Abemaciclib
(breast cancer, adjuvant treatment)

Benefit assessment according to §35a SGB V[1]
(expiry of the decision)

EXTRACT

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Patient and family involvement

The questionnaire on the disease and its treatment was answered by two persons.

IQWiG thanks the respondent(s) and the patient organisation Frauenselbsthilfe Krebs Bundesverband e. V. for participating in the written exchange and for their support. The respondent(s) and Frauenselbsthilfe Krebs Bundesverband e. V. were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
pALN	positive axillary lymph nodes
RCT	randomised controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 abemaciclib. 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 02 March 2026.

The company had already submitted a dossier for a previous benefit assessment of the drug to be assessed. In this procedure, the G-BA limited the decision until 1 July 2026. The reason for this was that the informative value of the results – particularly with regard to overall survival and recurrences – was limited, as the median observation period in the MONARCH-E study had only been 28 months at the time of data cut.

Research question

The aim of this report is the assessment of the added benefit of abemaciclib in combination with endocrine therapy in comparison with the appropriate comparator therapy (ACT) for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative, node-positive early breast cancer at high risk of recurrence.

The research questions presented in Table 2 were defined in accordance with the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of abemaciclib in combination with endocrine therapy

Research question	Therapeutic indication	**Appropriate comparator therapy (ACT)**[a]
Adjuvant treatment of patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence		
1	Premenopausal women[b, c, d]	▪ Tamoxifen (accompanied by ovarian function suppression, as appropriate) or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline breast cancer-associated gene [BRCA]1/2 mutations) or ▪ an aromatase inhibitor (anastrozole, letrozole or exemestane) in combination with ovarian function suppression (exemestane only in combination with triptorelin) or ▪ ribociclib in combination with an aromatase inhibitor
2	Postmenopausal women[c, d, e]	▪ An aromatase inhibitor (anastrozole or letrozole) alone; possibly tamoxifen if aromatase inhibitors are unsuitable or ▪ an aromatase inhibitor (anastrozole or exemestane) in sequence after tamoxifen or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations) or ▪ ribociclib in combination with an aromatase inhibitor

a. Presented is the respective ACT specified by the G-BA.
b. According to the Summary of product characteristics (SmPC), the aromatase inhibitor should be combined with an LH-RH agonist in pre- or perimenopausal women.
c. According to the G-BA, adjuvant chemotherapy – if indicated – is assumed to have been completed.
d. Adjuvant radiotherapy may be performed sequentially or in parallel with endocrine therapy. According to the G-BA, adjuvant radiotherapy is not part of the ACT.
e. As a further treatment option, postmenopausal patients with HR-positive breast cancer should be offered adjuvant bisphosphonate therapy.

ACT: appropriate comparator therapy; BRCA: breast cancer-associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; LHRH: luteinizing hormone-releasing hormone

The company followed the G-BA's specification of the ACT for both research questions. Contrary to the G-BA, the company identified ribociclib in combination with endocrine therapy as an option for the ACT in both research questions. However, the G-BA specified ribociclib in combination with an aromatase inhibitor for each case. This has no consequence for the present benefit assessment, as the company did not present any studies in comparison with ribociclib. This assessment was based on the ACT specified by the G-BA. The assessment was

conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomised controlled trials (RCTs) were used to derive the added benefit. This concurred with the company's inclusion criteria.

Results

Study pool and study design

The MONARCH-E study is an open-label RCT comparing abemaciclib in combination with standard endocrine therapy against standard endocrine therapy. The study included patients with node-positive, HR-positive, HER2-negative early breast cancer who had undergone definitive surgery, without distant metastases and at high risk of recurrence.

Cohort 1 of the MONARCH-E study is relevant to the benefit assessment. A total of 5,120 patients were included in Cohort 1. Randomisation was in a 1:1 ratio, stratified by prior treatment (neoadjuvant chemotherapy versus adjuvant chemotherapy versus no chemotherapy), menopausal status (premenopausal versus postmenopausal), and region (North America and Europe versus Asia versus others). The use of abemaciclib in the intervention arm is in compliance with the summary of product characteristics (SmPC). In both study arms, patients received standard adjuvant endocrine therapy of physician's choice. Patients included in the study could already have started adjuvant endocrine therapy up to 12 weeks before the start of the study.

Primary outcome of the study was invasive disease-free survival (IDFS). Relevant secondary outcomes are overall survival, symptoms, health-related quality of life, and adverse events (AEs).

The company presented subpopulations for each of the two research questions (premenopausal and postmenopausal patients).

