Enalapril
(heart failure, children and adolescents)

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

EXTRACT

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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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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACE	angiotensin converting enzyme
ACT	appropriate comparator therapy
ARB	angiotensin receptor blocker
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LVEF	left ventricular ejection fraction
LVFS	left ventricular fractional shortening
NYHA	New York Heart Association
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug enalapril. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 1 March 2024.

Research question

The aim of this report is to assess the added benefit of enalapril compared to the appropriate comparator therapy (ACT) in children from birth to under 18 years of age for the treatment of heart failure.

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of enalapril

Research question	Therapeutic indication	ACT[a]
1	Children and adolescents aged 1 to 17 years with heart failure	Sacubitril/valsartan or captopril[b, c]
2	Children aged < 1 year with heart failure	Captopril[b, c]

a. Presented is the ACT specified by the G-BA.
b. Essentially, the treatment recommendations regarding the off-label use of drugs in the paediatric patient population are only consensus-based recommendations based on the evidence for heart failure in adults. Accordingly, there is currently a lack of valid data from RCTs for paediatric heart failure to justify the current clinical treatment practice in off-label use in children and adolescents.
c. Infants, children and adolescents in both study arms are assumed to receive optimal care. If the children and adolescents show accompanying symptoms of the underlying disease(s) or risk factors such as tachycardia, tachypnoea, oedema, ascites, pain, hypertension, cardiac arrhythmias, individualized treatment must be ensured in accordance with the generally accepted state of scientific knowledge. According to the G-BA, the adequate treatment of the existing underlying diseases (in addition to heart failure, e.g. myocarditis, cardiomyopathies) or the accompanying symptoms should be comprehensibly documented in the dossier based on the patient characteristics (e.g. oedema, cardiac arrhythmias, etc.). The aetiology of heart failure (congenital heart defects, inadequate success of surgical correction, dilated or restrictive cardiomyopathy, myocardial involvement in genetic muscle diseases and metabolic defects) must be taken into account when deciding on treatment. It should be possible to adapt the foundational/concomitant medication to the patient's individual needs in both study arms. In this context, treatment adjustment can comprise both dose adjustments and treatment switches/initiations to respond to newly developed symptoms or the deterioration of existing symptoms. The concomitant and foundational medication at study entry as well as changes to the concomitant or foundational medication must be documented.

ACT: appropriate comparator therapy; CSR: clinical study report; RCT: randomized controlled trial; vs.: versus

The company deviates from the specifications of the G-BA and names a treatment of physician's choice as ACT for the entire therapeutic indication, referring to an outdated

definition of the G-BA. The present benefit assessment is carried out in comparison with the G-BA's current ACT. The deviation of the company is of no consequence for the present assessment, as the company did not provide comparative data for the benefit assessment.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 24 weeks were used for the derivation of added benefit.

Results

During the check of completeness of the study pool, for research question 1, the randomized controlled trial (RCT) PANORAMA-HF was identified for the direct comparison of enalapril with the ACT sacubitril/valsartan in children and adolescents from 1 month to < 18 years of age with symptomatic, chronic heart failure with left ventricular dysfunction. The company also identified the RCT PANORAMA-HF, but excluded it due to exclusion criterion A2 (intervention). According to the information in Module 4 A, the company only included RCTs with an enalapril maintenance dose of 0.15 to 0.3 mg/kg per day on the basis of exclusion criterion A2.

Excluding this study for research question 1 based on the available information is not appropriate. Although there are deviations between the dosing regimen of enalapril in the PANORAMA-HF study and the approval, these do not justify exclusion from the study for research question 1.

No RCT was identified for research question 2.

Evidence provided by the company

As the company did not identify any RCT for the direct comparison of enalapril in comparison with the ACT, it conducted an information retrieval for further investigations on enalapril. In this information retrieval, the company identified the single-arm studies WP08 and WP09 and the extension study WP10 of these two studies and used them to derive the added benefit.

This approach is not appropriate. The analyses of the single-arm studies WP08, WP09, and WP10 presented by the company do not allow a comparison of enalapril versus the ACT. Thus, the studies WP08, WP09, and WP10 are not suitable for assessing the added benefit of enalapril.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of enalapril in comparison with the ACT; an added benefit is therefore not proven.

