5 Dimensions; H: high; KCCQ: Kansas City Cardiomyopathy Questionnaire; L: low; MedDRA: Medical Dictionary for Regulatory Activities; NMQ: Novartis MedDRA Query; OSS: overall summary score; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

Contrary to the company's assessment, the outcomes "health status" (EQ-5D VAS) and "health-related quality of life" (KCCQ OSS) were rated as having a high risk of bias due to the high proportion of missing data. The risk of bias of the outcome "hypotension" was rated as high because of the low certainty of measurement of the present operationalization of this outcome. See Section 2.7.2.4.2 of the full dossier assessment for detailed reasons.

The risk of bias of the composite outcome of cardiovascular mortality, hospitalization due to cardiac failure, nonfatal myocardial infarction, nonfatal stroke and nonfatal cardiac arrest, which was recorded in addition to the company's presentation in Module 4 A of the dossier, was rated as low. The risk of bias of the outcomes "fatal myocardial infarction" and "fatal stroke", which were also recorded in addition to the company's presentation in Module 4 A of the dossier, was rated as low.

Only a qualitative assessment is possible of the results on the overall rates of SAEs and discontinuation due to AEs because of the high proportion of events recorded that represent the late complications and symptoms of the underlying disease. No regular rating of the risk of bias was therefore conducted for these results. The company rated the risk of bias for these outcomes as low.

The risk of bias for all remaining outcomes was rated as low. This concurs with the company's assessment.

The company assessed the available evidence overall as proof of an added benefit. The company drew no concrete conclusions on the probability of the evidence for the individual outcomes. It can therefore be assumed that the company considered there to be proof also for the individual outcomes in case of an added benefit.

2.4.3 Results

The results on the comparison of sacubitril/valsartan with enalapril (each in combination with a beta-blocker) in adult patients with symptomatic chronic heart failure with reduced ejection fraction are summarized in Table 13 and Table 14. Where necessary, the data from the company's dossier were supplemented by the Institute's calculations.

The Peto odds ratio (Peto OR) offers a good approximation of the relative risk in certain situations (see Section 2.7.2.2 of the full dossier assessment). Hence in these situations the Peto OR was calculated as estimator for the relative risk and used for the assessment.

Table 13: Results on mortality, morbidity, health-related quality of life and side effects at the end of the study – RCT, direct comparison: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker

Study **Outcome**	**Sacubitril/valsartan + beta-blocker**		**Enalapril + beta-blocker**		**Sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker**
	N	**25% quantile of survival time in months [95% CI][a]** **Patients with event n (%)**	**N**	**25% quantile of survival time in months [95% CI][a]** **Patients with event n (%)**	**HR [95% CI]; p-value**
PARADIGM-HF					
Mortality					
All-cause mortality	4187	NC [39.3; NC] 711 (16.98)	4212	36.9 [35.4; 39.5] 835 (19.82)	0.84 [0.76; 0.93]; < 0.001
Cardiovascular mortality	4187	NC 558 (13.33)	4212	47.1 [42.5; NC] 693 (16.45)	0.80 [0.71; 0.89]; < 0.001
Morbidity					
Composite outcome[b]	4187	ND 1019 (24.34)	4212	ND 1197 (28.42)	0.83 [0.77; 0.90]; < 0.001
Hospitalization due to cardiac failure	4187	NC [46.3; NC] 537 (12.83)	4212	NC [45.2; NC] 658 (15.62)	0.79 [0.71; 0.89]; < 0.001
Myocardial infarction	4187	ND 115 (2.75)	4212	ND 119 (2.83)	0.96 [0.74; 1.24]; 0.733
Nonfatal	4187	NC 107 (2.56)	4212	NC 105 (2.49)	1.01 [0.77; 1.32]; 0.960
Fatal	4187	ND 20 (0.48[c])	4212	ND 25 (0.59[c])	0.80 [0.45; 1.45][c, d]; 0.550[e]
Stroke	4187	ND 109 (2.60)	4212	ND 110 (2.61)	0.99 [0.76; 1.29]; 0.918
Nonfatal	4187	NC 106 (2.53)	4212	NC 107 (2.54)	0.99 [0.75; 1.29]; 0.918
Fatal	4187	ND 19 (0.45[c])	4212	ND 29 (0.69[c])	0.66 [0.38; 1.17][c, d]; 0.192[e]
Supplementary information: Nonfatal cardiac arrest	4187	NC 16 (0.38)	4212	NC 28 (0.66)	0.56 [0.31; 1.04]; 0.068
Terminal renal insufficiency	4187	NC 8 (0.19)	4212	NC 16 (0.38)	0.49 [0.21; 1.16] 0.157