The MONARCH-E study is generally considered relevant to both research questions (premenopausal and postmenopausal patients). However, the company's dossier lacks key information required for the benefit assessment, particularly with regard to the formation of the two subpopulations. Without this information, it is unclear whether the results presented are suitable for answering the research questions of the benefit assessment. An adequate assessment of the study data is therefore not possible, so that the results of the MONARCH-E study will overall not be used for the benefit assessment. This is explained below.

In order to analyse subpopulations of the MONARCH-E study on the basis of the endocrine therapies administered, it is necessary for the allocation of endocrine therapy to have taken place prior to randomisation, in order to maintain structural equivalence between the study arms. It is not comprehensible from the study documents whether endocrine therapies should be allocated before or after randomisation. The study also included patients who were already

receiving endocrine therapy before the start of the study. It is not clear to what extent the existing endocrine therapies were continued in the patients included in the subpopulations.

In the MONARCH-E study, endocrine therapy was to be continued in both study arms for at least 5 years after the start of the study. According to current guidelines, a significantly longer duration of adjuvant endocrine therapy is recommended for patients at high risk of recurrence. For example, the S3 guideline recommends a treatment duration with tamoxifen of more than 10 years for premenopausal women at high risk of recurrence. Postmenopausal women at high risk of recurrence should undergo extended endocrine therapy for 7 to 8 years. At the time of the data cut of 15 July 2025 presented by the company, the patients in both study arms had been followed for a median duration of slightly more than 6 years. The company presented information on the treatment duration only for the first two years of the study. It is therefore not possible to assess whether the patients in the study, particularly those in the comparator arm, received endocrine therapy for a sufficiently long period.

Overall, it cannot be inferred from the dossier on the basis of which criteria the company had formed the respective subpopulations. The company states that, for each of the two research questions, it provides analyses of subpopulations whose treatment sequence principally corresponds to those of the ACT. It must be assumed that the intention-to-treat (ITT) principle was not implemented in the presented analyses of the subpopulations, as patients who had switched to an endocrine therapy not comprised in the ACT during the course of the study were excluded.

Furthermore, particularly with regard to research question 2 (postmenopausal women), it is unclear whether the ACT was adequately implemented in the comparator arm.

Overall, the analyses presented by the company are unsuitable for drawing conclusions on the added benefit of abemaciclib in combination with endocrine therapy versus the ACT as adjuvant treatment in women with HR-positive, HER2-negative early breast cancer at high risk of recurrence.

Results on added benefit

No suitable data are available for the assessment of the added benefit of abemaciclib in combination with an aromatase inhibitor versus the ACT as adjuvant treatment in premenopausal and postmenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence. There is no hint of an added benefit of abemaciclib in combination with endocrine therapy compared with the ACT for either research question; 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 the probability and extent of added benefit of abemaciclib in combination with endocrine therapy.

[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 lesser benefit). For further details see [1,2].

Table 3: Abemaciclib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adjuvant treatment of patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence			
1	Premenopausal women[b, c, d]	▪ Tamoxifen (accompanied by ovarian function suppression, as appropriate) or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations) or ▪ an aromatase inhibitor (anastrozole, letrozole or exemestane) in combination with ovarian function suppression (exemestane only in combination with triptorelin) or ▪ ribociclib in combination with an aromatase inhibitor	Added benefit not proven
2	Postmenopausal women[b, c, e]	▪ An aromatase inhibitor (anastrozole or letrozole) alone; tamoxifen if aromatase inhibitors are unsuitable or ▪ an aromatase inhibitor (anastrozole or exemestane) in sequence after tamoxifen or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations) or ▪ ribociclib in combination with an aromatase inhibitor	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the SmPC, the aromatase inhibitor should be combined with an LH-RH agonist in pre- or perimenopausal women.
c. According to the G-BA, adjuvant chemotherapy – if indicated – is assumed to have been completed.
d. Adjuvant radiotherapy may be performed sequentially or in parallel with endocrine therapy. According to the G-BA, adjuvant radiotherapy is not part of the ACT.
e. As a further treatment option, postmenopausal patients with HR-positive breast cancer should be offered adjuvant bisphosphonate therapy.

ACT: appropriate comparator therapy; BRCA: breast cancer-associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; LHRH: luteinizing hormone-releasing hormone

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 the assessment of the added benefit of abemaciclib in combination with endocrine therapy in comparison with the ACT for the adjuvant treatment of patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence.

