Elacestrant (breast cancer)

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

EXTRACT

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[1] Translation of Sections I 1 to I 4 of the dossier assessment *Elacestrant (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V*. 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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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

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the 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
ACT	appropriate comparator therapy
BRCA	breast cancer associated gene
CDK	cyclin-dependent kinase
CSR	clinical study report
ctDNA	circulating tumour deoxyribonucleic acid
EMA	European Medicines Agency
EPAR	European Public Assessment Report
ER	oestrogen receptor
ESR1	oestrogen receptor 1
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GnRH	gonadotropin-releasing hormone
HER2	human epidermal growth factor receptor 2
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IRC	independent review committee
PFS	progression-free survival
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 elacestrant. 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 31 October 2023.

Research question

The aim of this report is to assess the added benefit of elacestrant compared with the appropriate comparator therapy (ACT) in postmenopausal women and men with oestrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative, locally advanced or metastatic breast cancer with an activating oestrogen receptor 1 (ESR1) mutation whose disease has progressed after at least one line of endocrine therapy, including a cyclin-dependent kinase (CDK) 4/6 inhibitor.

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

Table 2: Research questions of the benefit assessment of elacestrant (multipage table)

Research question	Therapeutic indication	ACT[a]
1	Postmenopausal women[b] with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed following at least one line of endocrine therapy including a CDK 4/6 inhibitor[c]	Treatment of physician's choice, taking into account a change of endocrine therapy[d]: ▪ tamoxifen ▪ anastrozole ▪ fulvestrante as monotherapy ▪ letrozolele ▪ exemestanee ▪ everolimus in combination with exemestane (only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor).
2	Men[f] with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed following at least one line of endocrine therapy including a CDK 4/6 inhibitor[c]	Treatment of physician's choice, taking into account a change of endocrine therapy[d]: ▪ tamoxifenf ▪ aromatase inhibitorf in combination with a gonadotropin-releasing hormone (GnRH) analogue ▪ fulvestrantf

Table 2: Research questions of the benefit assessment of elacestrant (multipage table)

Research question	Therapeutic indication	ACT[a]
a. Presented is the respective ACT specified by the G-BA. b. According to the G-BA, it is viewed critically to consider premenopausal women with supressed ovarian function as postmenopausal and to treat them as postmenopausal women. c. For the present therapeutic indication, it is assumed that re-treatment with a CDK 4/6 inhibitor is not an option, that further endocrine therapy is indicated for the patients and that there is no therapeutic indication for chemotherapy to achieve a rapid remission. Moreover, it is assumed that (secondary) resection or radiotherapy with curative intent is not indicated. It is also assumed that treatment with elacestrant is not indicated for patients with genomic BRCA1/2 mutations for whom BRCA-specific therapy is an option. d. It is assumed that there has been a change in treatment with respect to the drugs used for the previous endocrine-based therapy. e. In this therapeutic indication, the approvals of fulvestrant, letrozole and exemestane only provide for use after prior anti-oestrogen therapy. However, it is clear from the guidelines that the use of fulvestrant is also explicitly based on previous therapy with aromatase inhibitors, and that with regard to the use of the aromatase inhibitors letrozole and exemestane, switching from a steroidal to a non-steroidal aromatase inhibitor or vice versa is also explicitly recommended. According to the G-BA, the use of fulvestrant, letrozole and exemestane is generally preferable to the approved endocrine therapies for the patient group of postmenopausal women for the therapeutic indication after pretreatment with an endocrine therapy other than anti-oestrogens, in particular after prior therapy with aromatase inhibitors. For this reason, the G-BA considers it appropriate to determine the above-mentioned drugs as ACT for this therapeutic indication, even when used beyond the scope of the approval. f. The guidelines recommends the drugs tamoxifen, fulvestrant and aromatase inhibitor + GnRH analogue for the male patient group. However, in the therapeutic indication, aromatase inhibitors and fulvestrant are only approved for women. With regard to the approved drug tamoxifen, it can be assumed that the vast majority of patients have already received treatment with tamoxifen at an earlier stage of the disease or earlier in the treatment sequence. According to the G-BA, the use of fulvestrant and of aromatase inhibitors + GnRH analogue is therefore generally preferable to tamoxifen for the patient group of men in the described therapeutic indication. The G-BA therefore considers it appropriate to determine the off-label use of the above-mentioned drugs as ACT.		

BRCA: breast cancer susceptibility gene; CDK 4/6: cyclin-dependent kinase 4/6; ER: oestrogen receptor; ESR1: oestrogen receptor 1; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2

In the present benefit assessment, the following shortened terms are used for the patient populations of the 2 research questions:

- Research question 1: postmenopausal women
- Research question 2: men

The G-BA adjusted the ACT in October 2023 and January 2024, as shown in Table 2. The company follows the ACT initially specified by the G-BA in June 2022 and for research question 1 specifies a switch of endocrine therapy to tamoxifen or anastrozole or fulvestrant as monotherapy (only for patients with recurrence or progression after antiestrogen treatment) or letrozole (only for patients with recurrence or progression following anti-oestrogen therapy) or exemestane (only for patients with progression following anti-oestrogen therapy)

or everolimus in combination with exemestane (only for patients without symptomatic visceral metastasis, after progression occurred following a non-steroidal aromatase inhibitor). This deviation has no consequence for the present benefit assessment, as the company did not limit its information retrieval to certain treatment options and the review of the completeness of the study pool did not identify any additional relevant studies versus with the current ACT. For research question 2, the company followed the G-BA's specification of the ACT.

The present benefit assessment was conducted versus with the ACT. The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

Research question 1: postmenopausal women

Study pool and study design

The EMERALD study is used to compare elacestrant with the ACT. The EMERALD study compared elacestrant with a treatment of physician's choice chosing from fulvestrant, anastrozole, letrozole and exemestane, so that this study is only suitable for drawing conclusions on the added benefit of elacestrant for patients for whom fulvestrant, anastrozole, letrozole or exemestane is a suitable therapy of physician's choice. No data are available for patients for whom other treatment options (tamoxifen or everolimus in combination with exemestane) are suitable according to the treatment of physician's choice.

