IQWiG Reports – Commission No. A22-51

Abemaciclib (breast cancer; adjuvant therapy) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment *Abemaciclib (Mammakarzinom; adjuvante Therapie) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 21 October 2022). 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

No feedback was received in the framework of the present dossier assessment.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CMQ	Custom Medical Dictionary for Regulatory Activities Query
CTCAE	Common Terminology Criteria for Adverse Events
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EPAR	European Public Assessment Report
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue
FACT-B	Functional Assessment of Cancer Therapy – Breast
FACT-ES	Functional Assessment of Cancer Therapy – Endocrine Symptoms
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IDFS	invasive disease-free survival
ILD	interstitial lung disease
ITT	intention to treat
MMRM	mixed-effects model with repeated measures
pALN	positive axillary lymph nodes
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug 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 29 April 2022.

Research question

The aim of the present 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.

Depending on the sex and menopausal status of the patients, the G-BA distinguished between different treatment situations and specified an ACT for each of them. The present assessment refers to research questions 1 to 3 presented in Table 2.

Table 2: Research questions of the benefit assessment of abemaciclib

Research question	Subindication	ACT[a]
Adjuvant treatment of patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence		
1	Premenopausal women	▪ Tamoxifen (possibly in addition to suppression of the ovarian function)
2	Postmenopausal women	▪ An aromatase inhibitor (anastrozole or letrozole) alone, possibly tamoxifen if aromatase inhibitors are unsuitable, or ▪ anastrozole or exemestane in sequence after tamoxifen
3	Men	▪ Tamoxifen
a. Presented is the respective ACT specified by the GBA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor		

The company followed the G-BA's 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 the added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The MONARCH-E study is used for the benefit assessment of abemaciclib in combination with endocrine therapy.

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 5120 patients were enrolled in cohort 1. Randomization 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 (SPC). In both study arms, patients received standard adjuvant endocrine therapy of physician's choice.

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

Data cut-offs

The MONARCH-E study is an ongoing study. So far, 4 data cut-offs are available:

- first data cut-off (27 September 2019): planned interim analysis after 195 IDFS events
- second data cut-off (16 March 2020): planned interim analysis after 293 IDFS events
- third data cut-off (8 July 2020): planned final IDFS analysis after 390 IDFS events
- fourth data cut-off (1 April 2021): post hoc interim analysis on overall survival requested by the regulatory authorities

The study is ongoing. The company used the analysis at the fourth data cut-off (1 April 2021) for the benefit assessment. According to the company, this is a post hoc interim analysis on overall survival requested by the regulatory authorities. Further interim analyses on overall survival are planned 2 and 3 years after the final IDFS analysis, and the final analysis on overall survival after 650 events or 10 years after randomization of the last patient, whichever occurs earlier.

Relevant population for the research questions of the benefit assessment

For research questions 1 to 3, the company presented analyses of relevant subpopulations in which the patients in both study arms received endocrine therapy in accordance with the respective ACT.

Certainty of conclusions of the data cut-off used for the benefit assessment for the outcome of recurrence

At the time of the data cut-off used for the benefit assessment, the median observation period in the study was approximately 28 months. The effect of abemaciclib on the outcome of recurrence cannot yet be assessed with certainty after this relatively short observation period. On the basis of the available data cut-off, only hints, e.g. of an added benefit, can therefore be derived for the outcome of recurrence.

Research question 1: premenopausal women

Subpopulation relevant to the assessment of research question 1

Of the patients included in the MONARCH-E study, only the subpopulation of those premenopausal women who were treated with the G-BA's ACT is relevant to the assessment of research question 1. The company presented analyses of 1088 patients, 553 of whom were treated with abemaciclib in combination with endocrine therapy and 535 with endocrine therapy alone. These are used for the benefit assessment.

Risk of bias and certainty of results

Due to the high risk of bias across outcomes, there is a high risk of bias for the results on all outcomes. This is due to the fact that, according to the company, in the course of the study, an important proportion of patients switched to an endocrine therapy that does not correspond to the ACT or is not approved (N= 181; 14.3%) and these patients were not included in the analyses presented by the company. For non-severe/non-serious specific AE outcomes and discontinuation due to AEs, another reason for a high risk of bias is the open-label study design and the subjective recording of outcomes.

Results

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Morbidity

Recurrence

For the outcome of recurrence, there was a statistically significant effect in favour of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for both recurrence rate and disease-free survival. When assessing the certainty of results, the short median observation period of approximately 28 months at the time of the present data cut-off must be taken into account. This results in a hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

Symptoms, recorded using the FACIT-Fatigue

There are no usable data for the outcome of symptoms recorded using the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue). This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

There are no usable data for the outcome of health status, recorded using the EQ-5D visual analogue scale (VAS). This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life, recorded using the FACT-B and the FACT-ES

No usable data are available for the outcome of health-related quality of life, recorded using the Functional Assessment of Cancer Therapy – Breast (FACT-B) and the Functional Assessment of Cancer Therapy – Endocrine Symptoms (FACT-ES). This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Side effects

Discontinuation due to AEs

A statistically significant difference between treatment groups to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcome of discontinuation due to AEs. This results in a hint of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

SAEs and severe AEs (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcomes of serious AEs (SAEs) and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3). Due to consistent effects from additional analyses, there is an indication of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for each of these outcomes despite the high risk of bias.

Specific AEs

Neutropenia (severe AEs), diarrhoea (severe AEs), blood and lymphatic system disorders (severe AEs) and hepatic events (severe AEs)

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the specific AEs of neutropenia (severe AEs), diarrhoea (severe AEs), blood and lymphatic system disorders (severe AEs) and hepatic events (severe

AEs). Due to consistent effects from additional analyses, there is an indication of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for each of these outcomes despite the high risk of bias.

General disorders and administration site conditions (AEs), eye disorders (AEs), respiratory, thoracic and mediastinal disorders (AEs), gastrointestinal disorders (AEs) and skin and subcutaneous tissue disorders (AEs)

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the specific AEs of general disorders and administration site conditions (AEs), eye disorders (AEs), respiratory, thoracic and mediastinal disorders (AEs), gastrointestinal disorders (AEs) and skin and subcutaneous tissue disorders (AEs). This results in a hint of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for each of these outcomes.

Research question 2: postmenopausal women

Subpopulation relevant to the assessment of research question 2

Of the patients included in the MONARCH-E study, only the subpopulation of postmenopausal women who were treated with the G-BA's ACT is relevant to the assessment of research question 2. The company presented analyses of 2548 patients, 1284 of whom were treated with abemaciclib in combination with endocrine therapy and 1264 of whom were treated with endocrine therapy alone. These are used for the benefit assessment.

Risk of bias and certainty of results

The risk of bias across outcomes for research question 2 (postmenopausal women) is rated as low. The assessment of the risk of bias across outcomes that deviates from research question 1 is due to the fact that, according to the company, in the course of the study, a notably smaller proportion (7.3%) of the postmenopausal women switched to an endocrine therapy that does not correspond to the ACT or is not approved and were therefore not included in the company's analyses. The risk of bias of the results for the outcomes of discontinuation due to AEs and specific AEs (excluding specific SAEs and severe AEs) is rated as high due to the open-label study design.

Results

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Morbidity

Recurrence

For the outcome of recurrence, there was a statistically significant effect in favour of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for both recurrence rate and disease-free survival. When assessing the certainty of results, the short median observation period of approximately 28 months at the time of the present data cut-off must be taken into account. This results in a hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

Symptoms, recorded using the FACIT-Fatigue

There are no usable data for the outcome of symptoms recorded using the FACIT-Fatigue. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

There are no usable data for the outcome of health status, recorded using the EQ-5D VAS. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life, recorded using the FACT-B and the FACT-ES

No usable data are available. for the outcome of health-related quality of life, recorded using the FACT-B and the FACT-ES. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs (CTCAE ≥ 3)

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcomes of SAEs and severe AEs (CTCAE grade ≥ 3). This results in an indication of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for each of these outcomes.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcome of discontinuation due to AEs. This results in a hint of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

Specific AEs

Neutropenia (severe AEs), diarrhoea (severe AEs), fatigue (severe AEs), hypokalaemia (severe AEs), blood and lymphatic system disorders (severe AEs), hepatic events (severe AEs), and interstitial lung disease (ILD)/pneumonitis (SAE)

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for each of the specific AEs of neutropenia (severe AEs), diarrhoea (severe AEs), fatigue (severe AEs), hypokalaemia (severe AEs), blood and lymphatic system disorders (severe AEs), hepatic events (severe AEs), and ILD/pneumonitis. This results in an indication of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for each of these outcomes.

Venous thromboembolism (severe AEs)

A significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcome of venous thromboembolism (severe AEs). There is an effect modification by the characteristic of age for this outcome. A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown only for patients ≥ 65 years of age. This results in an indication of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for the outcome of venous thromboembolism (severe AEs) in patients ≥ 65 years. No statistically significant difference between treatment groups was found for patients < 65 years. This results in no hint of greater or lesser harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for patients < 65 years of age; greater or lesser harm for these patients is therefore not proven.

Arthralgia (AEs)

A significant difference in favour of abemaciclib in combination with endocrine therapy was shown for the outcome of arthralgia (AEs). This results in a hint of lesser harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

Alopecia (AEs), dizziness (AEs), eye disorders (AEs) and gastrointestinal disorders (AEs)

A significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the specific outcomes of alopecia (AEs), dizziness (AEs), eye disorders (AEs) and gastrointestinal disorders (AEs). This results in a hint of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for each of these outcomes.

Research question 3: men

For male patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence, the company considered 19 patients, 10 of whom were treated with abemaciclib in combination with endocrine therapy and 9 with endocrine therapy alone. It presented only descriptive data per treatment arm. There is no hint of added benefit; an added benefit is therefore not proven.

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

On the basis of the results presented, the probability and extent of added benefit of the drug abemaciclib in combination with endocrine therapy in comparison with the ACT are assessed as follows:

Research question 1 (premenopausal women)

Overall, there are both positive and negative effects of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy. On the side of positive effects, there is a hint of an added benefit with considerable extent for the outcome of recurrence. The negative effects are related exclusively to outcomes of the category of side effects. There are indications of greater harm of abemaciclib, partly with major extent, in particular for the overall rate of severe AEs and SAEs as well as for specific severe AEs. In addition, there are other disadvantages such as greater harm of considerable extent regarding specific AEs and discontinuation due to AEs.