(continued)

Table 13: Results on mortality, morbidity, health-related quality of life and side effects at the end of the study – RCT, direct comparison: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker (continued)

Study **Outcome**	**Sacubitril/valsartan + beta-blocker**		**Enalapril + beta-blocker**		**Sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
Health-related quality of life					
KCCQ OSS[f] responder[g]					
Clinically relevant deterioration[h]	3095	927 (29.95)	3009	1016 (33.77)	0.89 [0.82; 0.95]; 0.001
Clinically relevant improvement[h]	3095	1150 (37.16)	3009	1047 (34.80)	1.07 [1.00; 1.14]; 0.055
Side effects					
AEs	4203	3419 (81.35)	4229	3503 (82.83)	–
SAEs	4203	1937 (46.09)	4229	2142 (50.65)	Data not conclusively interpretable
Discontinuation due to AEs	4203	450 (10.71)	4229	516 (12.20)	Data not conclusively interpretable
Hypotension					
NMQ hypotension	4203	1027 (24.43)	4229	786 (18.59)	1.31 [1.21; 1.43]; < 0.001
Orthostatic hypotension	4203	64 (1.52)	4229	34 (0.80)	1.87 [1.26; 2.78][c, d]; p = 0.002[e]
Dizziness postural	4203	24 (0.57)	4229	12 (0.28)	1.97 [1.02; 3.78][c, d]; p = 0.046[e]
Presyncope	4203	15 (0.36)	4229	21 (0.50)	0.72 [0.37; 1.39][c, d]; p = 0.404[e]
Falls	4203	80 (1.90)	4229	54 (1.28)	1.49 [1.06; 2.10][c]; p = 0.023[e]
Syncope	4203	94 (2.24)	4229	117 (2.70)	0.83 [0.63; 1.09][c] p = 0.183[e]
Angioedema					
Angioedema[i]	4203	19 (0.45)	4229	10 (0.24)	1.88 [0.90; 3.89][c, d]; p = 0.097[e]
SMQ angioedema	4203	300 (7.14)	4229	312 (7.38)	0.97 [0.83; 1.13]; p = 0.675[e]

(continued)

Table 13: Results on mortality, morbidity, health-related quality of life and side effects at the end of the study – RCT, direct comparison: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker (continued)

a: The median time to event was not achieved in at least one treatment group. The 25% quantile provides the time at which the Kaplan-Meier estimator of the survival function reaches or falls below 75% for the first time.
b: Composite outcome consisting of the following components: cardiovascular mortality, hospitalization due to cardiac failure, nonfatal myocardial infarction, nonfatal stroke, nonfatal cardiac arrest.
c: Institute's calculation.
d: Peto OR used as estimator for the relative risk.
e: Institute's calculation, Fisher exact test.
f: KCCQ OSS is composed of the subdomains physical limitation, symptoms (frequency and severity), social limitation and quality of life; high scores reflect better status.
g: A last observation carried forward was conducted for survivors at the time point end of study. Patients who had died were not included in the analysis.
h: Clinically relevant deterioration or improvement: decrease or increase by ≥ 5 points (response criterion).
i: Adjudicated by Clinical Endpoint Adjudication Committee.

AE: adverse event; CI: confidence interval; HR: hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; N: number of analysed patients; NC: not calculable or not achieved; ND: no data; MedDRA: Medical Dictionary for Regulatory Activities; NMQ: Novartis MedDRA Query; OR: odds ratio; OSS: overall summary score; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standardized MedDRA Query; vs.: versus

Table 14: Results on morbidity (continuous results) – RCT, direct comparison: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker

Study **Outcome category** **Outcome**	**Sacubitril/valsartan + beta-blocker**			**Enalapril + beta-blocker**			**Sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker**
	N[a]	**Baseline values mean (SE)**	**Change at end of study mean[b] (SE)**	**N[a]**	**Baseline values mean (SE)**	**Change at end of study mean[b] (SE)**	**MD [95% CI]; p-value**
PARADIGM-HF							
Morbidity							
Health status (EQ-5D VAS)[c]	3352	68.82 (0.34)	3.81 (0.29)	3240	67.71 (0.35)	3.27 (0.30)	0.54 [−0.22; 1.30]; p = 0.161

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: A last observation carried forward was conducted for survivors at the time point end of study. Patients who had died were not included in the analysis.
c: The EQ-5D VAS represents the health status between 0 (worst status) and 100 (best status).

CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; N: number of analysed patients; RCT: randomized controlled trial; SE: standard error; VAS: visual analogue scale; vs.: versus

Mortality

The outcome "all-cause mortality" represents mortality irrespective of the cause of death, thus providing a more comprehensive picture than the outcome "cardiovascular mortality". Hence the outcome "all-cause mortality" was used for the derivation of the added benefit. Most deaths (about 81%) were due to cardiovascular causes, and the number of patients with non-cardiovascular deaths was comparable between the 2 treatment groups. Hence cardiovascular mortality was accepted as component of the composite outcome.

All-cause mortality

A statistically significant difference in favour of sacubitril/valsartan was shown for the outcome "all-cause mortality". This difference was mainly caused by a difference in cardiovascular mortality. This resulted in an indication of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker) for this outcome.

The company derived proof of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker) for this outcome.

Morbidity

Composite outcome: cardiovascular mortality, hospitalization due to cardiac failure, nonfatal myocardial infarction, nonfatal stroke, nonfatal cardiac arrest

A statistically significant difference in favour of sacubitril/valsartan (in combination with a beta-blocker) was shown for the composite outcome consisting of cardiovascular mortality, hospitalization due to cardiac failure, nonfatal myocardial infarction, nonfatal stroke and nonfatal cardiac arrest. The consideration of the individual components of the composite outcome revealed that only the outcomes "cardiovascular mortality" and "hospitalization due to cardiac failure" showed statistically significant differences in favour of sacubitril/valsartan (in combination with a beta-blocker) and therefore contributed to an important degree to the overall result of this outcome. Furthermore, an effect modification by the characteristic "severity grade (NYHA class)" was shown for the outcome "hospitalization due to cardiac failure". The derivation of the added benefit of sacubitril/valsartan (in combination with a beta-blocker) was therefore conducted at the level of the individual components of the composite outcome.

The company did not use this outcome for the derivation of an added benefit.

Hospitalization due to cardiac failure

A statistically significant difference in favour of sacubitril/valsartan (in combination with a beta-blocker) was shown for the outcome "hospitalization due to cardiac failure". Moreover, there was proof of an effect modification by the characteristic "severity grade (NYHA class)". This resulted in an indication of an added benefit for patients with severity grade of NYHA

class I/II. No hint of an added benefit was shown for patients with severity grade of NYHA class III/IV. An added benefit for these patients is therefore not proven.

The company derived proof of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker) for the total population.

Myocardial infarction

Overall events

There was no statistically significant difference between the treatment groups for the outcome "myocardial infarction". This resulted in no hint of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker). An added benefit for the outcome "myocardial infarction" is therefore not proven.

The company did not use this outcome for the derivation of an added benefit.

Nonfatal myocardial infarction

There was no statistically significant difference between the treatment groups for the outcome "nonfatal myocardial infarction". This resulted in no hint of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker). An added benefit for the outcome "nonfatal myocardial infarction" is therefore not proven.

This concurs with the company's assessment.

Fatal myocardial infarction

Based on the results of the Peto OR, there were no statistically significant differences for the outcome "fatal myocardial infarction". Hence there was no hint of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker). An added benefit for the outcome "fatal myocardial infarction" is therefore not proven.

The company did not consider this outcome in its analyses.

Stroke

Overall events

There was no statistically significant difference between the treatment groups for the outcome "stroke". Hence there was no hint of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker). An added benefit for the outcome "stroke" is therefore not proven.

The company did not use this outcome for the derivation of an added benefit.

Nonfatal stroke

There was no statistically significant difference between the treatment groups for the outcome "nonfatal stroke". Hence there was no hint of an added benefit of sacubitril/valsartan in

comparison with enalapril (each in combination with a beta-blocker). An added benefit for the outcome “nonfatal stroke” is therefore not proven.

This concurs with the company’s assessment.