However, the analyses on the EMERALD study presented by the company are not suitable for the benefit assessment, as the company post hoc further restricted the subpopulation of patients with ESR1 mutation without adequate justification. The EMERALD study is described below, and the unsuitability is justified.

The EMERALD study is an ongoing open-label, multicentre RCT. The study included postmenopausal women and men with ER-positive and HER2-negative advanced or metastatic breast cancer whose disease had progressed after at least 1 and at most 2 lines of endocrine therapy, including a CDK 4/6 inhibitor. Only patients for whom endocrine therapy was still indicated were included. Furthermore, the patients were allowed to have received at most 1 chemotherapy line in the advanced/metastatic stage. At the time of inclusion in the study, patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) ≤ 1 and no symptomatic visceral metastases.

A total of 478 patients were randomly allocated in a 1:1 ratio to treatment with elacestrant (N = 239) or treatment of physician's choice (N = 239). Prior to randomization, the physician determined which of the treatment options (fulvestrant, anastrozole, letrozole and

exemestane) available in the study the respective patient should receive if assigned to the comparator arm.

Elacestrant is only approved for patients with an activating ESR1 mutation. The ESR1-mut subpopulation of the EMERALD study comprised a total of 228 patients, i.e. 115 in the intervention arm and 113 in the comparator arm. The company presents a subpopulation of the ESR1-mut subpopulation in the dossier (see below).

In both study arms, patients were treated in compliance with the specifications of the respective Summary of Product Characteristics (SPC).

The study's primary outcome was progression-free survival (PFS) according to a blinded independent review committee (IRC). Patient-relevant secondary outcomes were overall survival, health status, health-related quality of life and adverse event (AEs).

The formation of the subpopulation presented by the company for research question 1 (postmenopausal women) is not comprehensible without further information

The approval of elacestrant is based on the ESR1-mut subpopulation (228 patients, 115 in the intervention arm and 113 in the comparator arm) of the EMERALD study. The analysis of this ESR1-mut subpopulation was predefined.

In Module 4 A, the company presents data on the subpopulation A 1, which was formed post hoc. It used the ESR1-mut subpopulation as a basis and explains having excluded the following patient groups:

- non-HER2-negative patients (n = 2)
- non-ER-positive patients (n = 2)
- patients with non clearly documented bilateral surgical oophorectomy and an age under 60 years at study entry (n = 21)
- patients with drug-induced menopause (n = 1)
- patients without pretreatment with a CDK 4/6 inhibitor in a locally advanced or metastatic setting (n = 4)

The company thus post hoc excluded a total of 30 patients (13.2%) from the analysis. This subpopulation A 1 thus comprises a total of 198 patients, i.e. 102 in the intervention arm and 96 in the comparator arm. The approach of the company is inadequate, as sufficient justification is lacking and the approach is not comprehensible without further information.

The reasons cited by the company for the retrospective exclusion of patients represent key inclusion criteria of the EMERALD study. It is not plausible that the 30 patients retrospectively

excluded by the company did not fulfil key inclusion criteria. In addition, the exclusion of patients took place with knowledge of the data and was therefore potentially selective. This is particularly serious in the present data situation, as positive effects relevant for the benefit assessment in the outcome of overall survival of subpopulation A 1 are only shown in the subgroup of patients with 2 previous lines of endocrine therapy. Whether and if so how the exclusion of the 30 patients affects the (subgroup) results of other outcomes is unclear, as the company did not present complete analyses of the ESR1-mut subpopulation (i.e., including the 30 patients).

Firstly, due to a lack of explanations by the company, it is unclear which subpopulation - the ESR1-mut subpopulation or the subpopulation A 1 presented by the company - represents the relevant subpopulation for the present benefit assessment. On the other hand, the effect of the 30 excluded patients on the results cannot be estimated, as corresponding analyses for the ESR1-mut subpopulation including the 30 patients are not available. The benefit assessment therefore requires a sufficient explanation for the retrospective exclusion of the 30 patients as well as a complete presentation of the results for the ESR1-mut population analogous to the subpopulation A 1.

Handling of patients with bilateral oophorectomy and patients with hormone-induced menopause

According to the G-BA's advice, it is viewed critically to consider premenopausal women with suppressed ovarian function as postmenopausal and to treat them as postmenopausal women.

The ESR1-mut subpopulation includes 46 patients (20.2%) and the subpopulation A 1 presented by the company includes 25 patients (12.6%) who were included as postmenopausal due to a bilateral oophorectomy. At least subgroup analyses for this characteristic would be necessary to assess the influence of these patients on the results. These were not presented by the company.

Implementation of the ACT in the EMERALD study

When determining the ACT, the G-BA specifically focused on a change in endocrine therapy, naming the corresponding drugs, and assumed that a change in treatment was going to take place with regard to the drugs used in the previous endocrine therapy. The EPAR information on the entire study population shows that the ACT was largely implemented in compliance with the above-mentioned requirements. However, the EPAR indicates that approximately 15% of patients in the comparator arm may not have received treatment according to the ACT. The company does not present the patients' previous therapies in relation to the selected treatment option for subpopulation A 1 analysed in Module 4 A; this information is also

missing for the ESR1-mut population. It is therefore unclear how many patients in these subpopulations were not treated in accordance with the ACT.

Further comments on the company's dossier

There are further points of criticism of the company's dossier:

- The information on the observation periods is not comprehensible.
- There is a discrepancy in the assessment of progression events by the investigators and the blinded assessment by the IRC, which is not explained by the company.
- The calculation of the response rates for patient-reported outcomes is incorrect.
- The threshold for the presentation of AEs by SOC and PTs was not interpreted correctly.

Results on added benefit

No suitable data are available for the assessment of the added benefit of elacestrant in comparison with the ACT in postmenopausal women with ER-positive, HER2-negative locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed after at least one line of endocrine therapy, including a CDK 4/6 inhibitor. There is no hint of an added benefit of elacestrant in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: men

Study pool and study design

The company identified the EMERALD study, which included a total of 7 men. However, the label-enabling subpopulation from the EMERALD study (ESR1-mut subpopulation) only includes women with an activating ESR1 mutation. None of the men included in the EMERALD study had an ESR1 mutation. Thus, no data were available for research question 2.