No conclusions can be drawn about longer-term effects of therapy with abemaciclib in the present therapeutic indication, as the observation period in the MONARCH-E study was only 28 months at the time of the data cut-off used. Furthermore, no conclusions can be drawn on the patient-reported outcomes on symptoms and health-related quality of life, as no usable data are available.

Overall, the negative effects do not completely call into question the positive effect, however. There is a hint of minor added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy alone for premenopausal patients with node-positive, HR-positive, HER2-negative early breast cancer at high risk of recurrence.

Research question 2 (postmenopausal women)

Overall, there are positive and negative effects of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy. The positive effects are one hint of minor added benefit in serious/severe symptoms for the outcome of recurrence and one hint of a considerable added benefit in non-serious/non-severe side effects for one specific AE.

[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].

The negative effects are related exclusively to outcomes of the category of side effects. There are indications of greater harm of abemaciclib, partly with major extent, in particular for the overall rates of serious and severe AEs as well as for specific severe AEs.

No conclusions can be drawn about longer-term effects of therapy with abemaciclib in the present therapeutic indication, as the observation period in the MONARCH-E study was only 28 months at the time of the data cut-off used. Furthermore, no conclusions can be drawn on the patient-reported outcomes on symptoms and health-related quality of life, as no usable data are available.

Overall, the negative effects call into question the positive ones. Hence, there is no hint of added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for postmenopausal patients with node-positive, HR-positive, HER2-negative early breast cancer at high risk of recurrence. An added benefit is therefore not proven.

Research question 3 (men)

For male patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence, the added benefit is not proven.

Table 3 shows a summary of the probability and extent of added benefit of abemaciclib in combination with endocrine therapy.

Table 3: Abemaciclib in combination with endocrine therapy – probability and extent of added benefit

Research question	Subindication	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	▪ Tamoxifen (possibly in addition to suppression of the ovarian function)	▪ Hint of minor added benefit
2	Postmenopausal women	▪ anastrozole or ▪ letrozole or ▪ possibly tamoxifen if aromatase inhibitors are unsuitable or ▪ anastrozole or ▪ exemestane ▪ in sequence after tamoxifen	▪ Added benefit not proven
3	Men	▪ Tamoxifen	▪ Added benefit not proven
a. Presented is the respective ACT specified by the GBA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor			

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

2.2 Research question

The aim of the present report 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.

Depending on the sex and menopausal status of the patients, the G-BA distinguished between different treatment situations and specified an ACT for each of them. The present assessment refers to research questions 1 to 3 presented in Table 4.

Table 4: Research questions of the benefit assessment of abemaciclib

Research question	Subindication	ACT[a]
Adjuvant treatment of patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence		
1	Premenopausal women	▪ Tamoxifen (possibly in addition to suppression of the ovarian function)
2	Postmenopausal women	▪ An aromatase inhibitor (anastrozole or letrozole) alone, possibly tamoxifen if aromatase inhibitors are unsuitable, or ▪ anastrozole or exemestane in sequence after tamoxifen
3	Men	▪ Tamoxifen
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor		

The company followed the G-BA's 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 the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on abemaciclib (status: 28 February 2022)
- bibliographical literature search on abemaciclib (last search on 28 February 2022)
- search in trial registries/trial results databases for studies on abemaciclib (last search on 28 February 2022)
- search on the G-BA website for abemaciclib (last search on 1 March 2022)

To check the completeness of the study pool:

- search in trial registries for studies on abemaciclib (last search on 12 May 2022); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

2.3.1 Studies included

The study presented in the following table is included in the benefit assessment.

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

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)	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]	Yes [4,5]	Yes [6-9]

a. Study for which the company was sponsor.
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. Hereinafter, the study is referred to with this abbreviated form.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

Table 6 shows the evidence base resulting for the research questions of the benefit assessment on the basis of the relevant MONARCH-E study.

Table 6: Evidence base of the research questions of the benefit assessment of abemaciclib

Research question	Subindication	Data presented by the company	Section in the benefit assessment
Patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence			
1	Premenopausal women	Subpopulation of the MONARCH-E study	Assessment in Section 2.4
2	Postmenopausal women	Subpopulation of the MONARCH-E study	Assessment in Section 2.5
3	Men	Subpopulation of the MONARCH-E study	Assessment in Section 2.6

HER2: human epidermal growth factor receptor 2; HR: hormone receptor

The MONARCH-E study, which compares the combination of abemaciclib + endocrine therapy with endocrine therapy, is used for the benefit assessment of abemaciclib in combination with endocrine therapy. Due to the G-BA's specification of the ACT, subpopulations from the MONARCH-E study for research questions 1, 2 and 3 are considered relevant for the benefit assessment and included. This concurs with the company's approach.

2.4 Research question 1: premenopausal women

2.4.1 Study characteristics

Table 7 and Table 8 describe the study used for the benefit assessment.

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

Study	Study design	Population	Interventions (number of randomized 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	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[d]: ▪ premenopausal women (1) ▫ abemaciclib + endocrine therapy (n = 553) ▫ endocrine therapy (n = 535) ▪ postmenopausal women (2) ▫ abemaciclib + endocrine therapy (n = 1283) ▫ endocrine therapy (n = 1265) ▪ men (3) ▫ abemaciclib + endocrine therapy (n = 10) ▫ endocrine therapy (n = 9)	Screening: cohort 1: 1–3 months Treatment ▪ abemaciclib: 2 years or until disease progression, pregnancy, treatment discontinuation following the decision of physician, patient or sponsor, or end of study. ▪ endocrine therapy: ≥ 5 years Observation[e]: 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 7/2017–ongoing Data cut-offs: ▪ 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) ▪ 1 April 2021 (first interim analysis on overall survival)[f]	Primary: IDFS Secondary: overall survival, symptoms, health-related quality of life, AEs

Table 7: Characteristics of the study included – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (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 consideration of the relevance for this benefit assessment. Secondary outcomes include only 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. The analysis of the company is based on the safety population of cohort 1 minus those patients who received a therapy that does not correspond to the ACT for the respective research question.
e. Outcome-specific information is described in Table 9.
f. This data cut-off was requested by the regulatory authorities and is the data cut-off relevant to the present benefit assessment.

ACT: appropriate comparator therapy; AE: adverse event; 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 randomized (included) patients; pALN: positive axillary lymph nodes; RCT: randomized controlled trial

Table 8: Characteristics of the intervention – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy

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 adjustments/interruptions: ▪ 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]. In the event that treatment was discontinued, endocrine therapy per the investigator's clinical judgment could be continued. ▫ In the case of planned surgical interventions, administration could be postponed for up to 28 days. ▪ Endocrine therapy: ▫ Dose adjustments or interruption were possible for up to 28 days[a]. ▫ If treatment was discontinued in the intervention arm for reasons other than an IDFS event, therapy with abemaciclib was to be continued. ▫ Switching to another standard endocrine therapy was allowed at the investigator's discretion and in the absence of an IDFS event during the treatment period of the study.	
	Permitted pretreatment: ▪ adjuvant radiotherapy[b] ▪ adjuvant and/or neoadjuvant chemotherapy[b] ▫ up to 12 weeks of endocrine therapy prior to randomization if patients were receiving endocrine therapy as standard adjuvant therapy[c] before study start **Prohibited prior and concomitant treatment:** ▪ CDK4/6 inhibitors ▪ endocrine therapy for breast cancer prevention (tamoxifen or aromatase inhibitors) or raloxifene ▪ exogenous reproductive hormone therapy (e.g., birth control pills, hormone replacement therapy, or megestrol acetate) ▪ ≤ 30 days prior to randomization and during the study: other investigational products of any kind **Permitted concomitant treatment:** ▪ supportive therapy, especially bisphosphonates and denosumab	

a. A delay > 28 days is permitted upon agreement between the investigator and the CRP/CRS. In case of toxicities, depending on type (haematological, non-haematological, diarrhoea, ALT increased, AST increased, ILD/pneumonitis) and severity, dose adjustment according to study protocol should be considered.
b. Adjuvant radiotherapy/chemotherapy must have been completed prior to randomization, and patients must have recovered from the acute effects of radiotherapy/chemotherapy (CTCAE grade ≤ 1; except for adjuvant chemotherapy: residual 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 did not receive radiotherapy) is required between end of radiotherapy/chemotherapy and randomization.
c. Use of gonadotropin-releasing hormone analogues for ovarian suppression is not considered endocrine therapy for the purposes of this criterion. Adjuvant treatment with fulvestrant is 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: randomized controlled trial

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. The MONARCH-E study has 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 a tumour size of ≥ 5 cm (corresponding to stage IIA to IIIC at diagnosis). This definition of a high risk of recurrence is considered adequate for the benefit assessment [10].

In the patients included in cohort 2, a high risk of recurrence was assessed primarily 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 [11].

A total of 5120 patients were enrolled in cohort 1. Randomization 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 SPC [11]. In both study arms, patients received standard adjuvant endocrine therapy of physician's choice. The company stated that this does not correspond to the G-BA's ACT in all cases. For the 3 research questions, the company therefore presented analyses of relevant subpopulations in which the patients in both study arms received endocrine therapy in accordance with the respective ACT. However, the company did not provide any information on the endocrine therapies administered during the course of the study for the subpopulations of the individual research questions. The company's dossier provides data on the endocrine therapies administered only on the basis of the entire study population. These data show that all endocrine therapies comprised by the ACT were used in the study.

Primary outcome of the study is IDFS (hereinafter referred to as "recurrence"). Relevant secondary outcomes are overall survival, symptoms, health-related quality of life, and AEs.

Data cut-offs

The MONARCH-E study is an ongoing study. So far, 4 data cut-offs are available:

- first data cut-off (27 September 2019): planned interim analysis after IDFS events
- second data cut-off (16 March 2020): planned interim analysis after 293 IDFS events
- third data cut-off (8 July 2020): planned final IDFS analysis after 390 IDFS events
- fourth data cut-off (1 April 2021): post hoc interim analysis on overall survival requested by the regulatory authorities

The study is ongoing. The company used the analysis at the fourth data cut-off (1 April 2021) for the benefit assessment. According to the company, this is a post hoc interim analysis on

overall survival requested by the regulatory authorities. Further interim analyses on overall survival are planned 2 years and 3 years after the final IDFS analysis, and the final analysis on overall survival after 650 events or 10 years after randomization of the last patient, whichever occurs earlier.