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

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

Table 3: Enalapril – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Children and adolescents aged 1 to 17 years with heart failure	Sacubitril/valsartan or captopril[b, c]	Added benefit not proven
2	Children aged < 1 year with heart failure	Captopril[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Essentially, the treatment recommendations regarding the off-label use of drugs in the paediatric patient population are only consensus-based recommendations based on the evidence for heart failure in adults. Accordingly, there is currently a lack of valid data from RCTs for paediatric heart failure to justify the current clinical treatment practice in off-label use in children and adolescents.
c. Infants, children and adolescents in both study arms are assumed to receive optimal care. If the children and adolescents show accompanying symptoms of the underlying disease(s) or risk factors such as tachycardia, tachypnoea, oedema, ascites, pain, hypertension, cardiac arrhythmias, individualized treatment must be ensured in accordance with the generally accepted state of scientific knowledge. According to the G-BA, the adequate treatment of the existing underlying diseases (in addition to heart failure, e.g. myocarditis, cardiomyopathies) or the accompanying symptoms should be comprehensibly documented in the dossier based on the patient characteristics (e.g. oedema, cardiac arrhythmias, etc.). The aetiology of heart failure (congenital heart defects, inadequate success of surgical correction, dilated or restrictive cardiomyopathy, myocardial involvement in genetic muscle diseases and metabolic defects) must be taken into account when deciding on treatment. It should be possible to adapt the foundational/concomitant medication to the patient's individual needs in both study arms. In this context, treatment adjustment can comprise both dose adjustments and treatment switches/initiations to respond to newly developed symptoms or the deterioration of existing symptoms. The concomitant and foundational medication at study entry as well as changes to the concomitant or foundational medication must be documented.

ACT: appropriate comparator therapy; CSR: clinical study report; RCT: randomized controlled trial; vs.: versus

The G-BA decides on the added benefit.

[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].

I 2 Research question

The aim of this report is to assess the added benefit of enalapril compared to the ACT in children from birth to under 18 years of age for the treatment of heart failure.

The research questions presented in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of enalapril

Research question	Therapeutic indication	ACT[a]
1	Children and adolescents aged 1 to 17 years with heart failure	Sacubitril/valsartan or captopril[b, c]
2	Children aged < 1 year with heart failure	Captopril[b, c]

a. Presented is the ACT specified by the G-BA.
b. Essentially, the treatment recommendations regarding the off-label use of drugs in the paediatric patient population are only consensus-based recommendations based on the evidence for heart failure in adults. Accordingly, there is currently a lack of valid data from RCTs for paediatric heart failure to justify the current clinical treatment practice in off-label use in children and adolescents.
c. Infants, children and adolescents in both study arms are assumed to receive optimal care. If the children and adolescents show accompanying symptoms of the underlying disease(s) or risk factors such as tachycardia, tachypnoea, oedema, ascites, pain, hypertension, cardiac arrhythmias, individualized treatment must be ensured in accordance with the generally accepted state of scientific knowledge. According to the G-BA, the adequate treatment of the existing underlying diseases (in addition to heart failure, e.g. myocarditis, cardiomyopathies) or the accompanying symptoms should be comprehensibly documented in the dossier based on the patient characteristics (e.g. oedema, cardiac arrhythmias, etc.). The aetiology of heart failure (congenital heart defects, inadequate success of surgical correction, dilated or restrictive cardiomyopathy, myocardial involvement in genetic muscle diseases and metabolic defects) must be taken into account when deciding on treatment. It should be possible to adapt the foundational/concomitant medication to the patient's individual needs in both study arms. In this context, treatment adjustment can comprise both dose adjustments and treatment switches/initiations to respond to newly developed symptoms or the deterioration of existing symptoms. The concomitant and foundational medication at study entry as well as changes to the concomitant or foundational medication must be documented.

ACT: appropriate comparator therapy; CSR: clinical study report; RCT: randomized controlled trial; vs.: versus

The company deviates from the specifications of the G-BA and names a treatment of physician's choice as ACT for the entire therapeutic indication, referring to an outdated definition of the G-BA. The present benefit assessment is carried out in comparison with the G-BA's current ACT. The deviation of the company is of no consequence for the present assessment, as the company did not provide comparative data for the benefit assessment (see Chapter I 3).

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 24 weeks were used for the derivation of added benefit. This deviates from the company's inclusion criteria, which specified no limitation in terms of study duration. This deviation is of no consequence for the present assessment, as the company did not present any data on the comparison of enalapril with the ACT (for reasons, see Chapter I 3).