Results on added benefit

No data for comparison with the ACT are available for the assessment of the added benefit of elacestrant in men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed after at least one line of endocrine therapy, including a CDK 4/6 inhibitor. There is no hint of an added benefit of elacestrant 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 elacestrant.

Table 3: Elacestrant – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Postmenopausal women[b] with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed following at least one line of endocrine therapy including a CDK 4/6 inhibitor[c]	Treatment of physician's choice, taking into account a change of endocrine therapy[d]: ▪ tamoxifen ▪ anastrozole ▪ fulvestrante as monotherapy ▪ letrozolele ▪ exemestanee ▪ everolimus in combination with exemestane (only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor)	Added benefit not proven
2	Men[f] with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed following at least one line of endocrine therapy including a CDK 4/6 inhibitor[c]	Treatment of physician's choice, taking into account a change of endocrine therapy[d]: ▪ tamoxifenf ▪ aromatase inhibitorf in combination with a gonadotropin-releasing hormone (GnRH) analogue ▪ fulvestrantf	Added benefit not proven

[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].

Table 3: Elacestrant – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
a. Presented is the respective ACT specified by the G-BA. b. According to the G-BA, it is viewed critically to consider premenopausal women with supressed ovarian function as postmenopausal and to treat them as postmenopausal women. c. For the present therapeutic indication, it is assumed that re-treatment with a CDK 4/6 inhibitor is not an option, that further endocrine therapy is indicated for the patients and that there is no therapeutic indication for chemotherapy to achieve a rapid remission. Moreover, it is assumed that (secondary) resection or radiotherapy with curative intent is not indicated. It is also assumed that treatment with elacestrant is not indicated for patients with genomic breast cancer associated gene (BRCA)1/2 mutations for whom BRCA-specific therapy is an option. d. It is assumed that there has been a change in treatment with respect to the drugs used for the previous endocrine-based therapy. e. In this therapeutic indication, the approvals of fulvestrant, letrozole and exemestane only provide for use after prior anti-oestrogen therapy. However, it is clear from the guidelines that the use of fulvestrant is also explicitly based on previous therapy with aromatase inhibitors, and that with regard to the use of the aromatase inhibitors letrozole and exemestane, switching from a steroidal to a non-steroidal aromatase inhibitor or vice versa is also explicitly recommended. According to the G-BA, the use of fulvestrant, letrozole and exemestane is generally preferable to the approved endocrine therapies for the patient group of postmenopausal women for the therapeutic indication after pretreatment with an endocrine therapy other than anti-oestrogens, in particular after prior therapy with aromatase inhibitors. For this reason, the G-BA considers it appropriate to determine the above-mentioned drugs as ACT for this therapeutic indication, even when used beyond the scope of the approval. f. The guidelines recommends the drugs tamoxifen, fulvestrant and aromatase inhibitor + GnRH analogue for the male patient group. However, in the therapeutic indication, aromatase inhibitors and fulvestrant are only approved for women. With regard to the approved drug tamoxifen, it can be assumed that the vast majority of patients have already received treatment with tamoxifen at an earlier stage of the disease or earlier in the treatment sequence. According to the G-BA, the use of fulvestrant and of aromatase inhibitors + GnRH analogue is therefore generally preferable to tamoxifen for the patient group of men in the described therapeutic indication. The G-BA therefore considers it appropriate to determine the off-label use of the above-mentioned drugs as ACT. BRCA: breast cancer susceptibility gene; CDK 4/6: cyclin-dependent kinase 4/6; ER: oestrogen receptor; ESR1: oestrogen receptor 1; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2			

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

I 2 Research question

The aim of this report is to assess the added benefit of elacestrant compared with the ACT in postmenopausal women and men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed after at least one line of endocrine therapy, including a CDK 4/6 inhibitor.

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

Table 4: Research questions of the benefit assessment of elacestrant (multipage table)

Research question	**Therapeutic indication**	**ACT[a]**
1	Postmenopausal women[b] with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed following at least one line of endocrine therapy including a CDK 4/6 inhibitor[c]	Treatment of physician's choice, taking into account a change of endocrine therapy[d]: ▪ tamoxifen ▪ anastrozole ▪ fulvestrante as monotherapy ▪ letrozolele ▪ exemestanee ▪ everolimus in combination with exemestane (only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor).
2	Men[f] with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed following at least one line of endocrine therapy including a CDK 4/6 inhibitor[c]	Treatment of physician's choice, taking into account a change of endocrine therapy[d]: ▪ tamoxifenf ▪ aromatase inhibitorf in combination with a gonadotropin-releasing hormone (GnRH) analogue ▪ fulvestrantf

Table 4: Research questions of the benefit assessment of elacestrant (multipage table)

Research question	Therapeutic indication	ACT[a]
a. Presented is the respective ACT specified by the G-BA. b. According to the G-BA, it is viewed critically to consider premenopausal women with supressed ovarian function as postmenopausal and to treat them as postmenopausal women. c. For the present therapeutic indication, it is assumed that re-treatment with a CDK 4/6 inhibitor is not an option, that further endocrine therapy is indicated for the patients and that there is no therapeutic indication for chemotherapy to achieve a rapid remission. Moreover, it is assumed that (secondary) resection or radiotherapy with curative intent is not indicated. It is also assumed that treatment with elacestrant is not indicated for patients with genomic breast cancer associated gene (BRCA)1/2 mutations for whom BRCA-specific therapy is an option. d. It is assumed that there has been a change in treatment with respect to the drugs used for the previous endocrine-based therapy. e. In this therapeutic indication, the approvals of fulvestrant, letrozole and exemestane only provide for use after prior anti-oestrogen therapy. However, it is clear from the guidelines that the use of fulvestrant is also explicitly based on previous therapy with aromatase inhibitors, and that with regard to the use of the aromatase inhibitors letrozole and exemestane, switching from a steroidal to a non-steroidal aromatase inhibitor or vice versa is also explicitly recommended. According to the G-BA, the use of fulvestrant, letrozole and exemestane is generally preferable to the approved endocrine therapies for the patient group of postmenopausal women for the therapeutic indication after pretreatment with an endocrine therapy other than anti-oestrogens, in particular after prior therapy with aromatase inhibitors. For this reason, the G-BA considers it appropriate to determine the above-mentioned drugs as ACT for this therapeutic indication, even when used beyond the scope of the approval. f. The guidelines recommends the drugs tamoxifen, fulvestrant and aromatase inhibitor + GnRH analogue for the male patient group. However, in the therapeutic indication, aromatase inhibitors and fulvestrant are only approved for women. With regard to the approved drug tamoxifen, it can be assumed that the vast majority of patients have already received treatment with tamoxifen at an earlier stage of the disease or earlier in the treatment sequence. According to the G-BA, the use of fulvestrant and of aromatase inhibitors + GnRH analogue is therefore generally preferable to tamoxifen for the patient group of men in the described therapeutic indication. The G-BA therefore considers it appropriate to determine the off-label use of the above-mentioned drugs as ACT.		