Table 9 shows the planned duration of patient follow-up observation for the individual outcomes.

Table 9: Planned duration of follow-up – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy

Study **Outcome category** **Outcome**	**Planned follow-up observation**
MONARCH-E	
Mortality	
Overall survival	Until death, maximum 10 years or end of study
Morbidity	
Recurrence[a]	Up to 10 years or end of study
Symptoms (FACIT-Fatigue)	Up to 12 months after end of treatment[b]
Health status (EQ-5D-5L VAS)	Up to 12 months after end of treatment[b]
Health-related quality of life	
FACT-B, FACT-ES	Up to 12 months after end of treatment[b]
Side effects	Up to 30 days after end of treatment[b]

a. Presented based on the recurrence rate and disease-free survival, includes the events of local breast cancer recurrence, regional invasive recurrence, distant recurrence, contralateral invasive breast cancer, second primary carcinoma, and death without recurrence.
b. End of treatment of any study medication.

FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; RCT: randomized controlled trial; VAS: visual analogue scale

In the study, only the outcomes of overall survival and recurrence are recorded until the end of the study. The observation periods for the outcomes of symptoms, health status, health-related quality of life and side effects are systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days or 12 months). For these outcomes, data are therefore available only for a shortened observation period, depending on the course of the study. However, to be able to draw a reliable conclusion on the total study period or the time to patient death, it would be necessary to record all outcomes for the total period, as was done for survival.

Subpopulation relevant to the assessment of research question 1

Of the patients included in the MONARCH-E study, only the subpopulation of those premenopausal women who were treated with the G-BA's ACT is relevant to the assessment

of research question 1 (see Section 2.2). These were 1269 patients in total, 630 of whom were treated with abemaciclib in combination with endocrine therapy and 639 with endocrine therapy alone. However, this population includes patients who, in the course of the study, switched to an endocrine therapy that, according to the company, does not correspond to the ACT or is not covered by a corresponding approval. For the benefit assessment, the company only used the results of those patients who received endocrine therapy corresponding to the ACT for the entire duration of the study. These were 1088 patients, 553 of whom were treated with abemaciclib in combination with endocrine therapy and 535 with endocrine therapy alone. These are used for the benefit assessment.

Table 10 shows the characteristics of the patients in the studies included (research question 1).

Table 10: Characteristics of the study population – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study **Characteristic** **Category**	**Abemaciclib + endocrine therapy** **N[a] = 553**	**Endocrine therapy** **N[a] = 535**
MONARCH-E		
Sex [F/M], %	100/0	100/0
Age [years], mean (SD)	44 (6)	43 (6)
Median (min–max)	44 (23–57)	44 (24–59)
Family origin, n (%)		
Asian	199 (36.0)	180 (33.6)
White/Caucasian	323 (58.4)	324 (60.6)
Other[b]	31 (5.6)	31 (5.8)
Region, n (%)		
North America/Europe	252 (45.6)	233 (43.6)
Asia	168 (30.4)	166 (31.0)
Other	133 (24.1)	136 (25.4)
ECOG PS, n (%)		
0	496 (89.7)	480 (89.7)
1	57 (10.3)	55 (10.3)
≥ 2	0 (0)	0 (0)
Primary tumour size by radiology prior to any systemic treatment, n (%)	531	519
< 20 mm	137 (24.8)	125 (23.4)
≥ 20 to < 50 mm	268 (48.5)	271 (50.7)
≥ 50 mm	126 (22.8)	123 (23.0)
Missing	22 (4.0)	16 (3.0)

Table 10: Characteristics of the study population – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study **Characteristic** **Category**	**Abemaciclib + endocrine therapy** **N[a] = 553**	**Endocrine therapy** **N[a] = 535**
Primary tumour size by pathology following definitive surgery, n (%)	541	530
< 20 mm	141 (25.5)	140 (26.2)
≥ 20 to < 50 mm	255 (46.1)	249 (46.5)
≥ 50 mm	145 (26.2)	141 (26.4)
Missing	12 (2.2)	5 (0.9)
Number of positive lymph nodes, n (%)		
0	4 (0.7)	0 (0.0)
1–3	199 (36.0)	214 (40.0)
4–9	242 (43.8)	231 (43.2)
≥ 10	108 (19.5)	90 (16.8)
Histopathological grading at diagnosis, n (%)		
G1 – favourable	47 (8.5)	41 (7.7)
G2 – moderately favourable	244 (44.1)	234 (43.7)
G3 – unfavourable	233 (42.1)	226 (42.2)
Gx – cannot be assessed	29 (5.2)	33 (6.2)
Missing	0 (0)	1 (0.2)
Tumour stage at first diagnosis, n (%)		
Stage IA	0 (0)	0 (0)
Stage IIA	59 (10.7)	62 (11.6)
Stage IIB	53 (9.6)	69 (12.9)
Stage IIIA	236 (42.7)	214 (40.0)
Stage IIIB	18 (3.3)	15 (2.8)
Stage IIIC	186 (33.6)	174 (32.5)
Missing	1 (0.2)	1 (0.2)
Oestrogen receptor status, n (%)		
Positive	548 (99.1)	533 (99.6)
Negative	4 (0.7)	2 (0.4)
Unknown	0 (0)	0 (0)
Missing	1 (0.2)	0 (0)
Progesterone receptor status, n (%)		
Positive	477 (86.3)	471 (88.0)
Negative	49 (8.9)	44 (8.2)
Unknown	4 (0.7)	8 (1.5)
Missing	23 (4.2)	12 (2.2)

Table 10: Characteristics of the study population – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study Characteristic Category	Abemaciclib + endocrine therapy N[a] = 553	Endocrine therapy N[a] = 535
HER2 status at time of first diagnosis, n (%)		
Positive	0 (0)	0 (0)
Negative	553 (100)	535 (100)
Missing	0 (0)	0 (0)
Prior chemotherapy, n (%)		
Adjuvant chemotherapy	327 (59.1)	312 (58.3)
Neoadjuvant chemotherapy	217 (39.2)	219 (40.9)
No chemotherapy	9 (1.6)	4 (0.7)
Endocrine therapy at baseline, n (%)		
Aromatase inhibitor	0 (0)	0 (0)
Tamoxifen	553 (100)	535 (100)
Treatment discontinuation, n (%)	ND[c]	ND[c]
Study discontinuation, n (%)	ND[d]	ND[d]

a. Number of patients who received ACT-compliant endocrine therapy during the entire study period. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Other includes Native American/Native Alaskan, African American, Native Hawaiian or Pacific Islander, multiple and missing data.
c. Data on treatment discontinuations are only available for AEs.
d. Data on study discontinuations of the intervention or comparator arm are only available at study level. Of the randomized patients, 18.0% in the intervention arm and 17.5% in the comparator arm discontinued the study prematurely.

ACT: appropriate comparator therapy; AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; HER2: human epidermal growth factor receptor 2; M: male; n: number of patients in the category; N: number of patients who received ACT-compliant endocrine therapy during the entire study period; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The demographic and clinical characteristics of the patients in both treatment arms are comparable.

The median age of the subpopulation of premenopausal patients in the MONARCH-E study analysed by the company was 44 years at study entry. About 60% of the patients were of Caucasian family origin. 90% of the patients had an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0. About 3 quarters of the patients had tumour stage III (A to C) at first diagnosis. Almost 60% of the patients were pretreated with adjuvant chemotherapy and about 40% with neoadjuvant chemotherapy.

Median treatment duration

Table 11 shows the median treatment duration of the patients and the median observation period for individual outcomes in the MONARCH-E study.

Table 11: Information on the course of the study – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women)

Study **Duration of the study phase** **Outcome category**	**Abemaciclib + endocrine therapy** **N = 553**	**Endocrine therapy** **N = 535**
MONARCH-E		
Duration of treatment with abemaciclib [months]		
Median [Q1; Q3]	23.7 [22.3; 23.7]	-
Duration of treatment with endocrine therapy [months]		
Median [Q1; Q3]	23.7 [23.0; 23.8]	23.7 [22.8; 23.7]
Observation period [months]		
Overall survival[a]		
Median [Q1; Q3]	28.0 [24.5; 33.0]	27.6 [24.5; 33.2]
Morbidity (recurrence)		
Median [Q1; Q3]	27.9 [24.5; 32.6]	27.8 [24.6; 33.3]
Morbidity (EQ-5D VAS)		
Median [Q1; Q3]	24.8 [23.2; 30.6]	24.7 [21.0; 30.6]
Morbidity (FACIT-Fatigue)		
Median [Q1; Q3]	24.7 [23.1; 30.6]	24.7 [21.4; 30.6]
Health-related quality of life (FACT-B)		
Median [Q1; Q3]	24.8 [23.3; 30.6]	24.8 [21.4; 30.6]
Health-related quality of life (FACT-ES)		
Median [Q1; Q3]	24.8 [23.5; 30.6]	24.8 [21.4; 30.6]
Side effects		
Median [Q1; Q3]	24.7 [23.5; 24.8]	24.7 [23.1; 24.7]

a. The company did not provide any information on the methods used to determine observation periods in the subpopulation.

FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; max.: maximum; min: minimum; N: number of analysed patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; VAS: visual analogue scale

In the analysis of the MONARCH-E study presented by the company, both the median treatment duration and the median observation period were approximately the same for all outcomes in both treatment arms.

It can be inferred from the study documents that approximately 72% of the patients in the total study population in the intervention arm had completed 2 years of treatment with abemaciclib at the time of the data cut-off.

In its dossier, the company did not provide any information on subsequent therapies after completion of the 2-year study therapy phase for the subpopulation of premenopausal women.

An overview of the subsequent therapies of the entire MONARCH-E study population is presented in Appendix B.1.4 (Table 37) of the full dossier assessment.

Risk of bias across outcomes (study level)

Table 12 shows the risk of bias across outcomes (risk of bias at study level).

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
MONARCH-E	Yes	Yes	No	No	Yes	No[a]	High

a. An important proportion (14.3%) of the relevant subpopulation was not included in the analyses because, during the study, the patients concerned switched to an endocrine therapy that does not correspond to the ACT.