The research questions presented in Table 4 were defined in accordance with the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of abemaciclib in combination with endocrine therapy

Research question	Therapeutic indication	ACT[a]
Adjuvant treatment of patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence		
1	Premenopausal women[b, c, d]	▪ Tamoxifen (accompanied by ovarian function suppression, as appropriate) or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations) or ▪ an aromatase inhibitor (anastrozole, letrozole or exemestane) in combination with ovarian function suppression (exemestane only in combination with triptorelin) or ▪ ribociclib in combination with an aromatase inhibitor
2	Postmenopausal women[c, d, e]	▪ An aromatase inhibitor (anastrozole or letrozole) alone; possibly tamoxifen if aromatase inhibitors are unsuitable or ▪ an aromatase inhibitor (anastrozole or exemestane) in sequence after tamoxifen or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations) or ▪ ribociclib in combination with an aromatase inhibitor

a. Presented is the respective ACT specified by the G-BA.
b. According to the SmPC, the aromatase inhibitor should be combined with an LH-RH agonist in pre- or perimenopausal women.
c. According to the G-BA, adjuvant chemotherapy – if indicated – is assumed to have been completed.
d. Adjuvant radiotherapy may be performed sequentially or in parallel with endocrine therapy. According to the G-BA, adjuvant radiotherapy is not part of the ACT.
e. As a further treatment option, postmenopausal patients with HR-positive breast cancer should be offered adjuvant bisphosphonate therapy.

ACT: appropriate comparator therapy; BRCA: breast cancer-associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; LHRH: luteinizing hormone-releasing hormone

The company followed the G-BA's specification of the ACT for both research questions. Contrary to the G-BA, the company identified ribociclib in combination with endocrine therapy as an option for the ACT in both research questions. However, the G-BA specified ribociclib in combination with an aromatase inhibitor for each case. This has no consequence for the present benefit assessment, as the company did not present any studies in comparison with ribociclib.

This assessment was based on the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on abemaciclib (status: 01 December 2025)
- Bibliographical literature search on abemaciclib (last search on 01 December 2025)
- Search of trial registries / trial results databases for studies on abemaciclib (last search on 01 December 2025)
- Search on the G-BA website for abemaciclib (last search on 1 December 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on abemaciclib (last search on 19 March 2026); for search strategies, see I Appendix A of the full benefit assessment.

The search did not identify any additional relevant studies.

I 3.1 Studies included

The study presented in the following Table 5 was included in the benefit assessment for both research questions.

Table 5: Study pool – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy

Study	Study category			Available sources		
	Study for the marketing authorisation of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication and other sources[c] (yes/no [citation])
I3Y-MC-JPCF (MONARCH-E[d])	Yes	Yes	No	Yes [3,4]	Yes [5-7]	Yes [8-11]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on 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.

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

In its dossier, the company also presented results of the MONARCH-E study. In order to answer the two research questions 1 (premenopausal women) and 2 (postmenopausal women), it formed one subpopulation for each of these research questions of the study.

The study is generally considered to be relevant and is therefore included in the benefit assessment. However, the company's dossier lacks key information required for the benefit assessment, particularly with regard to the formation of the two subpopulations. Without this information, it is unclear whether the results presented are suitable for answering the research questions of the benefit assessment. An adequate assessment of the study data is therefore not possible, so that the results of the MONARCH-E study will overall not be used for the benefit assessment.

Section I 3.2 below describes the study and the uncertainties, and explains why the results are not suitable for the benefit assessment without further information.

I 3.2 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (multipage table)

Study	Study design	Population	Interventions (number of randomised patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MONARCH-E	RCT, open-label, parallel	Adult patients with node-positive, HR-positive, HER2-negative early breast cancer who had undergone definitive surgery ▪ without evidence of distant metastases and at high risk of recurrence ▪ ECOG PS ≤ 1	Cohort 1[b]: abemaciclib + endocrine therapy (N = 2555) endocrine therapy (N = 2565) cohort 2[c]: abemaciclib + endocrine therapy (N = 253) endocrine therapy (N = 264) subpopulations from cohort 1 presented by the company: ▪ premenopausal women (1) ▫ abemaciclib + endocrine therapy (n = 777) ▫ endocrine therapy (n = 728) ▪ postmenopausal women (2) ▫ abemaciclib + endocrine therapy (n = 1284) ▫ endocrine therapy (n = 1263)	Screening: cohort 1: 1–3 months treatment: ▪ abemaciclib: 2 years or until disease progression, treatment discontinuation according to the physician's, patient's or sponsor's decision, or end of study. ▪ endocrine therapy: ≥ 5 years ▪ observation: maximum 10 years or until end of study, whichever occurs earlier	611 study centres in Argentina, Australia, Austria, Belgium, Brazil, Canada, China, Czech Republic, Denmark, Finland, France, Germany, Greece, Hong Kong, Hungary, India, Israel, Italy, Japan, Mexico, Netherlands, New Zealand, Poland, Portugal, Puerto Rico, Romania, Russia, Saudi Arabia, Singapore, South Africa, South Korea, Spain, Sweden, Taiwan, Turkey, Ukraine, United Kingdom, USA 07/2017–ongoing Data cuts: ▪ 27 September 2019 (first interim analysis after 195 IDFS events) ▪ 16 March 2020 (second interim analysis after 293 IDFS events) ▪ 8 July 2020 (final IDFS analysis after 390 IDFS events) ▪ 01 April 2021 (first OS interim analysis) ▪ 1 July 2022[d] (second OS interim analysis, 2 years after the final IDFS analysis) ▪ 3 July 2023 (third OS interim analysis, 3 years after the final IDFS analysis) ▪ 15 July 2025[e] (final analysis of overall survival following 650 events)	Primary: IDFS secondary: overall survival, symptoms, health-related quality of life, AEs

