Olaparib (endometrial cancer, pMMR; maintenance treatment in combination with durvalumab)

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.

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
FIGO	International Federation of Gynecology and Obstetrics
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMR	mismatch repair
pMMR	mismatch repair proficient
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) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug olaparib (maintenance treatment in combination with durvalumab). 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 22 August 2024.

Research question

The aim of the present report is to assess the added benefit of olaparib in combination with durvalumab (hereinafter referred to as "olaparib + durvalumab") in maintenance treatment compared with the appropriate comparator therapy (ACT) in adult patients with primary advanced or recurrent mismatch repair proficient (pMMR) endometrial cancer whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel. The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of olaparib + durvalumab

Therapeutic indication	**ACT[a]**
Maintenance treatment of adult patients with primary advanced or recurrent pMMR endometrial cancer whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel	Carboplatin + paclitaxel[b], followed by watchful waiting[c]

a. Presented is the ACT specified by the G-BA.
b. Treatment with carboplatin in combination with paclitaxel is not approved for this therapeutic indication. Accordingly, the use of carboplatin in combination with paclitaxel represents an off-label use. According to the G-BA, for patients in the present therapeutic indication, the off-label use is generally preferable to the drugs currently approved in the therapeutic indication, according to the generally recognized state of medical knowledge, §6 (2), sentence 3, number 2, AM-NutzenV.
c. The specification of the ACT by the G-BA reflects not only the maintenance phase but the entire therapeutic strategy. This is explained in more detail in the following text.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; G-BA: Federal Joint Committee; pMMR: mismatch repair proficient

Research question of the company

In its research question, the company cited the target population according to the approval or the target population in the G-BA's research question. This is appropriate. However, in deviation from the G-BA's specification of the ACT, the company formed 2 subpopulations for which it designated different comparator therapies:

- Subpopulation 1: patients who have not been pretreated with chemotherapy or for whom – despite pretreatment with chemotherapy – further chemotherapy alone is an option:
  - carboplatin + paclitaxel
- Subpopulation 2: patients who have been pretreated with chemotherapy and for whom re-induction with chemotherapy alone is not an option:
  - pembrolizumab in combination with lenvatinib

Regarding the specification of the ACT in the sense of a complete therapeutic strategy, the company largely followed the ACT specified by the G-BA for subpopulation 1. Although the company did not name maintenance treatment with watchful waiting, this deviation has no consequences for the benefit assessment, as it had no effect on the completeness of the study pool.

For subpopulation 2, the company departed from the ACT specified by the G-BA. This deviation of the company also remains without consequence, as it did not present any data for this subpopulation.

Research question of the present assessment

In this assessment, the initial phase of first-line therapy (durvalumab + carboplatin + paclitaxel or carboplatin + paclitaxel) is referred to as initial treatment. The subsequent treatment phase then comprises either maintenance treatment with olaparib + durvalumab or watchful waiting.

The approval of olaparib relates exclusively to maintenance treatment following initial therapy. Therefore, the target population for the present assessment of the added benefit of olaparib + durvalumab in maintenance treatment comprises adult patients with primary advanced or recurrent pMMR endometrial cancer whose disease has not progressed on initial treatment.

Determining treatment effects separately for maintenance therapy requires consideration of the maintenance phase alone. Thus, a randomized controlled trial (RCT) in which patients who did not progress during initial therapy were randomized to 2 different maintenance therapies before the start of the maintenance phase would be relevant for the benefit assessment of maintenance therapy.

Such a study design presupposes that the same initial therapies were available to the patients in both treatment arms. However, this is not the case in the present situation due to the approval situation of olaparib + durvalumab in maintenance therapy. According to the approval, maintenance therapy with olaparib + durvalumab is only permitted after initial

therapy with durvalumab in combination with carboplatin and paclitaxel. The initial therapy with durvalumab + carboplatin + paclitaxel, however, is only approved in combination with a maintenance therapy consisting of olaparib + durvalumab. An alternative maintenance therapy after first-line treatment with durvalumab + carboplatin + paclitaxel is not provided for in the approval of durvalumab. Thus, the combination of the 2 approvals (olaparib and durvalumab) means that patients in the intervention and control arm of a study investigating maintenance treatment must have received different initial therapies. This is also made clear by the ACT for maintenance therapy defined by the G-BA, which also includes initial therapy.