ACT: appropriate comparator therapy; RCT: randomized controlled trial

The risk of bias across outcomes of the subpopulation of premenopausal women in the MONARCH-E study is rated as high because an important proportion of patients switched to an endocrine therapy that does not correspond to the ACT or is not approved (N= 181; 14.3%) and these patients were not included in the analyses presented by the company. The company did not provide specific information on the endocrine therapies used in the respective subpopulations or on the reasons for switching these therapies.

Limitations resulting from the open-label study design are described under the outcome-specific risk of bias in Section 2.4.2.2.

Transferability of the study results to the German health care context

The company described that the results of the MONARCH-E study can be transferred to the German health care context. The characteristics of the patients included in the study did not differ notably from the population of early breast cancer patients in the current German health care context with regard to age, ECOG PS, tumour characteristics and prior therapies.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - recurrence
  - symptoms, recorded using the FACIT-Fatigue
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the FACT-B and the FACT-ES
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - neutropenia, Preferred Term (PT) (severe AEs [CTCAE grade ≥ 3])
  - diarrhoea, PT (severe AEs [CTCAE grade ≥ 3])
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4).

Table 13 shows for which outcomes data are available in the included study.

Table 13: Matrix of outcomes – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women)

Study	Outcomes											
	Overall survival	Recurrence[a]	Symptoms (FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-B)	Health-related quality of life (FACT-ES)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Neutropenia (PTs, severe AEs[b])	Diarrhoea (PT, severe AEs[b])	Further specific AEs[d]
MONARCH-E	Yes	Yes	No[e]	No[e]	No[e]	No[e]	Yes	Yes	Yes	Yes	Yes	Yes

a. Presented based on the recurrence rate and disease-free survival, includes the events of local breast cancer recurrence, regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, second primary carcinoma (no breast cancer), and death without recurrence.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Discontinuation of at least one of the drugs used.
d. The following events are considered (MedDRA coding): general disorders and administration site conditions (SOC, AEs), eye disorders (SOC, AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs), gastrointestinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), blood and lymphatic system disorders (SOC, severe AEs), and hepatic events (CMQ, severe AEs, includes the PTs ALT increased and AST increased).
e. No usable data available (for explanation see running text below, Section 2.4.2.1).

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CMQ: Custom MedDRA Query; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term, RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Recurrence

The outcome of recurrence is a composite outcome and includes the components of local breast cancer recurrence, regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, second primary carcinoma (no breast cancer), and death from any cause without previous recurrence. For the outcome of recurrence, the results of the operationalizations are presented as the proportion of patients with recurrence (hereinafter referred to as "recurrence rate") and as disease-free survival.

Certainty of conclusions of the data cut-off used for the benefit assessment for the outcome of recurrence

The patients considered in the present stage of the disease are a group of patients who were treated with a curative treatment approach. The occurrence of a recurrence in this situation means that the attempt at cure by the curative treatment approach was not successful. At the time of the data cut-off of 1 April 2021 used for the benefit assessment, the median observation period in the study was only approximately 28 months and therefore does not allow any reliable

conclusions to be drawn about the occurrence of recurrence after the end of the maximum 24-month treatment with abemaciclib. In the present therapeutic indication, recurrences can still occur many years after the initial therapy [12]. This is also described by the company in its dossier. Thus, the effect of abemaciclib on the outcome of recurrence cannot yet be assessed with certainty after this relatively short observation period. This uncertainty is also addressed in the European Public Assessment Report (EPAR). On the basis of the available data cut-off, only hints, e.g. of an added benefit, can therefore be derived for the outcome of recurrence. Furthermore, due to the short observation period, the recurrence rates provide more reliable information than the disease-free survival in the present data situation, and are therefore used to determine the extent, e.g. of an added benefit.

Usability of the analyses presented by the company on patient-reported outcomes on symptoms, health status and health-related quality of life

The company presented analyses using a mixed-effects model with repeated measures (MMRM) on course of disease and change from baseline for the outcomes on symptoms (FACIT-Fatigue), health status (EQ-5D VAS) and health-related quality of life (FACT-B, FACT-ES). In Module 4 of its dossier, the company did not provide any information on the total number of patients included in the MMRM analyses. Three other presentations provided different numbers of patients included in these presentations for the individual documentation times: Data differ between the descriptive tables on response rates, the graphical curves on the course and the tabulated changes from baseline. If the latter are used as the basis for an estimation, there are relevant proportions of patients who are not included in the analysis, e.g. a proportion of about 20% for the FACIT-Fatigue.

There are 2 additional aspects that hinder a reliable interpretation of the effect estimations of the MMRM model: On the one hand, the company assigned values that were recorded at different time points after randomization to a constructed time point. This was done for 3 constructed time points, which the company called 30-day, 6-month and 12-month follow-up. The actual observation time point for each patient resulted from the individual time point of the end of treatment plus the respective follow-up time (of 30 days, 6 months and 12 months) and not by the time interval from baseline, so that there are no uniform time points of analysis for all patients from baseline. These constructed time points, which were determined relative to the end of treatment, may differ both within a treatment arm as and between the treatment arms; the required equality of the time points of analysis between the arms is thus no longer given.

In this context, it is not possible to assess whether an interpretation would be possible despite the constructed time points of analysis in the present data situation with comparable median treatment and observation durations. This would require information on how many patients were affected by the problem of the constructed time points and for what reasons. The dossier does not contain any information on the reasons and time points of treatment discontinuations. In this context, treatment discontinuations that lead to termination of the regular recording of outcomes of the patient and initiation of the follow-up phase are particularly relevant.

It also remains unclear whether the effect presented by the company refers to the entire period or only represents the contrast at a specific point in time.

In addition, the patient-reported outcomes are subjectively influenced outcomes whose results have a high risk of bias due to the lack of blinding in the MONARCH-E study.

Under consideration of the aspects mentioned above, the analyses presented by the company on the patient-reported outcomes on symptoms, health status and health-related quality of life cannot be used for the benefit assessment.

The company did not provide any responder analyses for the patient-reported outcomes.

2.4.2.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes in the present analysis of the MONARCH-E study in research question 1 (premenopausal women).

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women)

Study		Outcomes											
	Study level	Overall survival	Recurrence[a]	Symptoms (FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-B)	Health-related quality of life (FACT-ES)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Neutropenia (PT, severe AEs[b])	Diarrhoea (PT, severe AEs[b])	Further specific AEs[d]
MONARCH-E	H[e]	H[e]	H[e]	-[f]	-[f]	-[f]	-[f]	H[e]	H[e]	H[e, g]	H[e]	H[e]	H[e, g]

a. Presented based on the recurrence rate and disease-free survival, includes the events of local breast cancer recurrence, regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, second primary carcinoma (no breast cancer), and death without recurrence.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Discontinuation of at least one of the drugs used.
d. The following events are considered (MedDRA coding): general disorders and administration site conditions (SOC, AEs), eye disorders (SOC, AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs), gastrointestinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), blood and lymphatic system disorders (SOC, severe AEs), and hepatic events (CMQ, severe AEs, includes the PTs ALT increased and AST increased).
e. High risk of bias across outcomes: an important proportion (14.3%) of the subpopulation was not included in the analyses because, during the study, the patients concerned switched to an endocrine therapy that does not correspond to the ACT.
f. No usable data available (see Section 2.4.2.1).
g. Subjectively influenced outcome in the absence of blinding (except specific AEs with CTCAE grade ≥ 3).

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CMQ: Custom MedDRA Query; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; H: high; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term, RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Due to the high risk of bias across outcomes, there is a high risk of bias for the results on all outcomes (see Section 2.4.1).

For non-severe/non-serious specific AE outcomes and discontinuation due to AEs, another reason for a high risk of bias is the open-label study design and the subjective recording of outcomes.

2.4.2.3 Results

Table 15 summarizes the results of the comparison of abemaciclib in combination with endocrine therapy against endocrine therapy in premenopausal patients with node-positive, HR-positive, HER2-negative early breast cancer at high risk of recurrence (research question 1).

Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves on the event time analyses of the outcomes in the MONARCH-E study are presented in Appendix B.1 of the full dossier assessment. Results on common AEs can be found in Appendix B.1.3 of the full dossier assessment.

Table 15: Results (mortality, morbidity and side effects) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study **Outcome category** **Outcome**	**Abemaciclib + endocrine therapy**		**Endocrine therapy**		**Abemaciclib + endocrine therapy vs. endocrine therapy**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
MONARCH-E[b]					
Mortality					
Overall survival	553	17 (3.1) Median time to event: NA [NC; NC]	535	11 (2.1) Median time to event: NA [NC; NC]	HR: 1.46 [0.69; 3.13]; 0.322[c, d]
Morbidity					
Recurrence					
Recurrence rate[e]	553	45 (8.1)	535	81 (15.1)	0.54 [0.38; 0.76]; < 0.001
Local breast cancer recurrence	553	4 (0.7)	535	10 (1.9)	–
Regional invasive breast cancer recurrence	553	2 (0.4)	535	3 (0.6)	–
Distant recurrence	553	36 (6.5)	535	62 (11.6)	–
Contralateral invasive breast cancer	553	1 (0.2)	535	4 (0.7)	–
Second primary carcinoma (no breast cancer)	553	2 (0.4)	535	3 (0.6)	–
Death without recurrence	553	0 (0)	535	0 (0)	–
Disease-free survival[f]	553	45 (8.1) Median time to event: NA [NC; NC]	535	81 (15.1) Median time to event: NA [NC; NC]	HR: 0.52 [0.36; 0.74]; < 0.001[c, d]
Symptoms (FACIT-Fatigue)				No usable data[g]	
Health status (EQ-5D VAS)				No usable data[g]	