Table 6: Characteristics of the study included – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (multipage table)

Study	Study design	Population	Interventions (number of randomised 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 only include information on relevant available outcomes for this benefit assessment.
b. High risk of recurrence defined as either ≥ 4 pALN, or 1–3 pALN and at least one of the following criteria: tumour size ≥ 5 cm or histological grade 3.
c. Cohort 2 (risk of recurrence assessed on the basis of the Ki-67 value: high risk defined as 1–3 pALN with a Ki--67 value of the tumour tissue of ≥ 20 %) is not relevant to the benefit assessment and is not considered further.
d. This data cut is the one relevant to this benefit assessment for patient-reported outcomes (symptoms, health status, health-related quality of life).
e. This data cut is the one relevant to the present benefit assessment for the outcome categories mortality, failure of the curative treatment approach and side effects.

ACT: appropriate comparator therapy; AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IDFS: invasive disease-free survival; Ki-67: antigen Ki(Kiel)-67; n: relevant subpopulation; N: number of randomised patients; OS: overall survival; pALN: positive axillary lymph nodes; RCT: randomised controlled trial

Table 7: Characteristics of the intervention – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (multipage table)

Study	Intervention	Comparison
MONARCH-E	Abemaciclib 150 mg orally, twice daily for 2 years + endocrine therapy of physician's choice for ≥ 5 years	Endocrine therapy of physician's choice for ≥ 5 years
	Dose modification: ▪ abemaciclib: ▫ in the event of toxicities, treatment interruptions of up to 28 days and a maximum of 2 dose reductions (first to 100 mg and subsequently to 50 mg, each twice daily) were permitted[a]. If treatment was discontinued, endocrine therapy could be continued at the investigator's discretion. ▫ in the case of planned surgical interventions, administration could be postponed for up to 28 days. ▪ endocrine therapy ▫ dose adjustments or interruptions for up to 28 days[a] were possible ▫ in case of discontinuation in the intervention arm for reasons other than an IDFS event, therapy with abemaciclib was to be continued. ▫ a switch to another endocrine therapy was allowed at the investigator's discretion and in the absence of an IDFS event during the treatment period of the study.	
	Allowed prior treatment ▪ adjuvant radiotherapy[b] ▪ adjuvant and/or neoadjuvant chemotherapy[b] ▫ up to 12 weeks of endocrine therapy prior to randomisation if patients were receiving endocrine therapy as adjuvant therapy[c] before the start of the study **disallowed prior treatment** ▪ CDK4 / 6 inhibitors ▪ endocrine therapy for breast cancer prevention (tamoxifen or aromatase inhibitors) or raloxifene ▪ ≤ 30 days prior to randomisation: other investigational products of any kind ▪ **allowed concomitant treatment** ▪ supportive therapy, especially bisphosphonates and denosumab ▪ **disallowed concomitant treatment** ▪ fulvestrant ▪ CDK4 / 6 inhibitors ▪ exogenous reproductive hormone therapy (e.g. oral contraceptives, hormone replacement therapy or megestrol acetate) ▪ other investigational products of any kind	