Despite these considerations, the present assessment of added benefit refers exclusively to olaparib + durvalumab in maintenance treatment. It is based on the patient population and the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive added benefit.

Results

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of olaparib + durvalumab in maintenance treatment in comparison with the ACT.

The DUO-E study presented by the company is unsuitable for assessing the added benefit of olaparib + durvalumab in maintenance treatment. This is justified below.

Evidence presented by the company – description of the DUO-E study

The DUO-E study is an ongoing 3-arm randomized, double-blind study comparing

- placebo + carboplatin + paclitaxel, followed by placebo (Arm A),
- durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab + placebo (Arm B),
- durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab + olaparib (Arm C).

The study included adult patients with histologically confirmed diagnosis of epithelial endometrial cancer of all histologies (including carcinosarcomas), regardless of mismatch repair (MMR) status. Besides patients with newly diagnosed International Federation of Gynecology and Obstetrics (FIGO) stage III or FIGO stage IV disease, the study also included patients with recurrence where the potential for cure by surgery alone or in combination with radiotherapy or systemic therapy was poor.

A total of 718 patients with endometrial cancer were randomly assigned in a 1:1:1 ratio to one of the 3 treatment arms (Arm A, N = 241; Arm B, N = 238; Arm C, N = 239).

Treatment with durvalumab and olaparib was in compliance with the recommendations of the Summaries of Product Characteristics (SPCs), and the choice of treatment regimens for carboplatin and paclitaxel are comprehensible, taking into account the guideline recommendations.

The DUO-E study is divided into 2 phases. In the 1st phase (initial treatment), all patients received carboplatin + paclitaxel in combination with durvalumab or placebo for a minimum of 4 to a maximum of 6 cycles. Patients without signs of radiological disease progression then received maintenance treatment with durvalumab + placebo (Arm B), durvalumab + olaparib (Arm C) or placebo (Arm A), depending on the treatment arm. The company used patients with pMMR status from Arm A and Arm C for its assessment.

A detailed characterization of the DUO-E study can be found in dossier assessment A24-86.

The DUO-E study is unsuitable for assessing the added benefit of olaparib + durvalumab in maintenance treatment

The DUO-E study is unsuitable for assessing the added benefit of olaparib + durvalumab in maintenance treatment. This is due to the fact that the DUO-E study includes not only maintenance treatment with olaparib + durvalumab or placebo, but also the initial therapy consisting of durvalumab or placebo in combination with carboplatin + paclitaxel. This results from the fact that randomization in the DUO-E study took place before the start of initial therapy. Thus, the DUO-E study represents the entire therapeutic strategy, but is unsuitable for drawing conclusions on the added benefit for the treatment phase of maintenance therapy.

It should also be noted that only part (79%) of the patients randomized to the intervention arm of the study also received maintenance treatment with olaparib + durvalumab.

The company therefore did not present any data on the separate consideration of maintenance treatment with olaparib + durvalumab. There are therefore no suitable data for the assessment of the added benefit of olaparib + durvalumab in maintenance treatment for the above-mentioned target population.

In this particular assessment situation, maintenance treatment with olaparib + durvalumab is part of a clearly defined therapeutic strategy due to the approval. The assessment of the entire therapeutic strategy consisting of initial therapy (durvalumab + carboplatin + paclitaxel) and maintenance therapy (durvalumab + olaparib) is subject of assessment A24-86.

Results on added benefit

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

In this particular assessment situation, maintenance treatment with olaparib + durvalumab is part of a clearly defined therapeutic strategy due to the approval. For a consideration of the entire therapeutic strategy, consisting of initial therapy (durvalumab + carboplatin + paclitaxel) and maintenance therapy (durvalumab + olaparib), which is represented by the DUO-E study, see dossier assessment A24-86.

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

Table 3 shows a summary of the probability and extent of the added benefit of olaparib + durvalumab in maintenance treatment.