BRCA: breast cancer susceptibility gene; CDK 4/6: cyclin-dependent kinase 4/6; ER: oestrogen receptor; ESR1: oestrogen receptor 1; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2

In the present benefit assessment, the following shortened terms are used for the patient populations of the 2 research questions:

- Research question 1: postmenopausal women
- Research question 2: men

The G-BA adjusted the ACT in October 2023 and January 2024, as shown in Table 4. The company follows the ACT initially specified by the G-BA in June 2022 and for research question 1 specifies a switch of endocrine therapy to tamoxifen or anastrozole or fulvestrant as monotherapy (only for patients with recurrence or progression after antiestrogen treatment) or letrozole (only for patients with recurrence or progression following anti-oestrogen therapy) or exemestane (only for patients with progression following anti-oestrogen therapy)

or everolimus in combination with exemestane (only for patients without symptomatic visceral metastasis, after progression occurred following a non-steroidal aromatase inhibitor). This deviation has no consequence for the present benefit assessment, as the company did not limit its information retrieval to certain treatment options and the review of the completeness of the study pool did not identify any additional relevant studies versus with the current ACT. (see Section I 3.1). For research question 2, the company followed the G-BA's current ACT.

The present benefit assessment was conducted versus with the ACT. 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 for the derivation of added benefit. This concurs with the company’s inclusion criteria.

I 3 Research question 1: postmenopausal women

I 3.1 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 elacestrant (status: 6 September 2023)
- bibliographical literature search on elacestrant (last search on 22 August 2023)
- search in trial registries/trial results databases for studies on elacestrant (last search on 22 August 2023)
- search on the G-BA website for elacestrant (last search on 22 August 2023)

To check the completeness of the study pool:

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

The check did not identify any additional relevant study.

I 3.1.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: elacestrant vs. treatment of physician's choice

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	Clinical study report (CSR) (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
RAD1901-308 (EMERALD[d])	Yes	Yes[e]	Yes[e]	Yes [3-5]	Yes [6,7]	Yes [8-11]

a. Study sponsored by the company.
b. References of trial registry entries and any available reports on the study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.
e. Radius Pharmaceuticals Inc. was the sponsor of the EMERALD study until the in-licensing of elacestrant (ORSERDU) by Stemline Therapeutics B.V. Marketing approval holder for the product elacestrant (ORSERDU) is Stemline Therapeutics B.V.

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

The study pool of the benefit assessment of elacestrant in comparison with the ACT for research question 1 consists of the RCT EMERALD and corresponds to the study pool of the company. The EMERALD study compared elacestrant with a treatment of physician's choice chosing from fulvestrant, anastrozole, letrozole and exemestane, so that this study is only suitable for drawing conclusions on the added benefit of elacestrant for patients for whom fulvestrant, anastrozole, letrozole or exemestane is a suitable therapy of physician's choice. No data are available for patients for whom other treatment options (tamoxifen or everolimus in combination with exemestane) are suitable according to the treatment of physician's choice.

However, the analyses on the EMERALD study presented by the company are not suitable for the benefit assessment, as the company post hoc further restricted the subpopulation of patients with ESR1 mutation without adequate justification. The EMERALD study is described below, and the unsuitability is justified.