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on enalapril (status: 6 February 2024)
- bibliographical literature search on enalapril (last search on 6 February 2024)
- search in trial registries/trial results databases for studies on enalapril (last search on 6 February 2024)
- search on the G-BA website for enalapril (last search on 6 February 2024)

To check the completeness of the study pool:

- bibliographic literature search on enalapril (last search on 27 March 2024); for search strategies, see Appendix A of the full dossier assessment
- search in trial registries for studies on enalapril (last search on 20 March 2024); for search strategies, see I Appendix A of the full dossier assessment

The information retrieval of the company for direct comparison and further investigations is not suitable to ensure the completeness of the search results. The company searched all bibliographic databases and trial registries for the administration form "orodispersible tablet/mini tablet" and linked the result with an AND link. However, administration forms are usually only shown incompletely or not at all in the title, abstract or keywords (for the general structure of a search strategy, see the Cochrane Handbook [3]).

Direct comparison

In agreement with the company, the check for completeness of the study pool did not show any RCTs for research question 2.

For research question 1, the RCT PANORAMA-HF [4] was identified for the direct comparison of enalapril with the ACT sacubitril/valsartan in children and adolescents from 1 month to < 18 years of age with symptomatic, chronic heart failure with left ventricular dysfunction. The company also identified the RCT PANORAMA-HF, but excluded it due to exclusion criterion A2 (intervention). According to the information in Module 4 A, the company only included RCTs with an enalapril maintenance dose of 0.15 to 0.3 mg/kg per day on the basis of exclusion criterion A2.

Excluding this study for research question 1 based on the available information is not appropriate. The therapeutic indication of symptomatic, chronic heart failure with left ventricular dysfunction investigated in the study is part of the therapeutic indication

considered in the present benefit assessment. A description of this study, including the presentation of the results for the age group of children aged 1 year or older and adolescents, is already available in the benefit assessment A23-56 [5] of sacubitril/valsartan. For the dosage regimens of enalapril and sacubitril/valsartan in the PANORAMA-HF study, there are indeed deviations from the approved use, but these do not justify exclusion from research question 1. This is explained in Section I 3.1.

Further investigations

As the company itself did not identify any RCT for the direct comparison of enalapril in comparison with the ACT, it conducted an information retrieval for further investigations on enalapril. In this information retrieval, the company identified the single-arm studies WP08 and WP09 [6] and the extension study WP10 [7] of these two studies and used them to derive the added benefit. The company conducted no information retrieval for the comparator part. The completeness of the study pool for further investigations was not checked.

The data presented by the company are unsuitable for drawing conclusions on the added benefit of enalapril in comparison with the ACT. This is explained in Section I 3.2.

I 3.1 Direct comparison

PANORAMA-HF study

The PANORAMA-HF study is a 2-part study. In part 1, it comprises an open-label pharmacokinetics/pharmacodynamics phase to determine the dose of sacubitril/valsartan (N = 26) and in part 2 a 52-week, randomised, double-blind treatment phase to assess sacubitril/valsartan in comparison with enalapril in children from 1 month of age and adolescents with symptomatic, chronic heart failure with left ventricular dysfunction (sacubitril/valsartan: N = 187; enalapril: N = 190). The following comments refer to part 2 of the PANORAMA-HF study.

The study included patients from 1 month to < 18 years of age with chronic heart failure due to left ventricular dysfunction. Of the 377 patients included, 366 patients were analysed for the age group ≥ 1 year. A left ventricular ejection fraction (LVEF) ≤ 45% or a left ventricular fractional shortening (LVFS) ≤ 22.5% had to be present. In terms of disease severity, the patients had to have a New York Heart Association (NYHA) or Ross class ≥ 2, depending on their age. Children ≥ 6 years of age could also enter the study if they had NYHA class I at the time of screening but had been categorised as class II or higher at an earlier point in time.

According to their randomization, the patients received either sacubitril/valsartan twice daily or enalapril twice daily for 52 weeks, each in addition to a placebo. Despite uncertainties, it is assumed that the treatment with sacubitril/valsartan was largely in line with their approved

use [8] (for details see benefit assessment A23-56 [5]). The dosage of enalapril is described in detail below.

In addition to the study medication, the patients included in both study arms were to continue their background therapy for chronic heart failure and any comorbidities, although angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and renin inhibitors were disallowed throughout the duration of treatment.