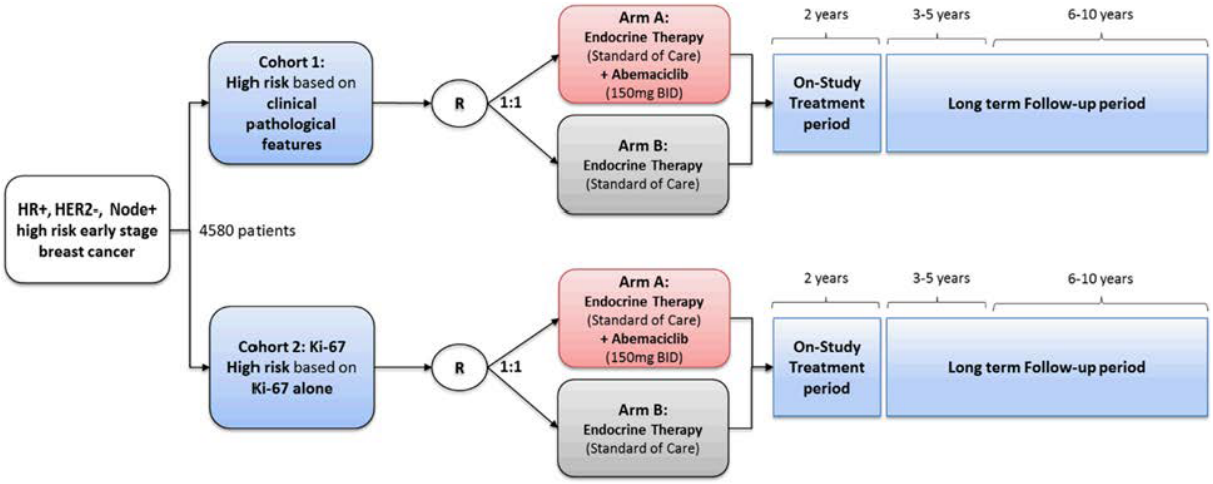
Table 7: Characteristics of the intervention – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (multipage table)

Study	Intervention	Comparison
a. A delay > 28 days was possible upon agreement between the investigator and the CRP/CRS. Dose adjustment according to the study protocol should be considered in case of toxicities, depending on type (haematological, non-haematological, diarrhoea, ALT increased, AST increased, ILD/pneumonitis) and severity. b. Adjuvant radiotherapy/chemotherapy had to be completed prior to randomisation, and patients had to have recovered from the acute effects of radiotherapy/chemotherapy (CTCAE grade ≤ 1; except for adjuvant chemotherapy: persistent alopecia or grade 2 peripheral neuropathy). A washout period of ≥ 14 days in adjuvant radiotherapy, and of ≥ 21 days in adjuvant chemotherapy (provided the patient had not received radiotherapy) was required between end of radiotherapy/chemotherapy and randomisation. c. Use of gonadotropin-releasing hormone analogues for ovarian suppression was not considered endocrine therapy in the sense of this criterion. Fulvestrant as adjuvant treatment was not allowed. ALT: alanine aminotransferase; AST: aspartate aminotransferase; CDK: cyclin-dependent kinase; CRP: clinical research physician; CRS: clinical research scientist; CTCAE: Common Terminology Criteria for Adverse Events; IDFS: invasive disease-free survival; ILD: interstitial lung disease; RCT: randomised controlled trial		

Study design

The MONARCH-E study is an ongoing, open-label multicentre RCT comparing abemaciclib in combination with standard endocrine therapy with standard endocrine therapy. The study included patients with node-positive, HR-positive, HER2-negative early breast cancer who had undergone definitive surgery, without distant metastases and at high risk of recurrence.

Figure 1 shows the design of the MONARCH-E study:



Abbreviations: BID = twice daily; HER2 = human epidermal growth factor receptor 2 negative; HR+ = hormone receptor-positive; ITT = intent to treat; Ki-67 = prognostic parameter; R = randomization.

Figure 1: Design of the MONARCH-E study

The MONARCH-E study is divided into 2 cohorts. In cohort 1, high risk of recurrence is defined as either ≥ 4 positive axillary lymph nodes (pALN) or 1 to 3 pALN and grade 3 tumour and/or tumour size of ≥ 5 cm (corresponding to stage IIA to IIIC upon diagnosis). This definition of a high risk of recurrence is considered appropriate in the therapeutic indication [12].

In the patients included in cohort 2 (N = 517), a high risk of recurrence was estimated on the basis of the proliferation marker Ki-67. Since the approval was granted solely on the basis of the results for cohort 1, cohort 2 is not relevant to the benefit assessment and is not considered further in the following [13].

Patients should be enrolled in the study within 16 months of their definitive breast cancer surgery. Neoadjuvant/adjuvant chemotherapy or adjuvant radiotherapy had to be completed before the start of the study.

A total of 5120 patients were included in cohort 1 and randomly allocated in a 1:1 ratio either to treatment with abemaciclib in combination with endocrine therapy (N = 2555) or to an endocrine therapy (N = 2565). Randomisation was stratified by prior treatment (neoadjuvant chemotherapy versus adjuvant chemotherapy versus no chemotherapy), menopausal status (premenopausal versus postmenopausal), and region (North America and Europe versus Asia versus others).

In the MONARCH-E study, patients in the intervention arm received abemaciclib for 2 years following randomisation. After randomisation, adjuvant endocrine therapy was to be continued in both study arms for at least 5 years from the start of the study (provided it is medically indicated). Regardless of the duration of adjuvant endocrine therapy, patients will be followed up for at most 10 years or until the end of the study, provided the study is not terminated prematurely.