Table 15: Results (mortality, morbidity and side effects) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study Outcome category Outcome	Abemaciclib + endocrine therapy		Endocrine therapy		Abemaciclib + endocrine therapy vs. endocrine therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Health-related quality of life					
FACT-B, FACT-ES	No usable data[g]				
Side effects					
AEs (supplementary information)	553	543 (98.2)	535	465 (86.9)	–
SAEs	553	63 (11.4)	535	39 (7.3)	1.56 [1.07; 2.29]; 0.021
Severe AEs[h]	553	244 (44.1)	535	73 (13.6)	3.23 [2.56; 4.08]; < 0.001
Discontinuation due to AEs[i]	553	69 (12.5)	535	6 (1.1)	11.13 [4.87; 25.41]; < 0.001
Neutropenia (severe AEs[h])	553	42 (7.6)	535	6 (1.1)	6.77 [2.90; 15.80]; < 0.001
General disorders and administration site conditions (SOC, AEs)	553	310 (56.1)	535	165 (30.8)	1.82 [1.57; 2.11]; < 0.001
Eye disorders (SOC, AEs)	553	78 (14.1)	535	32 (6.0)	2.36 [1.59; 3.50]; < 0.001
Respiratory, thoracic and mediastinal disorders (SOC, AEs)	553	157 (28.4)	535	74 (13.8)	2.05 [1.60; 2.63]; < 0.001
Gastrointestinal disorders (SOC, AEs)	553	496 (89.7)	535	177 (33.1)	2.71 [2.40; 3.07]; < 0.001
Diarrhoea (PT, severe AEs[h])	553	30 (5.4)	535	2 (0.4)	14.51 [3.49; 60.42]; < 0.001
Skin and subcutaneous tissue disorders (SOC, AEs)	553	220 (39.8)	535	107 (20.0)	1.99 [1.63; 2.42]; < 0.001
Blood and lymphatic system disorders (SOC, severe AEs)	553	62 (11.2)	535	8 (1.5)	7.50 [3.63; 15.51]; < 0.001
Hepatic events (CMQ, severe AEs)[j]	553	14 (2.5)	535	1 (0.2)	13.54 [1.79; 102.64]; < 0.001

a. Institute's calculation, unconditional exact test (CSZ method according to [13]).
b. Data cut-off: 1 April 2021.
c. Effect and CI: Cox proportional hazards model; p-value: log-rank test.
d. p-value: z-test.
e. The individual components are presented in the lines below.
f. For individual components, see recurrence.
g. No usable data; see Section 2.4.2.1 for reasons.
h. Operationalized as CTCAE grade ≥ 3.
i. Discontinuation of at least one of the drugs.
j. Includes the PTs ALT increased and AST increased.

Table 15: Results (mortality, morbidity and side effects) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study Outcome category Outcome	Abemaciclib + endocrine therapy		Endocrine therapy		Abemaciclib + endocrine therapy vs. endocrine therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CI: confidence interval; CMQ: Custom MedDRA Query; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; HR: hazard ratio; IDFS: invasive disease-free survival; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale					

Due to the high risk of bias across outcomes, no more than hints, e.g. of an added benefit, can be initially determined for all outcomes. For each outcome, it is checked whether the certainty of conclusions can still be increased on the basis of the available results, so that at most indications, e.g. of an added benefit, can be derived (see following description of results).

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Morbidity

Recurrence

For the outcome of recurrence, there was a statistically significant effect in favour of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for both recurrence rate and disease-free survival. When assessing the certainty of results, the short median observation period of approximately 28 months at the time of the present data cut-off must be taken into account (see Section 2.4.2.1). This results in a hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

Symptoms, recorded using the FACIT-Fatigue

There are no usable data for the outcome of symptoms recorded using the FACIT-Fatigue. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

There are no usable data for the outcome of health status, recorded using the EQ-5D VAS. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life, recorded using the FACT-B and the FACT-ES

No usable data are available for the outcome of health-related quality of life, recorded using the FACT-B and the FACT-ES. In each case, this results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Side effects

Discontinuation due to AEs

A statistically significant difference between treatment groups to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcome of discontinuation due to AEs. This results in a hint of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

SAEs and severe AEs (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcomes of SAEs and severe AEs (CTCAE grade ≥ 3). Due to consistent effects from additional analyses, which also included patients who switched to an endocrine therapy that does not correspond to the ACT or is not approved during the course of the study (intention to treat [ITT] analysis), there is an indication of a greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for each of these outcomes despite the high risk of bias.

Specific AEs

Neutropenia (severe AEs), diarrhoea (severe AEs), blood and lymphatic system disorders (severe AEs) and hepatic events (severe AEs)

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the specific AEs of neutropenia (severe AEs), diarrhoea (severe AEs), blood and lymphatic system disorders (severe AEs) and hepatic events (severe AEs). Due to consistent effects from additional analyses, which also included patients who switched to an endocrine therapy that does not correspond to the ACT or is not approved during the course of the study (ITT analysis), there is an indication of a greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for each of these outcomes despite the high risk of bias.

General disorders and administration site conditions (AEs), eye disorders (AEs), respiratory, thoracic and mediastinal disorders (AEs), gastrointestinal disorders (AEs) and skin and subcutaneous tissue disorders (AEs)

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the specific AEs of general disorders and administration site conditions (AEs), eye disorders (AEs), respiratory, thoracic and mediastinal disorders (AEs), gastrointestinal disorders (AEs) and skin and subcutaneous tissue disorders (AEs). This results in a hint of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for each of these outcomes.

2.4.2.4 Subgroups and other effect modifiers

The following subgroup characteristic is considered in the benefit assessment:

- severity of the disease (tumour stage IIA versus IIB versus IIIA versus IIIB versus IIIC)

There are no subgroup analyses for the characteristic of age.

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

There is no relevant effect modification with a statistically significant and relevant effect for any of the available subgroup analyses of the considered effect modifier on patient-relevant outcomes.

2.4.3 Probability and extent of added benefit

Probability and extent of the added benefit for research question 1 (premenopausal women) at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.4.2 (see Table 16).

Determination of the outcome category for the outcomes on side effects

It cannot be inferred from the dossier whether the following side effect outcomes are serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Side effects

No information is available on the severity classification of the specific AE outcomes of general disorders and administration site conditions, eye disorders, respiratory, thoracic and mediastinal disorders, gastrointestinal disorders, and skin and subcutaneous tissue disorders, as well as of the outcome of discontinuation due to AEs. Therefore, these outcomes are assigned to the outcome category of non-serious/non-severe side effects.

Table 16: Extent of added benefit at outcome level: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Outcome category **Outcome**	**Abemaciclib + endocrine therapy vs. endocrine therapy** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	Median time to event (months): NA vs. NA HR: 1.46 [0.69; 3.13] p = 0.322	Lesser benefit/added benefit not proven
Morbidity		
Recurrence		
Recurrence rate	8.1% vs. 15.1% RR: 0.54 [0.38; 0.76] p < 0.001 Probability: “hint”	Outcome category: serious/severe symptoms/late complications $0.75 \leq CI_u < 0.90$ Added benefit, extent: “considerable”[c]
Disease-free survival	8.1% vs. 15.1% HR: 0.52 [0.36; 0.74] p < 0.001 Probability: “hint”	
Symptoms		
FACIT-Fatigue	No usable data	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable data	Lesser benefit/added benefit not proven
Health-related quality of life		
FACT-B	No usable data	Lesser benefit/added benefit not proven
FACT-ES	No usable data	Lesser benefit/added benefit not proven

Table 16: Extent of added benefit at outcome level: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Outcome category **Outcome**	**Abemaciclib + endocrine therapy vs. endocrine therapy** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	11.4% vs. 7.3% RR: 1.56 [1.07; 2.29] RR: 0.64 [0.44; 0.94][d] p = 0.021 Probability: "indication"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ Greater harm, extent: "minor"
Severe AEs	44.1% vs. 13.6% RR: 3.23 [2.56; 4.08] RR: 0.31 [0.25; 0.39][d] p < 0.001 Probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"
Discontinuation due to AEs[e]	12.5% vs. 1.1% RR: 11.13 [4.87; 25.41] RR: 0.10 [0.04; 0.21][d] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"
Neutropenia (severe AEs)	7.6% vs. 1.1% RR: 6.77 [2.90; 15.80] RR: 0.15 [0.06; 0.34][d] p < 0.001 Probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"
General disorders and administration site conditions (AEs)	56.1% vs. 30.8% RR: 1.82 [1.57; 2.11] RR: 0.55 [0.47; 0.64][d] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"
Eye disorders (AEs)	14.1% vs. 6.0% RR: 2.36 [1.59; 3.50] RR: 0.42 [0.29; 0.63][d] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"
Respiratory, thoracic and mediastinal disorders (AEs)	28.4% vs. 13.8% RR: 2.05 [1.60; 2.63] RR: 0.49 [0.38; 0.63][d] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"

Table 16: Extent of added benefit at outcome level: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Outcome category **Outcome**	**Abemaciclib + endocrine therapy vs. endocrine therapy** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Gastrointestinal disorders (AEs)	89.7% vs. 33.1% RR: 2.71 [2.40; 3.07] RR: 0.40 [0.33; 0.42][d] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"
Diarrhoea (severe AEs)	5.4% vs. 0.4% RR: 14.51 [3.49; 60.42] RR: 0.07 [0.02; 0.29][d] p < 0.001 Probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"
Skin and subcutaneous tissue disorders (AEs)	39.8% vs. 20.0% RR: 1.99 [1.63; 2.42] RR: 0.50 [0.41; 0.61][d] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"
Blood and lymphatic system disorders (severe AEs)	11.2% vs. 1.5% RR: 7.50 [3.63; 15.51] RR: 0.13 [0.07; 0.28][d] p < 0.001 Probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"
Hepatic events (severe AEs)	2.5% vs. 0.2% RR: 13.54 [1.79; 102.64]; RR: 0.07 [0.01; 0.56][d] p < 0.001 Probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk < 5% Greater harm, extent: "considerable"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. The extent is derived from the result of the recurrence rate.
d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
e. Discontinuation of at least one of both drugs.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; NA: not achieved; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

2.4.3.2 Overall conclusion on added benefit

Table 17 summarizes the results included in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of abemaciclib + endocrine therapy in comparison with endocrine therapy (research question 1: premenopausal women)

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ Recurrence: hint of an added benefit – extent: "considerable"	
	Serious/severe side effects ▪ SAEs: indication of greater harm – extent: "minor" ▪ Severe AEs: indication of greater harm – extent: "major" ▫ Neutropenia, diarrhoea, blood and lymphatic system disorders (in each case severe AEs): indication of greater harm – extent: "major" ▫ Hepatic events (severe AEs): indication of greater harm – extent "considerable"
	Non-serious/non-severe side effects ▪ Discontinuation due to AEs: hint of greater harm – extent: "considerable" ▪ General disorders and administration site conditions, eye disorders, respiratory, thoracic and mediastinal disorders, gastrointestinal disorders, skin and subcutaneous tissue disorders (in each case AEs): hint of greater harm – extent: "considerable"
The data on symptoms and health-related quality of life are not usable.	
AE: adverse event	

Overall, there are both positive and negative effects of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy. On the side of positive effects, there is a hint of an added benefit with considerable extent for the outcome of recurrence. The negative effects are related exclusively to outcomes of the category of side effects. There are indications of greater harm of abemaciclib, partly with major extent, in particular for the overall rate of severe AEs and SAEs as well as for specific severe AEs. In addition, there are other disadvantages such as greater harm of considerable extent regarding specific AEs and discontinuation due to AEs.