The primary, combined outcome of the study was a global rank outcome comprising the outcomes of all-cause mortality and various outcomes in the categories of morbidity and health-related quality of life. Furthermore, outcomes in the categories of morbidity, health-related quality of life, and side effects were surveyed.

Further details on the study design of the PANORAMA-HF study can be found in dossier assessment A23-56 [5] and in addendum A23-103 [9].

Dosage of enalapril in the PANORAMA-HF study

At the time the PANORAMA-HF study was conducted, enalapril orodispersible tablets were not authorised for children and adolescents with heart failure. In the PANORAMA-HF study, 1 paediatric administration form (liquid) and 1 adult administration form (tablet) were available for treatment with enalapril, which were taken orally twice daily. The dosage of the paediatric administration form was dependent on the age, weight and pretreatment of the patients. For the age group ≥ 1 year, when using the liquid administration form, a starting dose of 0.1 or 0.2 mg/kg should gradually be increased to a target dose of 0.4 mg/kg per day or, when used as a tablet, from 5 to 10 mg per day gradually to 20 mg per day. From the available documents for the PANORAMA-HF study, it is not clear according to which criteria the patients in the age group ≥ 1 year received a paediatric or adult administration form.

There are the following deviations in the administration of enalapril in the PANORAMA-HF study compared to the approval [10]:

- The Summary of Product Characteristics (SPC) for enalapril in the form of orodispersible tablets recommends a starting dose of 0.01 to 0.04 mg/kg as a single dose. In the PANORAMA-HF study, treatment was started with a significantly higher dosage (liquid administration form: 0.1 or 0.2 mg/kg per day; tablet: 5 or 10 mg per day).
- 1 to 2 hours after the single starting dose, blood pressure should be checked at regular intervals according to the SPC. In the PANORAMA-HF study, however, close monitoring after the starting dose was only planned for children < 1 year of age. Such initial monitoring was not planned for children and adolescents ≥ 1 year of age. However, in the first 8 weeks after randomization, visits took place for all age groups at

approximately 2-week intervals (later every 4 or 12 weeks). This involved checking the blood pressure, potassium levels, and kidney function, among other things.

- The SPC for enalapril in the form of orodispersible tablets recommends a maintenance dose of 0.15 to 0.3 mg/kg per day. The maintenance dose for the liquid administration form in the PANORAMA-HF study was slightly higher at 0.4 mg/kg per day. When the tablet was administered, there was no weight-adapted dosage, but the maintenance dose was 20 mg per day. However, the maximum daily dose is the same for the approval of enalapril as an orodispersible tablet and the two administration forms in the PANORAMA-HF study (20 mg). From the available documents for the PANORAMA-HF study, it is not clear how many patients received the liquid administration form or the tablets. Therefore, it is unclear what exact dose of enalapril was administered.
- The SPC for enalapril in the form of orodispersible tablets contains criteria for dose increases/reductions, but no information on the time interval for testing these criteria and the size of the dose increments. In the PANORAMA-HF study, however, the decision on a dose increase/reduction is made according to a fixed time schedule with defined dose steps. In the first 8 weeks, a check was made every 2 weeks to see whether the criteria were met and the dose was increased or reduced if necessary. A total of 2 or 3 dose increase steps were planned until the maintenance dose was reached.

PANORAMA-HF study suitable for the benefit assessment

Despite the deviations described, the dosing regimen of enalapril in the PANORAMA-HF study is considered to be a sufficient approximation of the approved use. Based on the available information, the PANORAMA-HF study is suitable for research question 1 of the present benefit assessment – children and adolescents aged 1 to 17 years with heart failure.

I 3.2 Evidence presented by the company

In Module 4 B 3, the company presents single-arm studies and derives a non-quantifiable added benefit on this basis.

WP08 and WP09 studies

The WP08 and WP09 studies are two single-arm studies to evaluate the pharmacokinetics and pharmacodynamics as well as the acceptability and safety profile of enalapril as orodispersible tablets. Children aged 1 month to < 12 years of age with dilated cardiomyopathy were included in the WP08 study, and children from birth to < 6 years of age with heart failure due to a congenital heart defect were included in the WP09 study. Study WP08 included 32 patients, and study WP09 included 70 patients. Of these, a total of 86 patients were treated further in the WP10 study (24 from WP08 and 62 from WP09).

Both studies included patients who had already started treatment with an ACE inhibitor (ACE inhibitor-pretreated) or who were being treated with an ACE inhibitor for the first time (ACE inhibitor-naive).