Treatment with abemaciclib in the intervention arm was in compliance with the SmPC [13]. In both study arms, patients received standard adjuvant endocrine therapy of physician’s choice (e.g. tamoxifen or an aromatase inhibitor, with or without ovarian suppression). Patients included in the study could already have started adjuvant endocrine therapy before the start of the study. However, randomisation had to take place within 12 weeks of the start of endocrine therapy. The remaining patients began their endocrine therapy at the start of the study.

The company stated that the administered endocrine therapies did not correspond to the G-BA's ACT in all cases. For both research questions, the company therefore presented analyses of subpopulations in which the patients in both study arms received endocrine therapy in accordance with the respective ACT at the start of the study and during its course. Consequently, patients who were receiving endocrine therapy corresponding to the ACT at

the start of the study but who switched to endocrine therapy that did not correspond to the ACT during the course of the study were excluded.

Primary outcome of the study was invasive disease-free survival (IDFS). Relevant secondary outcomes were overall survival, symptoms, health-related quality of life, and AEs. The company presented subpopulations for both research questions (premenopausal and postmenopausal patients). However, these could not be used for the benefit assessment. This is explained below. The discussion will first address superordinate aspects and then move on to the two presented subpopulations.

Time of the allocation of endocrine therapy unclear

In the study, patients in both study arms were to receive adjuvant endocrine therapy of physician's choice.

In order to analyse subpopulations of the MONARCH-E study on the basis of the endocrine therapies administered, it is necessary that the allocation of endocrine therapy had taken place prior to randomisation, in order to maintain structural equivalence between the study arms.

The study documents do not specify whether the investigator should determine the endocrine therapy for the patients before or after randomisation.

In the study, patients could continue their existing endocrine therapy, provided that it had been started within 12 weeks prior to randomisation. The study data show that about 63% of the study population had already been treated with adjuvant endocrine therapy prior to randomisation. However, data on the proportion of patients in the subpopulations who continued with their existing endocrine therapy following randomisation are not available.

In order to prevent any breach of randomisation when forming the subpopulation, only those patients were allowed to be included in the respective subpopulation who

1) had either started endocrine therapy at the start of the study and whose endocrine therapy had been determined prior to randomisation, or
2) had already been receiving endocrine therapy prior to entering the study and who continued this therapy following randomisation at the start of the study.

Duration of treatment with endocrine therapies unclear

In the MONARCH-E study, endocrine therapy was to be continued in both study arms for at least 5 years after the start of the study. In accordance with current national [12,14] and international guidelines [15,16], a clearly longer duration of adjuvant endocrine therapy is recommended for patients at high risk of recurrence. For example, the S3 guideline

recommends a treatment duration with tamoxifen for 10 years for premenopausal women at high risk of recurrence [12]. Postmenopausal women at high risk of recurrence should undergo extended endocrine therapy for 7 to 8 years.

At the time of the data cut of 15 July 2025 presented by the company, the patients in both study arms had been followed for a median duration of slightly more than 6 years. In its dossier, the company presented information on the treatment duration only for the first two years of the study. No information is available on the total duration of treatment with endocrine therapies in the study. It is therefore unclear whether the patients received appropriate endocrine therapy in accordance with the recommendations set out in the guidelines [12,14,15]. In the MONARCH-E study, a shortened treatment with endocrine therapy means a particular disadvantage for the comparator arm.

Formation of the subpopulations presented by the company unclear

The company presented subpopulations for both research questions, separated by menopausal status and based on the study population from Cohort 1. The company stated that the administered endocrine therapies did not correspond to the G-BA's ACT in all cases. The company states that, for each of the two research questions, it provides analyses of subpopulations whose treatment sequence principally corresponds to the ACT. This means that it only presented analyses of those patients who received endocrine therapy in line with the respective ACT at the start of the study and throughout its course. For the benefit assessment, it is necessary (in the sense of the ITT principle) to include all patients in the analyses of the respective subpopulations who were receiving endocrine therapy corresponding to the ACT at the start of the study. In its dossier for the first assessment, the company addressed this aspect in sensitivity analyses that included all patients in the sense of the ITT principle. The company did not present such analyses for the current data cut.

Furthermore, for each of its subpopulations, the company only provided data on the proportion of patients who were receiving either tamoxifen or an aromatase inhibitor at the start of the study. However, the benefit assessment requires a detailed description of the endocrine therapies administered (e.g. the type of aromatase inhibitors used) at the start of the study. Overall, it cannot be inferred from the dossier on the basis of which criteria the company had formed the respective subpopulations. This is explained below.

Research question 1: Premenopausal women

The company presented a subpopulation of 1,505 patients, 777 of whom were treated with abemaciclib in combination with endocrine therapy and 728 with endocrine therapy alone. A total of 2,220 premenopausal women were included in Cohort 1 of the study. The subpopulation presented by the company comprised only 1,505 female patients (approx. 68%).