No conclusions can be drawn about longer-term effects of therapy with abemaciclib in the present therapeutic indication, as the median observation period in the MONARCH-E study was only 28 months at the time of the data cut-off used. Furthermore, no conclusions can be drawn on the patient-reported outcomes on symptoms and health-related quality of life, as no usable data are available.

Overall, the negative effects do not completely call into question the positive effect, however. There is a hint of minor added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy alone for premenopausal patients with node-positive, HR-positive, HER2-negative early breast cancer at high risk of recurrence.

The assessment described above deviates from that of the company, which derived an indication of major added benefit.

2.5 Research question 2: postmenopausal women

2.5.1 Study characteristics

The information on the study design, interventions used, data cut-offs and planned duration of follow-up of the outcomes is described in detail in Section 2.4.1.

Subpopulation relevant to the assessment of research question 2

Of the patients included in the MONARCH-E study, only the subpopulation of postmenopausal women who were treated with the G-BA's ACT is relevant to the assessment of research question 2 (see Section 2.2). These were 2748 patients in total, 1364 of whom were treated with abemaciclib in combination with endocrine therapy and 1384 with endocrine therapy alone. However, this population includes patients who, in the course of the study, switched to an endocrine therapy that, according to the company, does not correspond to the ACT or is not covered by a corresponding approval. For the benefit assessment, the company only used the results of those patients who received endocrine therapy corresponding to the ACT for the entire duration of the study. These were 2548 patients in total, 1284 of whom were treated with abemaciclib in combination with endocrine therapy and 1264 with endocrine therapy alone. These are used for the benefit assessment.

Patient characteristics

Table 18 shows the characteristics of the patients in the study included.

Table 18: Characteristics of the study population – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study Characteristic Category	Abemaciclib + endocrine therapy N[a] = 1284	Endocrine therapy N[a] = 1264
MONARCH-E		
Sex [F/M], %	100/0	100/0
Age [years], mean (SD)	59 (9)	59 (9)
Median (min–max)	59 (32–89)	59 (27–86)
Family origin, n (%)		
Asian	250 (19.5)	242 (19.1)
White/Caucasian	958 (74.6)	944 (74.7)
Other[b]	76 (5.9)	78 (6.2)
Region, n (%)		
North America/Europe	679 (52.9)	649 (51.3)
Asia	203 (15.8)	201 (15.9)
Other	402 (31.3)	414 (32.8)
ECOG PS, n (%)		
0	1070 (83.3)	1020 (80.7)
1	214 (16.7)	244 (19.3)
≥ 2	0 (0)	0 (0)
Primary tumour size by radiology prior to any systemic treatment, n (%)	1230	1204
< 20 mm	361 (28.1)	345 (27.3)
≥ 20 to < 50 mm	658 (51.2)	685 (54.2)
≥ 50 mm	211 (16.4)	174 (13.8)
Missing	54 (4.2)	60 (4.7)
Primary tumour size by pathology following definitive surgery, n (%)	1267	1252
< 20 mm	332 (25.9)	334 (26.4)
≥ 20 to < 50 mm	646 (50.3)	653 (51.7)
≥ 50 mm	289 (22.5)	265 (21.0)
Missing	17 (1.3)	12 (0.9)
Number of positive lymph nodes, n (%)		
0	0 (0)	5 (0.4)
1–3	427 (33.3)	413 (32.7)
4–9	548 (42.7)	543 (43.0)
≥ 10	309 (24.1)	303 (24.0)

Table 18: Characteristics of the study population – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study Characteristic Category	Abemaciclib + endocrine therapy N[a] = 1284	Endocrine therapy N[a] = 1264
Histopathological grading at diagnosis, n (%)		
G1 – favourable	91 (7.1)	93 (7.4)
G2 – moderately favourable	613 (47.7)	602 (47.6)
G3 – unfavourable	528 (41.1)	505 (40.0)
Gx – cannot be assessed	50 (3.9)	60 (4.7)
Missing	2 (0.2)	4 (0.3)
Tumour stage at first diagnosis, n (%)		
Stage IA	0 (0)	0 (0)
Stage IIA	113 (8.8)	114 (9.0)
Stage IIB	151 (11.8)	136 (10.8)
Stage IIIA	495 (38.6)	488 (38.6)
Stage IIIB	54 (4.2)	45 (3.6)
Stage IIIC	469 (36.5)	479 (37.9)
Missing	2 (0.2)	2 (0.2)
Oestrogen receptor status, n (%)		
Positive	1278 (99.5)	1251 (99.0)
Negative	5 (0.4)	13 (1.0)
Unknown	0 (0)	0 (0)
Missing	1 (0.1)	0 (0)
Progesterone receptor status, n (%)		
Positive	1089 (84.8)	1067 (84.4)
Negative	157 (12.2)	168 (13.3)
Unknown	10 (0.8)	7 (0.6)
Missing	28 (2.2)	22 (1.7)
HER2 status at time of first diagnosis, n (%)		
Positive	0 (0)	1 (0.1)
Negative	1284 (100)	1263 (99.9)
Missing	0 (0)	0 (0)
Prior chemotherapy, n (%)		
Adjuvant chemotherapy	785 (61.1)	768 (60.8)
Neoadjuvant chemotherapy	430 (33.5)	415 (32.8)
No chemotherapy	69 (5.4)	81 (6.4)
Endocrine therapy at baseline, n (%)		
Aromatase inhibitor	1170 (91.1)	1132 (89.6)
Tamoxifen	114 (8.9)	132 (10.4)
Treatment discontinuation, n (%)	ND[c]	ND[c]
Study discontinuation, n (%)	ND[d]	ND[d]

Table 18: Characteristics of the study population – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study Characteristic Category	Abemaciclib + endocrine therapy N[a] = 1284	Endocrine therapy N[a] = 1264

a. Number of patients who received ACT-compliant endocrine therapy during the entire study period. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Other includes Native American/Native Alaskan, African American, Native Hawaiian or Pacific Islander, multiple and missing data.
c. Data on treatment discontinuations are only available in relation to AEs.
d. Data on study discontinuations of the intervention or comparator arm are only available at study level. Of the randomized patients, 18.0% in the intervention arm and 17.5% in the comparator arm discontinued the study prematurely.

ACT: appropriate comparator therapy; AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; HER2: human epidermal growth factor receptor 2; M: male; n: number of patients in the category; N: number of patients who received ACT-compliant endocrine therapy during the entire study period; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The demographic and clinical characteristics of the patients in both treatment arms are comparable.

The median age of the subpopulation of premenopausal patients in the MONARCH-E study analysed by the company was 59 years at study entry. The majority (about 75%) of the patients were of Caucasian family origin. Over 80% of the patients had an ECOG PS of 0. About 80% of the patients had tumour stage III (A to C) at first diagnosis. The proportion of patients pretreated with chemotherapy was over 90%. Approximately 60% of the patients received adjuvant chemotherapy.

Median treatment duration

Table 19 shows the median treatment duration of the patients and the median observation period for individual outcomes in the MONARCH-E study.

Table 19: Information on the course of the study – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women)

Study **Duration of the study phase** **Outcome category**	**Abemaciclib + endocrine therapy** **N = 1283**	**Endocrine therapy** **N = 1265**
MONARCH-E		
Duration of treatment with abemaciclib [months]		
Median [Q1; Q3]	23.6 [11.6; 23.7]	-
Duration of treatment with endocrine therapy [months]		
Median [Q1; Q3]	23.7 [22.8; 23.8]	23.7 [23.2; 23.8]
Observation period [months]		
Overall survival[a]		
Median [Q1; Q3]	28.1 [24.6; 33.0]	28.5 [24.7; 33.2]
Morbidity (recurrence)		
Median [Q1; Q3]	28.1 [24.6; 32.9]	28.4 [24.7; 33.2]
Morbidity (EQ-5D VAS)		
Median [Q1; Q3]	24.7 [18.7; 30.6]	24.8 [23.0; 30.6]
Morbidity (FACIT-Fatigue)		
Median [Q1; Q3]	24.7 [18.3; 30.5]	24.8 [21.7; 30.6]
Health-related quality of life (FACT-B)		
Median [Q1; Q3]	24.8 [18.7; 30.6]	24.8 [23.2; 30.6]
Health-related quality of life (FACT-ES)		
Median [Q1; Q3]	24.8 [18.7; 30.6]	24.8 [23.2; 30.6]
Side effects		
Median [Q1; Q3]	24.7 [23.2; 24.8]	24.7 [23.6; 24.8]

a. The company did not provide any information on the methods used to determine observation periods in the subpopulation.

FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; max.: maximum; min: minimum; N: number of analysed patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; VAS: visual analogue scale

In the analysis of the MONARCH-E study presented by the company, both the median treatment duration and the median observation period were approximately the same for all outcomes in both treatment arms.

It can be inferred from the study documents that approximately 72% of the patients in the total study population in the intervention arm had completed 2 years of treatment with abemaciclib at the time of the data cut-off.

In its dossier, the company did not provide any information on subsequent therapies after completion of the 2-year study therapy phase for the subpopulation of postmenopausal women. An overview of the subsequent therapies after completion of the 2-year study therapy phase of

the entire MONARCH-E study population is presented in Appendix B.1.4 (Table 37) of the full dossier assessment.

Risk of bias across outcomes (study level)

Table 20 shows the risk of bias across outcomes (risk of bias at study level).