Fatal stroke

Based on the results of the Peto OR, there were no statistically significant differences for the outcome “fatal stroke”. Hence there was no hint of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker). An added benefit for the outcome “fatal stroke” is therefore not proven.

The company did not consider this outcome in its analyses.

Terminal renal insufficiency

There was no statistically significant difference between the treatment groups for the outcome “terminal renal insufficiency”. Hence there was no hint of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker). An added benefit for the outcome “terminal renal insufficiency” is therefore not proven.

This concurs with the company’s assessment.

Health status (EQ-5D VAS)

There was no statistically significant difference between the treatment groups for the outcome “health status”. Hence there was no hint of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker). An added benefit for this outcome is therefore not proven.

The company derived an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker) for health status measured with the EQ-5D VAS at the end of the study, imputing data of patients who had died with the worst possible score.

Health-related quality of life

Aspects of health-related quality of life were recorded using the domains of physical limitation, symptoms, social limitation and quality of life, which were summarized under the clinical summary score KCCQ OSS of the disease-specific questionnaire KCCQ.

Clinical summary score of the KCCQ (KCCQ OSS; responder for clinically relevant deterioration)

A statistically significant difference in favour of sacubitril/valsartan (in combination with a beta-blocker) was shown for the outcome “KCCQ OSS”. This resulted in a hint of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker) for this outcome.

Based on the analysis at the end of the study, imputing the results of patients who had died with the worst possible score, the company saw proof of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker) for patients with clinically relevant KCCQ OSS deterioration.

Clinical summary score of the KCCQ (KCCQ OSS; responder for clinically relevant improvement)

No statistically significant difference between the treatment groups was shown in the analysis of the KCCQ OSS. Hence there was no hint of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker). An added benefit for this outcome is therefore not proven.

Based on the analysis at the end of the study, imputing the results of patients who had died with the worst possible score, the company saw proof of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker) for patients with clinically relevant KCCQ OSS improvement.

Side effects

Overall rate of serious adverse events and discontinuation due to adverse events

Due to the large proportion of events that represent the late complications and symptoms of the underlying disease, the data on the overall rates of SAEs and discontinuation due to AEs were not conclusively usable for drawing a conclusion on side effects of sacubitril/valsartan. Cardiac disorders were the most common category in the overall rate of SAEs, for example. Cardiac disorders also occurred frequently in the analyses on treatment discontinuations (see Section 2.7.2.4.3 of the full dossier assessment). However, the non-cardiac AEs provided no sign that greater harm occurred overall in the outcomes “SAEs” and “discontinuation due to AEs” under sacubitril/valsartan than under enalapril (each in combination with a beta-blocker).

The company derived proof of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker) for both outcomes “overall rate of SAEs” and “discontinuation due to AEs”.

Specific adverse events

Hypotension

The conclusion on the outcome “hypotension” was derived on the basis of the NMQ “hypotension” planned a priori by the company. Besides events that are not patient-relevant (blood pressure measurements), this NMQ also contains patient-relevant events (orthostatic hypotension, dizziness [postural] and presyncope). Besides the patient-relevant NMQ events mentioned, further patient-relevant hypotension events recorded in the study as common AEs are additionally presented (falls and syncope).

There was a statistically significant disadvantage of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker) for the outcome "hypotension" operationalized as NMQ.

Furthermore, statistically significant disadvantages of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker) were shown for the events "orthostatic hypotension", "dizziness (postural)" and "falls". There was no statistically significant difference between the treatment groups for any of the AEs "presyncope" and "syncope".

In summary, this resulted in a hint of greater harm of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker) for the outcome "hypotension".

The company derived proof of greater harm of sacubitril/valsartan for the outcome "hypotension".

Angioedema

The assessment of the outcome "angioedema" was conducted based on the Preferred Term (PT) "angioedema" (adjudicated by a Clinical Endpoint Adjudication Committee) and the Standardized MedDRA Query (SMQ) "angioedema" defined a priori.

There was no statistically significant difference between the treatment groups for the 2 operationalizations. Hence there was no hint of lesser/greater harm of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker). Greater/lesser harm of sacubitril/valsartan is therefore not proven for this outcome.

This concurs with the assessment of the company, which derived no greater/lesser harm on the basis of the analysis of non-adjudicated events for the outcome "angioedema".