The study documents show that, within the total study population, antioestrogens (tamoxifen and toremifene) and aromatase inhibitors (anastrozole, letrozole and exemestane) were used as endocrine therapies. Of these drugs, only the antioestrogen toremifene is not included in the G-BA's ACT (see Chapter I 2). However, this was used in only a very small number of patients (n = 21 [0.4%]).

In accordance with the ACT, aromatase inhibitors (anastrozole, letrozole or exemestane) should be administered in combination with ovarian function suppression (exemestane only in combination with triptorelin). In the case of tamoxifen, ovarian function may also need to be suppressed. The study documents of the company show that the GnRH agonists goserelin, leuprorelin and triptorelin were used in the study. The European Public Assessment Report (EPAR) states that 680 of the premenopausal patients in Cohort 1 received an aromatase inhibitor in combination with a GnRH agonist. However, the subpopulation presented by the company only included 418 patients receiving an aromatase inhibitor therapy at baseline. The EPAR also shows that 1,284 premenopausal patients received tamoxifen treatment; however, only 1,087 with tamoxifen treatment were included in the presented subpopulation. The company's dossier does not contain any detailed information on the combinations of the administered aromatase inhibitors and GnRH agonists in the presented subpopulation. However, these would be necessary in order to assess whether the endocrine therapies used correspond to the ACTs, particularly with regard to the limitation of the ACT in the case of exemestane only in combination with triptorelin, and whether a comparability between the study arms is ensured.

Overall, the company did not include relevant proportions of premenopausal women in the subpopulation presented for research question 1. Based on the available information, the reasons for this are not comprehensible.

Research question 2: Postmenopausal women

The company presented analyses of a subpopulation of 2,547 menopausal patients, 1,284 of whom were treated with abemaciclib in combination with endocrine therapy and 1,263 with endocrine therapy alone. The analyses of the subpopulation now presented include 2,301 ,patients who were receiving an aromatase inhibitor at the start of the study and 246 patients who were receiving tamoxifen.

The information in the EPAR shows that 2,873 postmenopausal patients were receiving an aromatase inhibitor and 302 were receiving tamoxifen at baseline.

Implementation of the ACT

The G-BA's ACT also provides for a sequential treatment strategy with tamoxifen followed by anastrozole or exemestane in addition to therapy with an aromatase inhibitor (anastrozole or letrozole) or possibly tamoxifen (if aromatase inhibitors are not suitable). In order to take

account of treatment sequences in the sense of the ITT principle, the sequence of treatment must be determined at the start of the study. However, the study documents provide no information stating that the patients' treatment sequence was determined at the start of the study.

In its dossier, the company states that it did not include patients in the presented subpopulation who had received initial therapy with exemestane, a treatment sequence starting with tamoxifen followed by letrozole, or a treatment sequence starting with an aromatase inhibitor followed by tamoxifen. This is appropriate for patients who received exemestane as their initial treatment. However, patients who received initial treatment with tamoxifen or an aromatase inhibitor were to be included in the analyses of the subpopulation in the sense of the ITT principle, unless a treatment sequence not covered by the ACT had been determined prior to randomisation. However, there is no information on this in the company's dossier.

Furthermore, according to the G-BA's ACT, tamoxifen was only permitted if aromatase inhibitors are not suitable for the patients. The company did not specify whether, and on what criteria, treatment with an aromatase inhibitor (anastrozole or letrozole) was unsuitable for patients who received tamoxifen. Only if predefined criteria were applied in the study when selecting tamoxifen as a treatment for postmenopausal women, and these reasons for the unsuitability of treatment with an aromatase inhibitor were present, patients receiving tamoxifen could be included in the subpopulation. However, the EPAR shows that only around 10% of postmenopausal patients were treated with tamoxifen.

Use of adjuvant bisphosphonate therapy

Supportive therapy with bisphosphonates or denosumab was permitted in the MONARCH-E study. This corresponds to the guideline recommendations [12,15]. When determining the ACT, the G-BA also points out that postmenopausal women should be offered adjuvant bisphosphonate therapy . The study documents show that 15% of the patients in the study population were administered bisphosphonates or denosumab. Information on the subpopulation presented is not available. However, it was already noted in the EPAR that the number of administered bisphosphonate therapies appears low given a proportion of approx. 57% postmenopausal women in the study. Information on the proportion of postmenopausal women who received adjuvant bisphosphonate therapy or denosumab is necessary to assess whether the ACT had been implemented adequately.