Table 3: Olaparib + durvalumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Maintenance treatment of adult patients with primary advanced or recurrent pMMR endometrial cancer whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel	Carboplatin + paclitaxel[b], followed by watchful waiting[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Treatment with carboplatin in combination with paclitaxel is not approved for this therapeutic indication. Accordingly, the use of carboplatin in combination with paclitaxel represents an off-label use. According to the G-BA, for patients in the present therapeutic indication, the off-label use is generally preferable to the drugs currently approved in the therapeutic indication, according to the generally recognized state of medical knowledge, §6 (2), sentence 3, number 2, AM-NutzenV.
c. The specification of the ACT by the G-BA reflects not only the maintenance phase but the entire therapeutic strategy.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; G-BA: Federal Joint Committee; pMMR: mismatch repair proficient

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 the present report is to assess the added benefit of olaparib in combination with durvalumab (hereinafter referred to as "olaparib + durvalumab") in maintenance treatment compared with the ACT in adult patients with primary advanced or recurrent pMMR endometrial cancer whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel. The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of olaparib + durvalumab

Therapeutic indication	**ACT**[a]
Maintenance treatment of adult patients with primary advanced or recurrent pMMR endometrial cancer whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel	Carboplatin + paclitaxel[b], followed by watchful waiting[c]

a. Presented is the ACT specified by the G-BA.
b. Treatment with carboplatin in combination with paclitaxel is not approved for this therapeutic indication. Accordingly, the use of carboplatin in combination with paclitaxel represents an off-label use. According to the G-BA, for patients in the present therapeutic indication, the off-label use is generally preferable to the drugs currently approved in the therapeutic indication, according to the generally recognized state of medical knowledge, §6 (2), sentence 3, number 2, AM-NutzenV.
c. The specification of the ACT by the G-BA reflects not only the maintenance phase but the entire therapeutic strategy. This is explained in more detail in the following text.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; G-BA: Federal Joint Committee; pMMR: mismatch repair proficient

Research question of the company

In its research question, the company cited the target population according to the approval or the target population in the G-BA's research question. This is appropriate. However, in deviation from the G-BA's specification of the ACT, the company formed 2 subpopulations for which it designated different comparator therapies:

- Subpopulation 1: patients who have not been pretreated with chemotherapy or for whom – despite pretreatment with chemotherapy – further chemotherapy alone is an option:
  - carboplatin + paclitaxel
- Subpopulation 2: patients who have been pretreated with chemotherapy and for whom re-induction with chemotherapy alone is not an option:
  - pembrolizumab in combination with lenvatinib

Regarding the specification of the ACT in the sense of a complete therapeutic strategy, the company largely followed the ACT specified by the G-BA for subpopulation 1. Although the

company did not name maintenance treatment with watchful waiting, this deviation has no consequences for the benefit assessment, as it had no effect on the completeness of the study pool.

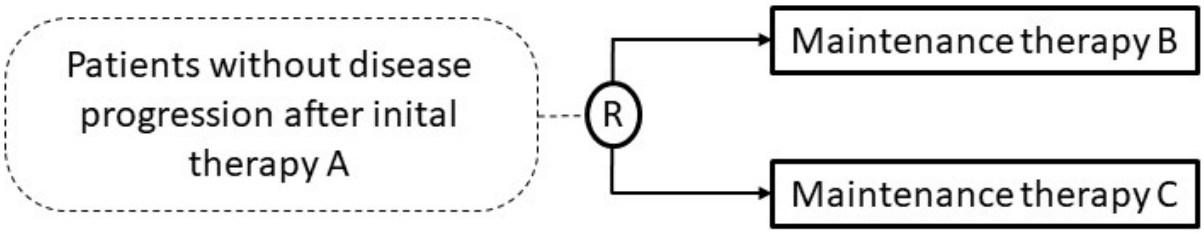
For subpopulation 2, the company departed from the ACT specified by the G-BA. This deviation of the company also remains without consequence, as it did not present any data for this subpopulation.

Research question of the present assessment

In this assessment, the initial phase of first-line therapy (durvalumab + carboplatin + paclitaxel or carboplatin + paclitaxel) is referred to as initial treatment. The subsequent treatment phase then comprises either maintenance treatment with olaparib + durvalumab or watchful waiting.