Table 20: Risk of bias across outcomes (study level) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
MONARCH-E	Yes	Yes	No	No	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for research question 2 (postmenopausal women) is rated as low. The assessment of the risk of bias across outcomes that deviates from research question 1 is due to the fact that, in the course of the study, a notably smaller proportion (7.3%) of the postmenopausal women switched to an endocrine therapy that does not correspond to the ACT or is not approved, and that these were not included in the company's analyses.

Transferability of the study results to the German health care context

The company's assessment of the transferability of the MONARCH-E study to the German health care context is described in Section 2.4.1 (see text section on transferability).

2.5.2 Results on added benefit

2.5.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment:

- Mortality
  - overall survival
- Morbidity
  - recurrence
  - symptoms, recorded using the FACIT-Fatigue
  - health status, recorded using the EQ-5D VAS

- Health-related quality of life
  - recorded using the FACT-B and the FACT-ES
- Side effects
  - SAEs
  - Severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - neutropenia, PT (severe AEs [CTCAE grade ≥ 3])
  - diarrhoea, PT (severe AEs [CTCAE grade ≥ 3])
  - further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4).

Table 21 shows for which outcomes data are available in the included study.

Table 21: Matrix of outcomes – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women)

Study	Outcomes											
	Overall survival	Recurrence[a]	Symptoms (FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-B)	Health-related quality of life (FACT-ES)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Neutropenia (PTs, severe AEs[b])	Diarrhoea (PT, severe AEs[b])	Further specific AEs[d]
MONARCH-E	Yes	Yes	No[e]	No[e]	No[e]	No[e]	Yes	Yes	Yes	Yes	Yes	Yes

a. Presented based on the recurrence rate and disease-free survival, includes the events of local breast cancer recurrence, regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, second primary carcinoma (no breast cancer), and death without recurrence.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Discontinuation of at least one of the drugs used.
d. The following events are considered (MedDRA coding): alopecia (PT, AEs), arthralgia (PT, AEs), dizziness (PT; AEs), eye disorders (SOC, AEs), gastrointestinal disorders (SOC, AEs), fatigue (PT, severe AEs), hypokalaemia (PT, severe AEs), blood and lymphatic system disorders (SOC, severe AEs), hepatic events (CMQ, severe AEs, includes the PTs ALT increased and AST increased). venous thromboembolism (CMQ, severe AEs, includes the PTs pulmonary embolism and deep vein thrombosis) and ILD/pneumonitis (SMQ, SAE).
e. No usable data available (for explanation see running text below and Section 2.4.2.1).

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CMQ: Custom MedDRA Query; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; ILD: interstitial lung disease; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term, RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

For details on these outcomes, see Section 2.4.2.1.

2.5.2.2 Risk of bias

Table 22 describes the risk of bias for the results of the relevant outcomes in the present analysis of the MONARCH-E study in research question 2 (postmenopausal women).

Table 22: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women)

Study	Study level	Outcomes												
		Overall survival	Recurrence[a]	Symptoms (FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-B)	Health-related quality of life (FACT-ES)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Neutropenia (PTs, severe AEs[b])	Diarrhoea (PT, severe AEs[b])	Further specific AEs[d]
MONARCH-E	L	L	L	-[e]	-[e]	-[e]	-[e]	L	L	H[f]	L	L	H[f]

a. Presented based on the recurrence rate and disease-free survival, includes the events of local breast cancer recurrence, regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, second primary carcinoma (no breast cancer), and death without recurrence.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Discontinuation of at least one of the drugs used.
d. The following events are considered (MedDRA coding): alopecia (PT, AEs), arthralgia (PT, AEs), dizziness (PT; AEs), eye disorders (SOC, AEs), gastrointestinal disorders (SOC, AEs), fatigue (PT, severe AEs), hypokalaemia (PT, severe AEs), blood and lymphatic system disorders (SOC, severe AEs), hepatic events (CMQ, severe AEs, includes the PTs ALT increased and AST increased). venous thromboembolism (CMQ, severe AEs, includes the PTs pulmonary embolism and deep vein thrombosis) and ILD/pneumonitis (SMQ, SAE).
e. No usable data available (for explanation see Sections 2.5.2.1 and 2.4.2.1).
f. Subjectively influenced outcome in the absence of blinding (except specific SAEs and AEs with CTCAE grade ≥ 3).

AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CMQ: Custom MedDRA Query; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; H: high; ILD: interstitial lung disease; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term, RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

The outcome-specific risk of bias of the results of most outcomes is low. The risk of bias of the results for the outcomes of discontinuation due to AEs and specific AEs (excluding specific SAEs and severe AEs) is rated as high due to the open-label study design.

2.5.2.3 Results

Table 23 summarizes the results of the comparison of abemaciclib in combination with endocrine therapy against endocrine therapy in postmenopausal patients with node-positive, HR-positive, HER2-negative early breast cancer at high risk of recurrence (research question 2). Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves on the event time analyses of the outcomes in the MONARCH-E study are presented in Appendix C.1 of the full dossier assessment. Results on common AEs can be found in Appendix C.1.3 of the full dossier assessment.

Table 23: Results (mortality, morbidity and side effects) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study **Outcome category** **Outcome**	**Abemaciclib + endocrine therapy**		**Endocrine therapy**		**Abemaciclib + endocrine therapy vs. endocrine therapy**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value[a]**
MONARCH-E[b]					
Mortality					
Overall survival	1284	54 (4.2) median time to event: NA [NC; NC]	1264	58 (4.6) median time to event: NA [NC; NC]	HR: 0.94 [0.65; 1.36]; 0.738[c, d]
Morbidity					
Recurrence					
Recurrence rate[e]	1284	122 (9.5)	1264	165 (13.1)	0.73 [0.58; 0.91]; 0.005
Local breast cancer recurrence	1284	13 (1.0)	1264	12 (0.9)	–
Regional invasive breast cancer recurrence	1284	8 (0.6)	1264	12 (0.9)	–
Distant recurrence	1284	74 (5.8)	1264	117 (9.3)	–
Contralateral invasive breast cancer	1284	3 (0.2)	1264	7 (0.6)	–
Second primary carcinoma (no breast cancer)	1284	13 (1.0)	1264	12 (0.9)	–
Death without recurrence	1284	14 (1.1)	1264	9 (0.7)	–
Disease-free survival[f]	1284	122 (9.5) median time to event: NA [NC; NC]	1264	165 (13.1) median time to event: NA [NC; NC]	HR: 0.74 [0.58; 0.93]; 0.010[c, d]
Symptoms (FACIT-Fatigue)	No usable data[g]				
Health status (EQ-5D VAS)	No usable data[g]				
Health-related quality of life					
FACT-B, FACT-ES	No usable data[g]				

Table 23: Results (mortality, morbidity and side effects) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study Outcome category Outcome	Abemaciclib + endocrine therapy		Endocrine therapy		Abemaciclib + endocrine therapy vs. endocrine therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
Side effects					
AEs (supplementary information)	1283	1260 (98.2)	1265	1119 (88.5)	–
SAEs	1283	200 (15.6)	1265	123 (9.7)	1.60 [1.30; 1.98]; < 0.001
Severe AEs[h]	1283	645 (50.3)	1265	213 (16.8)	2.99 [2.61; 3.41]; < 0.001
Discontinuation due to AEs[i]	1283	282 (22.0)	1265	14 (1.1)	19.86 [11.68; 33.78]; < 0.001
Neutropenia (PTs, severe AEs[h])	1283	257 (20.0)	1265	7 (0.6)	36.20 [17.15; 76.39]; < 0.001
Alopecia (PT, AEs)	1283	150 (11.7)	1265	34 (2.7)	4.35 [3.02; 6.26]; < 0.001
Arthralgia (PT, AEs)	1283	342 (26.7)	1265	488 (38.6)	0.69 [0.62; 0.77]; < 0.001
Dizziness (PT, AEs)	1283	137 (10.7)	1265	83 (6.6)	1.63 [1.25; 2.11]; < 0.001
Eye disorders (SOC, AEs)	1283	195 (15.2)	1265	66 (5.2)	2.91 [2.23; 3.81]; < 0.001
Gastrointestinal disorders (SOC, AEs)	1283	1142 (89.0)	1265	408 (32.3)	2.76 [2.54; 3.00]; < 0.001
Diarrhoea (PT, severe AEs[h])	1283	125 (9.7)	1265	2 (0.2)	61.62 [15.28; 248.59]; < 0.001
Fatigue (PT, severe AEs[h])	1283	34 (2.7)	1265	2 (0.2)	16.76 [4.04; 69.62]; < 0.001
Hypokalaemia (PT, severe AEs[h])	1283	18 (1.4)	1265	5 (0.4)	3.55 [1.32; 9.53]; 0.007
Blood and lymphatic system disorders (SOC, severe AEs[h])	1283	209 (16.3)	1265	13 (1.0)	15.85 [9.10; 27.61]; < 0.001
Hepatic events (CMQ, severe AEs[h])[j]	1283	45 (3.5)	1265	11 (0.9)	4.03 [2.10; 7.76]; 0.001
Venous thromboembolism (CMQ, severe AEs[h])[k]	1283	14 (1.1)	1265	4 (0.3)	3.45 [1.14; 10.46]; 0.020
ILD/pneumonitis (SMQ, SAE)	1283	7 (0.5)	1265	1 (0.1)	6.90 [0.85; 56.02]; 0.036

Table 23: Results (mortality, morbidity and side effects) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study Outcome category Outcome	Abemaciclib + endocrine therapy		Endocrine therapy		Abemaciclib + endocrine therapy vs. endocrine therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
a. Institute's calculation, unconditional exact test (CSZ method according to [13]). b. Data cut-off: 1 April 2021. c. Effect and CI: Cox proportional hazards model; p-value: log-rank test. d. p-value: z-test. e. The individual components are presented in the lines below. f. For individual components, see recurrence (IDFS). g. No usable data; see Section 2.4.2.1 for reasons. h. Operationalized as CTCAE grade ≥ 3. i. Discontinuation of at least one of the drugs. j. Includes the PTs ALT increased and AST increased. k. includes the PTs pulmonary embolism and deep vein thrombosis. AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CI: confidence interval; CMQ: Custom MedDRA Query; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; HR: hazard ratio; IDFS: invasive disease-free survival; n: number of patients with (at least one) event; ILD: interstitial lung disease; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: Standardized MedDRA Query; VAS: visual analogue scale					

Based on the available information, at most indications, e.g. of an added benefit, can be determined for the outcomes of mortality, SAEs and severe AEs, and at most hints for all other outcomes. For the outcome of recurrence, only a hint can be granted due to the short observation period (see Section 2.4.2.1).