2.4.4 Subgroups and other effect modifiers

The following effect modifiers were considered in the benefit assessment:

- age (< 65 years/≥ 65 years)
- sex (male/female)
- region (North America/Latin America/Western Europe/Central Europe/Asia/Pacific)
- severity grade (NYHA I, II/III, IV)
- pretreatment with ACE inhibitor (yes/no)
- pretreatment with ARB (yes/no)

Below, only the results on subgroups and outcomes are presented in which there were at least indications of an interaction between treatment effect and subgroup characteristic. Furthermore, subgroups are not shown if there were no statistically significant results in the total population or in the subgroups.

The prerequisite for proof of an effect modification was a statistically significant interaction with a p-value < 0.05. A p-value ≥ 0.05 and < 0.2 provided an indication of an effect modification.

The subgroup results on the comparison of sacubitril/valsartan with enalapril (each in combination with a beta-blocker) in adult patients with symptomatic chronic heart failure with reduced ejection fraction are summarized in Table 15.

Table 15: Subgroups – RCT, direct comparison: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker

Study Outcome	Sacubitril/valsartan + beta-blocker		Enalapril + beta-blocker		Sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker	
	N	25% quantile of survival time[a] in months [95% CI] Patients with event n (%)	N	25% quantile of survival time[a] in months [95% CI] Patients with event n (%)	HR [95% CI]	p-value
PARADIGM-HF						
Morbidity						
Hospitalization due to cardiac failure						
Severity grade NYHA class						
NYHA I/II	3178	NC [46.3; NC] 352 (11.08)	3130	NC [45.2; NC] 480 (15.34)	0.70 [0.61; 0.80]	< 0.001
NYHA III/IV	1002	NC [32.0; NC] 184 (18.36)	1076	NC [41.9; NC] 178 (16.54)	1.07 [0.87; 1.32]	0.493
					Interaction:	< 0.001

a: The median time to event was not achieved in at least one treatment group. The 25% quantile provides the time at which the Kaplan-Meier estimator of the survival function reaches or falls below 75% for the first time.

CI: confidence interval; HR: hazard ratio; N: number of analysed patients; n: patients with (at least) one event; NC: not calculable or not achieved; NYHA: New York Heart Association; RCT: randomized controlled trial; vs.: versus

Morbidity

Hospitalization due to cardiac failure

There was proof of an effect modification by the characteristic “severity grade (NYHA class)” for the outcome “hospitalization due to cardiac failure”. There was a statistically significant advantage in favour of sacubitril/valsartan (in combination with a beta-blocker) for patients with severity grades NYHA I and II. This resulted in an indication of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker) for patients with NYHA classes I and II. No statistically significant difference between the treatment groups was shown for patients with severity classes III and IV. This resulted in no

hint of an added benefit of sacubitril/valsartan in comparison with enalapril (each in combination with a beta-blocker) for these patients. Hence an added benefit of sacubitril/valsartan for this outcome is not proven for patients with severity classes NYHA III/IV.

This deviates from the company's assessment, which derived proof of an added benefit of sacubitril/valsartan (in combination with a beta-blocker) at the level of the total population.

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, 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 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 added benefit at outcome level

The data presented in Section 2.4 resulted in indications or hints of an added benefit for the outcomes "all-cause mortality/cardiovascular mortality", "hospitalization due to cardiac failure" and "health-related quality of life recorded with the KCCQ OSS (patients with clinically relevant deterioration). An effect modification by the characteristic "severity grade (NYHA class)" was shown for the outcome "hospitalization due to cardiac failure". This resulted in an indication of an added benefit for patients with NYHA classes I and II. There was hint of greater harm for the specific AE "hypotension". The extent of the respective added benefit at outcome level was estimated from these results (see Table 16).

The composite outcome consisting of the components "cardiovascular mortality", "hospitalization due to cardiac failure", "nonfatal myocardial infarction", "nonfatal stroke" and "nonfatal cardiac arrest" was not included in the balancing of the overall extent. This approach was chosen because there was an effect modification in the outcome "hospitalization due to cardiac failure". In addition, the result of the composite outcome was largely influenced by the events of the 2 individual components "cardiovascular mortality" and "hospitalization due to cardiac failure". The components of the composite outcome were therefore considered separately for the derivation of the added benefit of sacubitril/valsartan.