Missing data on study and treatment discontinuations as well as on discontinuations due to AEs in the subpopulations presented

As already noted in the previous benefit assessment [8], a presentation of treatment and study discontinuations for the presented subpopulations of pre- and postmenopausal women

is missing once again. The company's study documents show that, at the time of the relevant data cut (15 July 2025), the number of treatment drop-outs was balanced between the study arms (approx. 18% in each study arm). Over the entire course of the study, approx. 27% of patients in the intervention arm and 30% in the control arm discontinued the study prematurely. On the basis of the data for the study population, it is not possible to assess the distribution of study and treatment discontinuations within the respective subpopulations. In order to assess these research questions, it is necessary to analyse the number of and reasons for treatment and study discontinuations over the entire course of the study, separated by subpopulation.

Furthermore, as was the case with the first assessment, the company's dossier lacks a detailed presentation of the reasons for discontinuation due to AEs. For the outcome discontinuation due to AEs, the reasons for discontinuation must be fully described for both subpopulations.

Summary

In summary, the MONARCH-E study is principally relevant to the benefit assessment.

For the subpopulations presented, it is not possible to assess the extent to which endocrine therapies were appropriately allocated prior to randomisation and whether the duration of treatment with these therapies was in compliance with the guidelines. It must be assumed that the ITT principle was not implemented in the analyses of the subpopulations presented. Furthermore, it is unclear whether the ACT was implemented adequately in the comparator arm, particularly with regard to research question 2 (postmenopausal women).

The following points should be considered when forming subpopulations of pre- and postmenopausal patients:

- Only patients for whom the relevant endocrine therapy was determined prior to randomisation, or who continued an endocrine therapy already ongoing prior to randomisation at the start of the study, may be included.
- The implementation of the ACT must be explained in a way that is comprehensible to the included patients.
- A comprehensible description of the criteria used to compile the respective subpopulation must be provided. The benefit assessment requires analyses in the sense of the ITT principle, as described above.
- Detailed information on the duration of treatment with endocrine therapies over the entire course of the study as well as on the drugs used is required for the respective subpopulations. In addition, data on study and treatment discontinuations must be provided on the level of the respective subpopulation over the entire study or treatment

duration. For the outcome discontinuation due to AEs, the reasons for discontinuation must be fully described for both subpopulations.

Unless the respective endocrine therapy had been determined prior to randomisation for all patients who received a new endocrine therapy at the start of the study, the company should provide further analyses in addition to those described above. These should include all patients in the relevant subpopulation who, at the start of the study, were being treated with one of the ACT options. The endocrine therapies administered in each case should be presented, both for patients who continued with an endocrine therapy that had already been in place prior to randomisation and for those who received a new endocrine therapy at the start of the study. Such analyses can be used to assess the robustness of the effects.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of abemaciclib in combination with an aromatase inhibitor versus the ACT as adjuvant treatment in premenopausal and postmenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence. There is no hint of an added benefit of abemaciclib in combination with endocrine therapy compared with the ACT for either research question; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit – summary

Table 8 shows a summary of the probability and extent of added benefit of abemaciclib in combination with endocrine therapy for research questions 1 (premenopausal women) and 2 (postmenopausal women).

Table 8: Abemaciclib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adjuvant treatment of patients with HR-positive, HER2-negative, node-positive early-stage breast cancer at high risk of recurrence			
1	Premenopausal women[b, c, d]	▪ Tamoxifen (accompanied by ovarian function suppression, as appropriate) or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations) or ▪ an aromatase inhibitor (anastrozole, letrozole or exemestane) in combination with ovarian function suppression (exemestane only in combination with triptorelin) or ▪ ribociclib in combination with an aromatase inhibitor	Added benefit not proven
2	Postmenopausal women[b, c, e]	▪ An aromatase inhibitor (anastrozole or letrozole) alone; tamoxifen if aromatase inhibitors are unsuitable or ▪ an aromatase inhibitor (anastrozole or exemestane) in sequence after tamoxifen or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations) or ▪ ribociclib in combination with an aromatase inhibitor	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the SmPC, the aromatase inhibitor should be combined with an LH-RH agonist in pre- or perimenopausal women.
c. According to the G-BA, adjuvant chemotherapy – if indicated – is assumed to have been completed.
d. Adjuvant radiotherapy may be performed sequentially or in parallel with endocrine therapy. According to the G-BA, adjuvant radiotherapy is not part of the ACT.
e. As a further treatment option, postmenopausal patients with HR-positive breast cancer should be offered adjuvant bisphosphonate therapy.

ACT: appropriate comparator therapy; BRCA: breast cancer-associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; LHRH: luteinizing hormone-releasing hormone

The assessment described above deviates from that of the company, which derived an indication of major added benefit for premenopausal women (research question 1) on the

basis of its MONARCH-E study, and an indication of considerable added benefit for postmenopausal women (research question 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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