I 3.1.2 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: elacestrant vs. treatment of physician's choice choosing from fulvestrant, anastrozol, letrozol and exemestan (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
EMERALD	RCT, open-label, parallel-group	Postmenopausal[b] women and men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer whose disease has progressed after 1 or 2 lines of endocrine therapy, including a CDK 4/6 inhibitor[c], with ECOG PS 0 or 1	Elacestrant (N = 239) Treatment of physician's choice[d] (N = 239) of which with ESR1 mutation[e] elacestrant (n = 115) treatment of physician's choice[d] (n = 113) <u>subpopulation A 1[e] analysed by the company:</u> elacestrant (n = 102) treatment of physician's choice[d] (n = 96)	Screening: 35 days treatment: until disease progression, clinically relevant AE, significant non-compliance with study requirements, failure to take study medication for > 14 days, decision of the patient/investigator observation: outcome-specific, at most until death, withdrawal of consent, lost to follow-up or end of study	150 study centres in: Argentina, Australia, Austria, Belgium, Canada, Denmark; France, Germany, Greece, Hungary, Ireland, Israel, Italy, Portugal, South Korea, Spain, United Kingdom, USA 05/2019–ongoing data cut-offs: ▪ 6 September 2021 (final PFS data cut-off)f ▪ 8 July 2022 (FDA safety data cut-off)g ▪ 2 September 2022 (final data cut-off on overall survival)[h]	Primary: PFS secondary: overall survival, symptoms, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: elacestrant vs. treatment of physician's choice choosing from fulvestrant, anastrozol, letrozol and exemestan (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes include information only on relevant available outcomes for this benefit assessment.
b. According to study protocol version 6.0, women were included as postmenopausal if they met 1 of the following criteria: 1) documented bilateral surgical oophorectomy, 2) age ≥ 60 years with amenorrhoea ≥ 1 year since last menstruation, 3) age < 60 years with amenorrhoea ≥ 1 year since last menstruation and no alternative pathological or physiological cause (including ongoing or recent chemotherapy, treatment with tamoxifen or toremifene or a GnRH agonist) and serum oestradiol and follicle-stimulating hormone (FSH) levels within the laboratory reference range for postmenopausal women, or 4) age < 60 years with tamoxifen or toremifene therapy in the last 12 months with confirmed 12 months of amenorrhoea prior to tamoxifen or toremifene therapy and serum oestradiol and FSH levels within the laboratory reference range for postmenopausal women. Women with hormone-induced menopause (i.e. who required continuous hormone suppression) were not eligible to participate (from protocol version 5).
c. Histologically or cytologically confirmed diagnosis of adenocarcinoma of the breast with evidence of locally advanced disease that cannot be treated by resection or radiotherapy with curative intent or metastatic disease that is not amenable to curative therapy.
The disease had to progress within 28 days after completion of each endocrine therapy line.
An adjuvant endocrine therapy line only counts as prior therapy for advanced or metastasised breast cancer if there is progression of the disease within 12 months of the therapy.
d. Choosing from fulvestrant, anastrozole, letrozole and exemestane.
e. In Module 4 A, the company does not present analyses of the ESR1-mut subpopulation, but only data on a subpopulation A 1 formed post hoc by it. This approach is not comprehensible. See the running text below for an explanation.
f. The final PFS analysis was originally planned at around 160 PFS events in the ESR1-mut patients and 340 PFS events in all patients (ESR1-mut and ESR1-mut-nd) (based on the assessment by the IRC). Deviating from this, the analysis was brought forward and carried out when 140 PFS events had occurred in the ESR1-mut patients and 300 PFS events in all patients. The decision to do so was based on a blinded PFS event prediction analysis prior to unblinding, which showed that an additional year would have been required to observe the pre-specified number of events.
g. According to the company, this is a safety data cut-off required by the FDA.
h. The final analysis of overall survival was planned after the death of 50% of all patients included.

AE: adverse event; CDK 4/6: cyclin-dependent kinase 4/6; ER: oestrogen receptor; ESR1: estrogen receptor 1; ESR1-mut-nd: ESR1 mutation not confirmed or not determinable; FDA: Food and Drug Administration; FSH: follicle-stimulating hormone; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2; IRC: independent review committee; n: number of patients in the respective subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: elacestrant versus treatment of physician's choice, chosing from fulvestrant, anastrozole, letrozole and exemestane (multipage table)

Study	Intervention	Comparison
EMERALD	Elacestrant 400 mg[a]/day, orally	Treatment of physician's choice[b]: fulvestrant 500 mg IM (2x 5 mL injections) on Day 1 and Day 15 of Cycle 1, thereafter on Day 1 of each subsequent 28-day cycle or anastrozole 1 mg/day orally or letrozole 2.5 mg/day, orally or exemestane 25 mg/day orally
	Dose adjustment: ▪ dose reduction to 300 mg/day or 200 mg/day possible ▪ dose interruption for ≤ 14 days	▪ dose reduction to 250 mg fulvestrant possible for patients who develop moderate liver dysfunctions (Child-Pugh class B), provided this is not associated with the study medication or disease progressionc ▪ dose interruption up to 28 days (fulvestrant) or 14 days (aromatase inhibitors)
	Pretreatment <u>required</u> ▪ 1 to 2 endocrine pretreatments (monotherapy or as combination therapy with another drug [e.g. PI3K inhibitor]) ▪ CDK 4/6 in combination with fulvestrant or aromatase inhibitors ▪ time window prior therapies: ▫ fulvestrant: > 42 daysd before the first dose of the study medication ▫ further endocrine therapies: > 14 Tage before the first dose of the study medication <u>allowed</u> ▪ 1 chemotherapy line in advanced/metastatic stagee, also possible in combination with endocrine therapy > 21 days before the 1st dose of study medication ▪ bisphosphonates or RANKL inhibitors for bone metastases in stable doses > 3 months before the 1st dose of study medication ▪ radiotherapy > 14 days (> 28 days for brain lesions) before the 1st dose of study medication **concomitant treatment** <u>not allowed</u> ▪ hormonal drugs or drugs affecting serum LH, FSH (except spironolactone) or oestrogen-oestradiol levels within 14 days (42 days for fulvestrant) before the 1st dose of study medication and during the studyf ▪ systemic anti-cancer treatments or other chemotherapeutic agents ▪ surgical tumour resection, tumour embolization and radiotherapyg ▪ elacestrant arm: moderate or strong inhibitors or inducers of CYP3A ▪ exemestane in the comparator arm: strong CYP3A4 inducers	

Table 7: Characteristics of the intervention – RCT, direct comparison: elacestrant versus treatment of physician's choice, chosing from fulvestrant, anastrozole, letrozole and exemestane (multipage table)

Study	Intervention	Comparison
a. One 400 mg tablet of elacestrant dihydrochloride contains 345 mg of pure elacestrant. b. Prior to randomization, investigators should select one of the 4 available options after assessing the treatment history and considering specific guidelines. These were not to be administered in combination with other anticancer therapies. c. The SPC does not recommend a dose adjustment of fulvestrant. According to the study report, there were no patients in the study who had a dose adjustment of fulvestrant. d. From protocol version 5, before that the time window was 28 days. e. This also includes neoadjuvant/adjuvant chemotherapy followed by progression within 12 months of completion of therapy. f. This includes, but is not limited to, drugs, herbal drugs and/or dietary supplements for the treatment of vasomotor hot flushes administered by any route, including topical or intravaginal administration. g. Local palliative radiotherapy could be carried out in consultation with the monitor if there was no other option for pain treatment. CDK 4/6: Cyclin-dependent kinase 4/6; CYP3A(4/5): cytochrome P450 3A(4/5); FSH: follicle-stimulating hormone; IM: intramuscular; LH: luteinising hormone; PI3K: phosphoinositide 3-kinase; RANKL: receptor activator of nuclear factor kappa-B ligand; RCT: randomized controlled trial		

The EMERALD study is an ongoing, open-label, multicentre RCT for the direct comparison of elacestrant with a treatment of physician's choice choosing from fulvestrant, anastrozole, letrozole and exemestane. The study included postmenopausal women and men with ER-positive and HER2-negative advanced or metastatic breast cancer whose disease had progressed after at least 1 and at most 2 lines of endocrine therapy, including a CDK 4/6 inhibitor. Only patients for whom endocrine therapy was still indicated were included. Furthermore, the patients were allowed to have received at most 1 chemotherapy line in the advanced/metastatic stage. At the time of inclusion in the study, patients had to have an ECOG PS ≤ 1 and no symptomatic visceral metastases.