Table 16: Extent of added benefit at outcome level: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker** **Quantile of time [months] to event or proportion of events or MD** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	25% quantile[d]: NC vs. 36.9 HR: 0.84 [0.76; 0.93] p < 0.001 probability: "indication"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent "considerable"
Cardiovascular mortality[c]	25% quantile[d]: NC vs. 47.1 months HR: 0.80 [0.71; 0.89] p < 0.001	
Morbidity		
Hospitalization due to cardiac failure		
Severity: NYHA I/II	25% quantile[d]: NC vs. NC HR: 0.70 [0.61; 0.80] p < 0.001 probability: "indication"	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ added benefit, extent "considerable"
Severity: NYHA III/IV	25% quantile[d]: NC vs. NC HR: 1.07 [0.87; 1.32] p = 0.493	Lesser benefit/added benefit not proven
Myocardial infarction	25% quantile[d]: ND vs. ND HR: 0.96 [0.74; 1.24]; p = 0.733	Lesser benefit/added benefit not proven
Nonfatal	25% quantile[d]: NC vs. NC HR: 1.01 [0.77; 1.32]; p = 0.960	
Fatal	0.48% vs. 0.59% RR: 0.80 [0.45; 1.45]; p = 0.550	
Stroke	25% quantile[d]: ND vs. ND HR: 0.99 [0.76; 1.29]; p = 0.918	Lesser benefit/added benefit not proven
Nonfatal	25% quantile[d]: NC vs. NC HR: 0.99 [0.75; 1.29]; p = 0.918	
Fatal	0.45% vs. 0.69% RR: 0.66 [0.38; 1.17]; p = 0.192	
Terminal renal insufficiency	25% quantile[d]: NC vs. NC HR: 0.49 [0.21; 1.16] p = 0.157	Lesser benefit/added benefit not proven

(continued)

Table 16: Extent of added benefit at outcome level: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker (continued)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker** **Quantile of time [months] to event or proportion of events or MD** **Effect estimates [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Health status (EQ-5D VAS)	MD: 0.54 [−0.22; 1.30] p = 0.161	Lesser benefit/added benefit not proven
Health-related quality of life		
KCCQ OSS responder		
Clinically relevant deterioration	29.95% vs. 33.77% RR: 0.89 [0.82; 0.95] p = 0.001 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: "minor"
Clinically relevant improvement	37.16% vs. 34.80% RR: 1.07 [1.00; 1.14] p = 0.055	Lesser benefit/added benefit not proven
Side effects		
SAEs	No conclusively interpretable data. No sign of greater harm under sacubitril/valsartan.	
Discontinuation due to AEs	No conclusively interpretable data. No sign of greater harm under sacubitril/valsartan.	
Hypotension (NMQ)	24.43% vs. 18.59% RR: 1.31 [1.21; 1.43] RR: 0.76 [0.70; 0.83][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe AEs greater harm, extent: "non-quantifiable"[f]
Angioedema Angioedema (adjudicated) Angioedema (SMQ)	 0.45% vs. 0.24% RR: 1.88 [0.90; 3.89]; p = 0.097 7.14% vs. 7.38% RR: 0.97 [0.83; 1.13]; p = 0.675	Greater/lesser harm not proven

(continued)

Table 16: Extent of added benefit at outcome level: sacubitril/valsartan + beta-blocker vs. enalapril + beta-blocker (continued)

a: Probability provided if statistically significant differences were present. b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u. c: (All-cause) mortality was mostly due to cardiovascular causes d: The 25% quantile provides the time at which the Kaplan-Meier estimator of the survival function falls below 75% for the first time. e: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit. f: Due to the low certainty of measurement of the chosen operationalization of this outcome, the extent cannot be estimated (see Section 2.7.2.4.3 of the full dossier assessment). AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; MD: mean difference; MedDRA: Medical Dictionary for Regulatory Activities; NMQ: Novartis MedDRA Query; NC: not calculable; ND: no data; NYHA: New York Heart Association; OSS: overall summary score; RR: relative risk; SAE: serious adverse event; SMQ: Standardized MedDRA Query; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

Table 17 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of sacubitril/valsartan + beta-blocker in comparison with enalapril + beta-blocker