The approval of olaparib relates exclusively to maintenance treatment following initial therapy. Therefore, the target population for the present assessment of the added benefit of olaparib + durvalumab in maintenance treatment comprises adult patients with primary advanced or recurrent pMMR endometrial cancer whose disease has not progressed on initial treatment.

Determining treatment effects separately for maintenance therapy requires consideration of the maintenance phase alone. Thus, an RCT in which patients who did not progress during initial therapy were randomized to 2 different maintenance therapies before the start of the maintenance phase would be relevant for the benefit assessment of maintenance therapy (see Figure 1).



R: randomization

Figure 1: Design of an RCT to investigate maintenance therapy

Such a study design presupposes that the same initial therapies were available to the patients in both treatment arms. However, this is not the case in the present situation due to the approval situation of olaparib + durvalumab in maintenance therapy. According to the approval, maintenance therapy with olaparib + durvalumab is only permitted after initial therapy with durvalumab in combination with carboplatin and paclitaxel. The initial therapy with durvalumab + carboplatin + paclitaxel, however, is only approved in combination with a

maintenance therapy consisting of olaparib + durvalumab. An alternative maintenance therapy after first-line treatment with durvalumab + carboplatin + paclitaxel is not provided for in the approval of durvalumab. Thus, the combination of the 2 approvals (olaparib and durvalumab) means that patients in the intervention and control arm of a study investigating maintenance treatment must have received different initial therapies. This is also made clear by the ACT for maintenance therapy defined by the G-BA, which also includes initial therapy (see Table 4).

Despite these considerations, the present assessment of added benefit refers exclusively to olaparib + durvalumab in maintenance treatment. It is based on the patient population and the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs are used to derive added benefit. This concurs with the company’s inclusion criteria.

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on olaparib + durvalumab (status: 2 July 2024)
- bibliographical literature search on olaparib + durvalumab (last search on 2 July 2024)
- search in trial registries/trial results databases for studies on olaparib + durvalumab (last search on 1 July 2024)
- search on the G-BA website for olaparib + durvalumab (last search on 2 July 2024)

To check the completeness of the study pool:

- search in trial registries for studies on olaparib (last search on 3 September 2024); for search strategies, see I Appendix A of the full dossier assessment

The check of completeness of the study pool – based on the research question and the ACT according to the G-BA – did not reveal any relevant study for assessing the added benefit of olaparib + durvalumab in maintenance treatment in comparison with the ACT.

Based on its information retrieval, which contained no restriction to the treatment phase, the company identified the RCT DUO-E [3] and used this study to assess the added benefit for its subpopulation 1 (see Chapter I 2). The company did not identify any study for its subpopulation 2 and did not present any data in Module 4 A of the dossier.

The DUO-E study presented by the company is unsuitable for assessing the added benefit of olaparib + durvalumab in maintenance treatment. This is justified below.

Evidence presented by the company – description of the DUO-E study

The DUO-E study is an ongoing 3-arm randomized, double-blind study comparing

- placebo + carboplatin + paclitaxel, followed by placebo (Arm A),
- durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab + placebo (Arm B),
- durvalumab + carboplatin + paclitaxel, followed by maintenance treatment with durvalumab + olaparib (Arm C).

The study included adult patients with histologically confirmed diagnosis of epithelial endometrial cancer of all histologies (including carcinosarcomas) and regardless of MMR status. Besides patients with newly diagnosed FIGO stage III or FIGO stage IV disease, the study

also included patients with recurrence where the potential for cure by surgery alone or in combination with radiotherapy or systemic therapy was poor.

A total of 718 patients with endometrial cancer were randomly assigned in a 1:1:1 ratio to one of the 3 treatment arms (Arm A, N = 241; Arm B, N = 238; Arm C, N = 239).

Treatment with durvalumab and olaparib was in compliance with the recommendations of the SPCs [4,5], and the choice of treatment regimens for carboplatin and paclitaxel are comprehensible, taking into account the guideline recommendations [6,7].