As part of the screening, the circulating tumour deoxyribonucleic acid (ctDNA) obtained from a blood sample was examined for the presence of an activating ESR1 mutation (test system used: Guardant360 CDx). Patients with and without an ESR1 mutation in the tumour tissue were included.

A total of 478 patients were randomly allocated in a 1:1 ratio to treatment with elacestrant (N = 239) or treatment of physician's choice (N = 239). Prior to randomization, the physician determined which of the treatment options (fulvestrant, anastrozole, letrozole and exemestane) available in the study the respective patient should receive if assigned to the comparator arm. Randomization was stratified by ESR1 mutation status (ESR1-mut [mutated] vs. ESR1-mut-nd [not confirmed or not determinable]), pretreatment with fulvestrant (yes vs. no) and presence of visceral metastases (yes vs. no).

Elacestrant is exclusively approved for patients with activating ESR1 mutation [11,12]. The ESR1-mut subpopulation of the EMERALD study comprised a total of 228 patients, i.e. 115 in the intervention arm and 113 in the comparator arm. The company presents a subpopulation of the ESR1-mut subpopulation in the dossier (for information on the formation of the subpopulation presented by the company, see below).

In both study arms, the treatment of the patients complied with the specifications of the respective SPC [12-16]. Treatment should be continued until disease progression, occurrence of a clinically relevant AE, significant non-compliance with study requirements, failure to take study medication for more than 14 days or until the decision of the patient or the investigator. Treatment switching from the intervention to the comparator therapy or vice versa was not permitted. The study protocol provides no information on requirements for the use of possible subsequent therapies.

The study's primary outcome was PFS according to a blinded IRC. Patient-relevant secondary outcomes were overall survival, health status, health-related quality of life and AEs.

Data cut-offs

The following 3 data cut-offs are currently available for the EMERALD study:

- 1. Data cut-off of 6 September 2021: final PFS analysis; originally planned after approximately 160 PFS events in patients with ESR1 mutation and 340 PFS events in all patients (based on IRC assessment); however, the analysis was brought forward and conducted when 140 PFS events had occurred in ESR1-mut patients and 300 PFS events in all patients. The decision to do so was based on a blinded PFS event prediction analysis prior to unblinding, which showed that an additional year would have been required to observe the pre-specified number of events.
- 2nd data cut-off of 8 July 2022: safety data cut-off requested by the Food and Drug Administration (FDA)
- 3rd data cut-off of 2 September 2022: planned as final analysis of overall survival after the death of 50% of the included patients

The company describes the study as ongoing at the time of the present benefit assessment and states August 2024 as the expected study end. According to the study protocol, the study is considered completed as soon as 50% of the patients included have died. This corresponds to the time point of the 3rd data cut-off. However, the remaining patients will continue to be treated with the study medication until all patients stop participating in the study or elacestrant is approved for market placement in a patient's respective country. According to the study documents, further data cut-offs are not planned .

In the dossier, the company presents data on the 2nd (results on patient-reported outcomes and side effects) and 3rd data cut-off (overall survival). These are only around 2 months apart and it is therefore not assumed that there is a relevant difference of the results between these two data cut-offs. Accordingly, analogous to the company's approach, the 2nd data cut-off is considered for the results on patient-reported outcomes and side effects and the 3rd data cut-off for the results on the outcome "overall survival".

The formation of the subpopulation presented by the company for research question 1 (postmenopausal women) is not comprehensible without further information

The approval of elacestrant is based on the ESR1-mut subpopulation of the EMERALD study. This comprises all patients with a proven activating ESR1 mutation and comprises a total of 228 patients, 115 of whom were in the intervention arm and 113 in the comparator arm. The analysis of this ESR1-mut subpopulation was predefined. e. However, in Module 4 A, the company does not present analyses of the ESR1-mut subpopulation, but only data on a subpopulation A 1 formed post hoc by it. Subpopulation A1 is based on the ESR1-mut subpopulation, from which the following patient groups were excluded:

- non-HER2-negative patients (n = 2)
- non-ER-positive patients (n = 2)
- Patients with non clearly documented bilateral surgical oophorectomy and an age under 60 years at study entry (n = 21)
- Patients with drug-induced menopause (n = 1)
- Patients without pretreatment with a CDK 4/6 inhibitor in a locally advanced or metastatic setting (n = 4)

Through this procedure, the company excluded a total of 30 patients (13.2%) of the ESR1-mut subpopulation post hoc from the analysis. Subpopulation A 1 thus comprised a total of 198 patients, 102 in the intervention arm and 96 in the comparator arm. The approach of the company is inadequate, as sufficient justification is lacking and the approach is not comprehensible without further information. This is explained below.

The reasons cited by the company for the retrospective exclusion of patients represent key inclusion criteria of the EMERALD study. Compliance with these inclusion criteria (HER2 status, bilateral oophorectomy, etc.) should therefore already be ensured by the inclusion of patients in the study. The study documents show that a violation of the main inclusion and exclusion criteria constitutes a serious protocol violation. The study report shows that this only applies to 1 patient in the ESR1-mut subpopulation. Therefore, it is not plausible that the 30 patients retrospectively excluded by the company did not fulfil key inclusion criteria. In addition, any uncertainties regarding the ER status of the 2 excluded patients in subpopulation A 1 were

already clarified at the request of the European Medicines Agency (EMA) and the unclear ER status was confirmed as positive [11].