Positive effects	**Negative effects**
Mortality ▪ overall survival/cardiovascular mortality: indication of an added benefit; extent: "considerable"	Non-serious/non-severe adverse events ▪ hypotension; hint of greater harm; extent: "non-quantifiable"
Morbidity – serious/severe symptoms/late complications ▪ Hospitalization due to cardiac failure ▫ NYHA class I and II: indication of added benefit; extent: "considerable"	
Health-related quality of life ▪ KCCQ OSS (physical limitation, symptoms, social limitation and quality of life; clinically relevant deterioration); hint of added benefit; extent: "minor"	
No conclusively interpretable data were available on the overall rates of SAEs and discontinuations due to AEs. However, there was no sign of greater harm under sacubitril/valsartan.	
KCCQ: Kansas City Cardiomyopathy Questionnaire; NYHA: New York Heart Association; OSS: overall summary score	

Overall, positive effects of sacubitril/valsartan (in combination with a beta-blocker) remain in the outcome categories “mortality”, “morbidity” and “health-related quality of life”, and a negative effect for the outcome category “side effects”.

On the side of positive effects, there was an indication of considerable added benefit in comparison with the ACT for the outcome “all-cause mortality”. This added benefit was mainly caused by cardiovascular mortality. Moreover, there was a hint of a minor added benefit for health-related quality of life. In addition, there was an indication of considerable added benefit for the outcome “hospitalization due to cardiac failure” for the patient population with severity grade of NYHA class I and II. This subgroup result did not lead to a different assessment of the added benefit for this patient population in comparison with the total population, however.

The positive effects are in contrast to a negative effect in the category of non-serious/non-severe side effects. There was a hint of greater harm with non-quantifiable extent for the outcome “hypotension”. This did not challenge the positive effects of sacubitril/valsartan.

There were no conclusively interpretable data for the outcomes “SAEs” and “discontinuation due to AEs”, but there were no signs of greater harm under sacubitril/valsartan.

In summary, there is an indication of considerable added benefit of sacubitril/valsartan in comparison with the ACT ACE inhibitor (enalapril) (each in combination with a beta-blocker) for adult patients for treatment of symptomatic chronic heart failure with reduced ejection fraction.

The result of the assessment of the added benefit of sacubitril/valsartan in comparison with an ACE inhibitor (each in combination with a beta-blocker) is summarized in Table 18.

Table 18: Sacubitril/valsartan – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Treatment of symptomatic chronic heart failure with reduced ejection fraction in adult patients	ACE inhibitor (**enalapril**) and, if indicated, beta-blocker under consideration of the approval status Guideline-conforming treatment of the underlying diseases such as hypertension, cardiac arrhythmias or diabetes mellitus, as well as of the concomitant symptoms such as cardiac oedema, is presumed.	Indication of considerable added benefit
a: Presentation of the ACT specified by the G-BA. In cases where the company, because of the G-BA’s specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in bold. ACE: angiotensin converting enzyme; ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

This deviates from the company's approach, which derived proof of major added benefit for sacubitril/valsartan in comparison with an ACE inhibitor (enalapril) (each in combination with a beta-blocker).

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

2.6 List of included studies

PARADIGM-HF

McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014; 371(11): 993-1004.

Novartis Pharma. A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction: study CLCZ696B2314; full clinical study report [unpublished]. 2014.

Novartis Pharma Services. A multicenter, randomized, double-blind, parallel group, active-controlled study to evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality in patients with chronic heart failure and reduced ejection fraction [online]. In: EU-Clinical Trials Register. [Accessed: 21.01.2016]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-015834-31.

Novartis Pharmaceuticals. This study will evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality of patients with chronic heart failure: study results [online]. In: ClinicalTrials.gov. 09.09.2015 [accessed: 21.01.2016]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01035255.

Novartis Pharmaceuticals. This study will evaluate the efficacy and safety of LCZ696 compared to enalapril on morbidity and mortality of patients with chronic heart failure: full text view [online]. In: ClinicalTrials.gov. 09.09.2015 [accessed: 07.03.2016]. URL: https://clinicaltrials.gov/ct2/show/study/NCT01035255.

References for English extract

Please see full dossier assessment for full reference list.

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2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

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5. The SI. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. N Engl J Med 1992; 327: 685-691.

The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a15-60-sacubitril/valsartan-nutzenbewertung-gemaess-35a-sgb-v.7186.html.