The DUO-E study is divided into 2 phases. In the 1st phase (initial treatment), all patients received carboplatin + paclitaxel in combination with durvalumab or placebo for a minimum of 4 to a maximum of 6 cycles. Patients without signs of radiological disease progression then received maintenance treatment with durvalumab + placebo (Arm B), durvalumab + olaparib (Arm C) or placebo (Arm A), depending on the treatment arm. The company used patients with pMMR status from Arm A and Arm C for its assessment.

A detailed characterization of the DUO-E study can be found in dossier assessment A24-86 [8].

The DUO-E study is unsuitable for assessing the added benefit of olaparib + durvalumab in maintenance treatment

The DUO-E study is unsuitable for assessing the added benefit of olaparib + durvalumab in maintenance treatment. This is due to the fact that the DUO-E study includes not only maintenance treatment with olaparib + durvalumab or placebo, but also the initial therapy consisting of durvalumab or placebo in combination with carboplatin + paclitaxel. This results from the fact that randomization in the DUO-E study took place before the start of initial therapy. Thus, the DUO-E study represents the entire therapeutic strategy, but is unsuitable for drawing conclusions on the added benefit for the treatment phase of maintenance therapy.

It should also be noted that only part (79%) of the patients randomized to the intervention arm of the study also received maintenance treatment with olaparib + durvalumab.

The company therefore did not present any data on the separate consideration of maintenance treatment with olaparib + durvalumab. There are therefore no suitable data for the assessment of the added benefit of olaparib + durvalumab in maintenance treatment for the above-mentioned target population.

In this particular assessment situation, maintenance treatment with olaparib + durvalumab is part of a clearly defined therapeutic strategy due to the approval. The assessment of the entire therapeutic strategy consisting of initial therapy (durvalumab + carboplatin + paclitaxel) and maintenance therapy (durvalumab + olaparib) is subject of assessment A24-86 [8].

I 4 Results on added benefit

No suitable data are available to assess the added benefit of olaparib in combination with durvalumab in maintenance treatment in adult patients with primary advanced or recurrent pMMR endometrial cancer whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel. There is no hint of an added benefit of olaparib + durvalumab in maintenance treatment in comparison with the ACT; an added benefit is therefore not proven.

In this particular assessment situation, maintenance treatment with olaparib + durvalumab is part of a clearly defined therapeutic strategy due to the approval. For a consideration of the entire therapeutic strategy, consisting of initial therapy (durvalumab + carboplatin + paclitaxel) and maintenance therapy (durvalumab + olaparib), which is represented by the DUO-E study, see dossier assessment A24-86 [8].

I 5 Probability and extent of added benefit

The result of the assessment of added benefit of olaparib + durvalumab in maintenance treatment in comparison with the ACT is summarized in Table 5.

Table 5: Olaparib + durvalumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Maintenance treatment of adult patients with primary advanced or recurrent pMMR endometrial cancer whose disease has not progressed on first-line treatment with durvalumab in combination with carboplatin and paclitaxel	Carboplatin + paclitaxel[b], followed by watchful waiting[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Treatment with carboplatin in combination with paclitaxel is not approved for this therapeutic indication. Accordingly, the use of carboplatin in combination with paclitaxel represents an off-label use. According to the G-BA, for patients in the present therapeutic indication, the off-label use is generally preferable to the drugs currently approved in the therapeutic indication, according to the generally recognized state of medical knowledge, §6 (2), sentence 3, number 2, AM-NutzenV.
c. The specification of the ACT by the G-BA reflects not only the maintenance phase but the entire therapeutic strategy. This is explained in more detail in Chapter I 2.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; G-BA: Federal Joint Committee; pMMR: mismatch repair proficient

The assessment described above differs from that of the company, which derived an indication of minor added benefit for patients who have not been pretreated with chemotherapy or for whom, despite pretreatment, further chemotherapy alone is an option (subpopulation 1). In addition, the company derived an indication of major added benefit for the subgroup of patients with newly diagnosed disease at the start of the study from subpopulation 1. The company derived no added benefit for patients who have been pretreated with chemotherapy and for whom re-induction with chemotherapy alone is not an option (subpopulation 2).

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a24-88.html.