Treatment with enalapril

The ACE inhibitor-naive children received an age- and weight-adapted starting dose of enalapril as an orodispersible tablet in both studies, with blood pressure being monitored for 8 hours. If this starting dose was well tolerated, it also formed the first dose of the titration for the next 1 to 6 days or, if the child was 3 years or older, a second administration of this dose was started in the evening. This was followed by 3 to 4 gradual dose increases to target doses of between 1 and 8 mg enalapril per day, depending on age and weight. Dose increases were decided on the basis of investigations into parameters such as blood pressure, renal function, hyperkalaemia and worsening heart failure. This should be done weekly. Depending on these parameters, it was also possible to reduce the dose or discontinue treatment.

ACE inhibitor-pretreated children (cohort A in both studies) were switched to a clinically comparable enalapril dose and, if necessary, gradually up-dosed to the maintenance dose of enalapril at the investigator's discretion.

In total, all children should be treated with enalapril for a maximum of 8 weeks.

Concomitant treatment

The WP08 and WP09 studies allowed drug treatments for chronic heart failure. According to the guideline recommendations for chronic heart failure in children and adolescents, diuretics, beta-receptor blockers and mineralocorticoid receptor antagonists were administered among other things in the two studies.

WP10 extension study

The patients of the WP08 and WP09 studies who were treated with enalapril for at least 3 days were able to continue their treatment in the WP10 study for 10 months. In this case, the patients continued to receive their last dose from the WP08 or WP09 studies. Dose adjustments were possible at the physician's discretion.

Like the studies WP08 and WP09, the WP10 study surveyed outcomes on pharmacokinetics/pharmacodynamics, acceptance and the safety profile.

WP08, WP09, and WP10 studies unsuitable for the benefit assessment

The company presented analyses for the WP08, WP09, and WP10 studies. The studies have a single-arm design and thus do not allow a direct comparison of enalapril versus the ACT. Thus, contrary to the company's assessment, the WP08, WP09, and WP10 studies are not suitable for assessing the added benefit of enalapril.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of enalapril in comparison with the ACT in children and adolescents with heart failure. This applies both to children and adolescents aged 1 to 17 years (research question 1) and to children aged < 1 year (research question 2). As part of the completeness check of the company's study pool, the RCT PANORAMA-HF was identified for research question 1. There is no hint of an added benefit of enalapril in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of enalapril in comparison with the ACT is summarized in Table 5.

Table 5: Enalapril – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Children and adolescents aged 1 to 17 years with heart failure	Sacubitril/valsartan or captopril[b, c]	Added benefit not proven
2	Children aged < 1 year with heart failure	Captopril[b, c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Essentially, the treatment recommendations regarding the off-label use of drugs in the paediatric patient population are only consensus-based recommendations based on the evidence for heart failure in adults. Accordingly, there is currently a lack of valid data from RCTs for paediatric heart failure to justify the current clinical treatment practice in off-label use in children and adolescents.
c. Infants, children and adolescents in both study arms are assumed to receive optimal care. If the children and adolescents show accompanying symptoms of the underlying disease(s) or risk factors such as tachycardia, tachypnoea, oedema, ascites, pain, hypertension, cardiac arrhythmias, individualized treatment must be ensured in accordance with the generally accepted state of scientific knowledge. According to the G-BA, the adequate treatment of the existing underlying diseases (in addition to heart failure, e.g. myocarditis, cardiomyopathies) or the accompanying symptoms should be comprehensibly documented in the dossier based on the patient characteristics (e.g. oedema, cardiac arrhythmias, etc.). The aetiology of heart failure (congenital heart defects, inadequate success of surgical correction, dilated or restrictive cardiomyopathy, myocardial involvement in genetic muscle diseases and metabolic defects) must be taken into account when deciding on treatment. It should be possible to adapt the foundational/concomitant medication to the patient's individual needs in both study arms. In this context, treatment adjustment can comprise both dose adjustments and treatment switches/initiations to respond to newly developed symptoms or the deterioration of existing symptoms. The concomitant and foundational medication at study entry as well as changes to the concomitant or foundational medication must be documented.

ACT: appropriate comparator therapy; CSR: clinical study report; RCT: randomized controlled trial; vs.: versus

The assessment described above deviates from that by the company, which derived a non-quantifiable added benefit.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under https://www.iqwig.de/en/projects/a24-25.html.