Although only 13.2% of patients were excluded post-hoc from the analysis, the exclusion of patients took place with knowledge of the data and was therefore potentially selective. This is particularly serious in the present data situation, as positive effects relevant for the benefit assessment in the outcome of overall survival of subpopulation A 1 are only shown in the subgroup of patients with 2 previous lines of endocrine therapy. Whether and if so how the exclusion of the 30 patients affects the (subgroup) results of other outcomes is unclear, as the company did not present complete analyses of the ESR1-mut subpopulation (i.e., including the 30 patients). It is therefore possible that the ESR1-mut subpopulation may show further or different positive and/or negative effects than the subpopulation A 1 presented by the company.

Due to a lack of explanations by the company, it is overall unclear which subpopulation - the ESR1-mut subpopulation or the subpopulation A 1 presented by the company - represents the relevant subpopulation for the present benefit assessment. On the other hand, the effect of the 30 excluded patients on the results cannot be estimated, as corresponding analyses for the ESR1-mut subpopulation including the 30 patients are not available. The benefit assessment therefore requires a sufficient explanation for the retrospective exclusion of the 30 patients as well as a complete presentation of the results for the ESR1-mut population analogous to the subpopulation A 1.

Handling of patients with bilateral oophorectomy and patients with hormone-induced menopause

According to the G-BA's advice, it is viewed critically to consider premenopausal women with suppressed ovarian function as postmenopausal and to treat them as postmenopausal women (see Table 4).

In accordance with the inclusion criteria of the EMERALD study, patients with bilateral oophorectomy were also included in the study (see also Table 6 for the definition of postmenopausal status). Patients with hormone-induced menopause should not be included. This criterion was introduced from protocol version 5. As only 9 patients (3.9%) had been included in the ESR1-mut subpopulation up to the start of protocol version 5, of whom only 2 had a drug-induced menopause according to the company, the inclusion of these patients has no consequences for the benefit assessment.

The ESR1-mut subpopulation includes 46 patients (20.2%) and the subpopulation A 1 presented by the company includes 25 patients (12.6%) who were included as postmenopausal due to a bilateral oophorectomy. At least subgroup analyses for this

characteristic would be necessary to assess the influence of these patients on the results. These were not presented by the company.

Implementation of the ACT in the EMERALD study

As part of the endocrine therapy of advanced hormone receptor-positive breast cancer, a change of the substance class used is recommended as an essential component of the treatment algorithm. Against this background, when determining the ACT, the G-BA specifically focused on a change in endocrine therapy, naming the corresponding drugs, and assumed that a change in treatment was going to take place with regard to the drugs used in the previous endocrine therapy.

In the case of prior therapy with an aromatase inhibitor, the guidelines [17,18] recommend switching to treatment with an anti-oestrogen or an ER antagonist. In this regard, it is clear from these guidelines that the use of fulvestrant is also explicitly based on previous treatment with aromatase inhibitors. With regard to the use of the aromatase inhibitors letrozole and exemestane, the present guidelines [17] also show that the change of aromatase inhibitor from a steroidal to a non-steroidal aromatase inhibitor or vice versa is explicitly recommended with regard to the treatment algorithm in this therapeutic indication.

According to the study protocol, the investigators were required to select the comparator therapy option at their own discretion according to the patient's previous therapy. Care was to be taken to ensure that patients who had not previously been treated with fulvestrant were treated with fulvestrant unless there was a known contraindication. If patients had progression under pretreatment with fulvestrant, they should receive an aromatase inhibitor. In addition, the change of an aromatase inhibitor from a steroidal to a non-steroidal aromatase inhibitor or vice versa was recommended (taking into account any contraindications).

The EPAR information on the entire study population shows that the ACT was largely implemented in compliance with the above-mentioned requirements. However, the EPAR indicates that approximately 15% of patients in the comparator arm may not have received treatment according to the ACT. For example, 5 patients who had failed prior therapy with aromatase inhibitors and fulvestrant received subsequent monotherapy with fulvestrant within the framework of the study. This does not correspond to the specifications of the ACT, according to which a change of treatment should take place with regard to the drugs used in the previous endocrine therapy.

The company does not present the patients' previous therapies in relation to the selected treatment option for subpopulation A 1 analysed in Module 4 A; this information is also missing for the ESR1-mut population. It is therefore unclear how many patients in these subpopulations were not treated in accordance with the ACT. The assessment requires

information on the therapies used in the study in relation to the previous therapy for the subpopulations.

Further comments on the company's dossier

Information on observation periods is not comprehensible

The information on the actual observation periods of the outcomes on morbidity, health-related quality of life and side effects in the company's dossier is not comprehensible. In Module 4 A, for example, median observation periods of < 1 month are stated for the outcomes and AEs recorded using the EORTC-QLQ-C30, whereby these were to be observed until the last dose of the study medication + 30 days according to the study protocol and the median treatment duration in both study arms was over 2 months in relation to the subpopulation A 1 presented by the company. Moreover, different observation periods were specified, for example, for the individual symptom items of the EORTC-QLQ-C30. This is also not plausible.

Discrepancy in the assessment of progression events

At the 1st data cut-off, the EMERALD study already showed that the assessment of progression by the investigators differed clearly from the retrospective, blinded assessment by the IRC [11]. In comparison with the assessment by the investigators, the independent assessment by the IRC confirmed 27.8% fewer events (32 of 115 patients had no progress according to the IRC) in the intervention arm and 16.8% fewer events (19 of 113 patients had no progress according to the IRC) in the comparator arm. The company does not explain the reasons for these discrepancies.

Symptoms, health status, and health-related quality of life

The calculation of the response rates is incorrect

When calculating the response rates per time point, the company states the number of expected responses as the number of patients who could theoretically complete the questionnaire (i.e. living patients, patients without lost to follow-up, etc.). The number of expected responses at the respective time points should correspond to the number of all patients who have not died by this point in time.

Side effects

The threshold for the presentation of AEs by System Organ Class (SOC) and Preferred Terms (PT) was not interpreted correctly

According to the dossier template, all events that occurred in at least 10% of patients in a study arm and additionally all events that occurred in at least 10 patients and in at least 1% of patients in a study arm should be presented for AEs (regardless of severity). Contrary to its information in Appendix 4 G to Module 4 A, the company only presents the event time

analyses for events that occurred in at least 10% of the patients in a study arm. This approach is not appropriate. Due to the company's approach, the presentation of the event time analysis for the event “asthenia” (PT), which occurred in 10 patients (9.8%) in the elacestrant arm and 6 patients (6.6%) in the comparator arm, is missing in subpopulation A 1.

I 3.2 Results on added benefit

No suitable data are available for the assessment of the added benefit of elacestrant in postmenopausal women with ER-positive, HER2-negative locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed after at least one line of endocrine therapy, including a CDK 4/6 inhibitor. There is no hint of an added benefit of elacestrant in comparison with the ACT; an added benefit is therefore not proven.

I 3.3 Probability and extent of added benefit

No suitable data are available for the assessment of the added benefit of elacestrant in postmenopausal women with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed after at least one line of endocrine therapy, including a CDK 4/6 inhibitor. Hence, an added benefit of elacestrant in comparison with the ACT is not proven for these patients.

The assessment described above deviates from that of the company, which derived an indication of a minor added benefit for the specified patient population on the basis of the subpopulation A 1 presented by it. For the subgroup of patients with 2 previous lines of endocrine therapy, the company derives an indication of major added benefit.

I 4 Research question 2: men

I 4.1 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 elacestrant (status: 6 September 2023)
- bibliographical literature search on elacestrant (last search on 22 August 2023)
- search in trial registries/trial results databases for studies on elacestrant (last search on 22 August 2023)
- search on the G-BA website for elacestrant (last search on 22 August 2023)

To check the completeness of the study pool:

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

The company identified the EMERALD study, which included a total of 7 men. However, the label-enabling subpopulation from the EMERALD study (ESR1-mut subpopulation) only includes women with an activating ESR1 mutation. None of the men included in the EMERALD study had an ESR1 mutation. Thus, no data were available for research question 2.

I 4.2 Results on added benefit

No data for comparison with the ACT are available for the assessment of the added benefit of elacestrant in men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed after at least one line of endocrine therapy, including a CDK 4/6 inhibitor. There is no hint of an added benefit of elacestrant in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

No data are available for the assessment of the added benefit of elacestrant in men with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed after at least one line of endocrine therapy, including a CDK 4/6 inhibitor. Hence, an added benefit of elacestrant in comparison with the ACT is not proven for these patients.

This concurs with the company’s assessment.

I 5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of elacestrant in comparison with the ACT is summarized in Table 8.

Table 8: Elacestrant – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Postmenopausal women[b] with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed following at least one line of endocrine therapy including a CDK 4/6 inhibitor[c]	Treatment of physician's choice, taking into account a change of endocrine therapy[d]: ▪ tamoxifen ▪ anastrozole ▪ fulvestrante as monotherapy ▪ letrozolele ▪ exemestanee ▪ everolimus in combination with exemestane (only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor)	Added benefit not proven
2	Men[f] with ER-positive, HER2-negative, locally advanced or metastatic breast cancer with an activating ESR1 mutation whose disease has progressed following at least one line of endocrine therapy including a CDK 4/6 inhibitor[c]	Treatment of physician's choice, taking into account a change of endocrine therapy[d]: ▪ tamoxifenf ▪ aromatase inhibitorf in combination with a gonadotropin-releasing hormone (GnRH) analogue ▪ fulvestrantf	Added benefit not proven

Table 8: Elacestrant – probability and extent of added benefit (multipage table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit

a. Presented is the respective ACT specified by the G-BA.
b. According to the G-BA, it is viewed critically to consider premenopausal women with supressed ovarian function as postmenopausal and to treat them as postmenopausal women.
c. For the present therapeutic indication, it is assumed that re-treatment with a CDK 4/6 inhibitor is not an option, that further endocrine therapy is indicated for the patients and that there is no therapeutic indication for chemotherapy to achieve a rapid remission. Moreover, it is assumed that (secondary) resection or radiotherapy with curative intent is not indicated. It is also assumed that treatment with elacestrant is not indicated for patients with genomic breast cancer associated gene (BRCA)1/2 mutations for whom BRCA-specific therapy is an option.
d. It is assumed that there has been a change in treatment with respect to the drugs used for the previous endocrine-based therapy.
e. In this therapeutic indication, the approvals of fulvestrant, letrozole and exemestane only provide for use after prior anti-oestrogen therapy. However, it is clear from the guidelines that the use of fulvestrant is also explicitly based on previous therapy with aromatase inhibitors, and that with regard to the use of the aromatase inhibitors letrozole and exemestane, switching from a steroidal to a non-steroidal aromatase inhibitor or vice versa is also explicitly recommended. According to the G-BA, the use of fulvestrant, letrozole and exemestane is generally preferable to the approved endocrine therapies for the patient group of postmenopausal women for the therapeutic indication after pretreatment with an endocrine therapy other than anti-oestrogens, in particular after prior therapy with aromatase inhibitors. For this reason, the G-BA considers it appropriate to determine the above-mentioned drugs as ACT for this therapeutic indication, even when used beyond the scope of the approval.
f. The guidelines recommends the drugs tamoxifen, fulvestrant and aromatase inhibitor + GnRH analogue for the male patient group. However, in the therapeutic indication, aromatase inhibitors and fulvestrant are only approved for women. With regard to the approved drug tamoxifen, it can be assumed that the vast majority of patients have already received treatment with tamoxifen at an earlier stage of the disease or earlier in the treatment sequence. According to the G-BA, the use of fulvestrant and of aromatase inhibitors + GnRH analogue is therefore generally preferable to tamoxifen for the patient group of men in the described therapeutic indication. The G-BA therefore considers it appropriate to determine the off-label use of the above-mentioned drugs as ACT.

BRCA: breast cancer susceptibility gene; CDK 4/6: cyclin-dependent kinase 4/6; ER: oestrogen receptor; ESR1: oestrogen receptor 1; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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