Mortality

Overall survival

For the outcome of overall survival, no statistically significant difference between treatment groups was found. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Morbidity

Recurrence

For the outcome of recurrence, there was a statistically significant effect in favour of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for both recurrence rate and disease-free survival. When assessing the certainty of results, the short median observation period of approximately 28 months at the time of the present data cut-off

must be taken into account (see Section 2.4.2.1). This results in a hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

Symptoms, recorded using the FACIT-Fatigue

There are no usable data for the outcome of symptoms recorded using the FACIT-Fatigue. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

There are no usable data for the outcome of health status, recorded using the EQ-5D VAS. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life, recorded using the FACT-B and the FACT-ES

No usable data are available for the outcome of health-related quality of life, recorded using the FACT-B and the FACT-ES. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Side effects

SAEs and severe AEs (CTCAE ≥ 3)

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcomes of SAEs and severe AEs (CTCAE grade ≥ 3). This results in an indication of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for each of these outcomes.

Discontinuation due to AEs

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcome of discontinuation due to AEs. This results in a hint of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

Specific AEs

Neutropenia (severe AEs), diarrhoea (severe AEs), fatigue (severe AEs), hypokalaemia (severe AEs), blood and lymphatic system disorders (severe AEs), hepatic events (severe AEs), and ILD/pneumonitis (SAE)

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for each of the specific AEs of neutropenia (severe AEs), diarrhoea (severe AEs), fatigue (severe AEs), hypokalaemia (severe AEs), blood and lymphatic system disorders (severe AEs), hepatic events (severe AEs), and ILD/pneumonitis (SAE). This

results in an indication of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for each of these outcomes.

Venous thromboembolism (severe AEs)

A significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcome of venous thromboembolism (severe AEs). There is an effect modification by the characteristic of age for this outcome (see Section 2.5.2.4). A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown only for patients ≥ 65 years of age. This results in an indication of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for the outcome of venous thromboembolism (severe AEs) in patients ≥ 65 years. No statistically significant difference between treatment groups was found for patients < 65 years. This results in no hint of greater or lesser harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for patients < 65 years of age; greater or lesser harm for these patients is therefore not proven.

Arthralgia (AEs)

A significant difference in favour of abemaciclib in combination with endocrine therapy was shown for the outcome of arthralgia (AEs). This results in a hint of lesser harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

Alopecia (AEs), dizziness (AEs), eye disorders (AEs) and gastrointestinal disorders (AEs)

A significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the specific outcomes of alopecia (AEs), dizziness (AEs), eye disorders (AEs) and gastrointestinal disorders (AEs). This results in a hint of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for each of these outcomes.

2.5.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are considered in the benefit assessment:

- age (< 65 years/≥ 65 years)
- severity of the disease (tumour stage IIA versus IIB versus IIIA versus IIIB versus IIIC)

Interaction tests are performed if at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

The results are presented in Table 24.

Table 24: Subgroups (side effects) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women)

Study Outcome Characteristic Subgroup	Abemaciclib + endocrine therapy		Endocrine therapy		Abemaciclib + endocrine therapy vs. endocrine therapy	
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]	p-value
Study MONARCH-E						
Venous thromboembolism (CMQ, severe AEs[a])						
Age						
< 65 years	918	8 (0.9)	937	4 (0.4)	2.04 [0.62; 6.76]	0.249[b]
≥ 65 years	365	6 (1.6)	328	0 (0)	11.69 [0.66; 206.64]	0.020[b]
Total					Interaction:	< 0.001

a. Operationalized as CTCAE grade ≥ 3.
b. Institute's calculation, unconditional exact test (CSZ method according to [13]).

CI: confidence interval; CMQ: Custom MedDRA Query; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; vs.: versus

There is an effect modification by age for the outcome of venous thromboembolism (Custom Medical Dictionary for Regulatory Activities Query [CMQ], severe AEs). Based on the data presented by the company in Module 4, there is no statistically significant difference between the treatment groups for patients < 65 years of age. This results in no hint of greater or lesser harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for patients < 65 years of age; greater or lesser harm for these patients is therefore not proven. For patients ≥ 65 years of age, there was a statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy. This results in an indication of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome in patients ≥ 65 years.

2.5.3 Probability and extent of added benefit

Probability and extent of the added benefit for research question 2 (postmenopausal women) at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.5.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.5.2 (see Table 25).

Determination of the outcome category for the outcomes on side effects

It cannot be inferred from the dossier whether the following side effect outcomes are serious/severe or non-serious/non-severe. The classification of this outcome is explained below.

Side effects

Also for this research question, no information is available on the severity classification of the specific AE outcomes of alopecia, arthralgia, dizziness, eye disorders, and gastrointestinal disorders, as well as of the events that led to discontinuation due to AEs. Therefore, these outcomes are assigned to the outcome category of non-serious/non-severe side effects.

Table 25: Extent of added benefit at outcome level: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Abemaciclib + endocrine therapy vs. endocrine therapy** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median time to event (months): NA vs. NA HR: 0.94 [0.65; 1.36] p = 0.738	Lesser benefit/added benefit not proven
Morbidity		
Recurrence		
Recurrence rate	9.5% vs. 13.1% RR: 0.73 [0.58; 0.91] p = 0.005 Probability: “hint”	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”
Disease-free survival	9.5% vs. 13.1% HR: 0.74 [0.58; 0.93] p = 0.010 Probability: “hint”	
Symptoms		
FACIT-Fatigue	No usable data	Lesser benefit/added benefit not proven
Health status (EQ-5D VAS)	No usable data	Lesser benefit/added benefit not proven

Table 25: Extent of added benefit at outcome level: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Abemaciclib + endocrine therapy vs. endocrine therapy** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
FACT-B	No usable data	Lesser benefit/added benefit not proven
FACT-ES	No usable data	Lesser benefit/added benefit not proven
Side effects		
SAEs	15.6% vs. 9.7% RR: 1.60 [1.30; 1.98] RR: 0.63 [0.51; 0.77][c] p < 0.001 Probability: “indication”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ Greater harm, extent: “considerable”
Severe AEs	50.3% vs. 16.8% RR: 2.99 [2.61; 3.41] RR: 0.34 [0.29; 0.38][c] p < 0.001 Probability: “indication”	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: “major”
Discontinuation due to AEs	22.0% vs. 1.1% RR: 19.86 [11.68; 33.78] RR: 0.05 [0.01; 0.09][c] p < 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: “considerable”
Neutropenia (severe AEs)	20.0% vs. 0.6% RR: 36.20 [17.15; 76.39] RR: 0.03 [0.01; 0.06][c] p < 0.001 Probability: “indication”	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: “major”
Alopecia (PT, AEs)	11.7% vs. 2.7% RR: 4.35 [3.02; 6.26] RR: 0.23 [0.16; 0.33][c] p < 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: “considerable”
Arthralgia (PT, AEs)	26.7% vs. 38.6% 0.69 [0.62; 0.77] p < 0.001 Probability: “hint”	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ added benefit, extent: “considerable”

Table 25: Extent of added benefit at outcome level: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Abemaciclib + endocrine therapy vs. endocrine therapy** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Dizziness (AEs)	10.7% vs. 6.6% RR: 1.63 [1.25; 2.11] RR: 0.61 [0.47; 0.798][c] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"
Eye disorders (AEs)	15.2% vs. 5.2% RR: 2.91 [2.23; 3.81] RR: 0.34 [0.26; 0.45][c] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"
Gastrointestinal disorders (AEs)	89.0% vs. 32.3% RR: 2.76 [2.54; 3.00] RR: 0.36 [0.33; 0.39][c] p < 0.001 Probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ Greater harm, extent: "considerable"
Diarrhoea (severe AEs)	9.7% vs. 0.2% RR: 61.62 [15.28; 248.59] RR: 0.02 [0.004; 0.07][c] p < 0.001 Probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"
Fatigue (severe AEs)	2.7% vs. 0.2% RR: 16.76 [4.04; 69.62] RR: 0.06 [0.01; 0.25][c] p < 0.001 Probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk < 5% Greater harm, extent: "considerable"
Hypokalaemia (severe AEs)	1.4% vs. 0.4% RR: 3.55 [1.32; 9.53] RR: 0.28 [0.11; 0.76][c] p = 0.007 Probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.90$ Greater harm, extent: "considerable"
Blood and lymphatic system disorders (severe AEs)	16.3% vs. 1.0% RR: 15.85 [9.10; 27.61] RR: 0.06 [0.04; 0.11][c] p < 0.001 Probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% Greater harm, extent: "major"

Table 25: Extent of added benefit at outcome level: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Abemaciclib + endocrine therapy vs. endocrine therapy** **Proportion of events (%)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Hepatic events (severe AEs)	3.5% vs. 0.9% RR: 4.03 [2.10; 7.76] RR: 0.25 [0.13; 0.48][c] p < 0.001 Probability: "indication"	Outcome category: serious/severe side effects CI_u < 0.75, risk < 5% Greater harm, extent: "considerable"
Venous thromboembolism (severe AEs)		
Age		
< 65 years	0.9% vs. 0.4% RR: 2.04 [0.62; 6.76] p = 0.249	Lesser benefit/added benefit not proven
≥ 65 years	1.6% vs. 0% RR: 11.69 [0.66; 206.64] RR: 0.09 [0.01; 1.52][c] p = 0.020 Probability: "indication"	Outcome category: serious/severe side effects CI_u > 1.0[d] Greater harm, extent: "minor"
ILD/pneumonitis (SAEs)	0.5% vs. 0.1% RR: 6.90 [0.85; 56.02] RR: 0.15 [0.02; 1.18][c] p = 0.036 Probability: "indication"	Outcome category: serious/severe side effects CI_u > 1.0[d] Greater harm, extent: "minor"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods. The decisive factor is the p-value.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; ILD: interstitial lung disease; NA: not achieved; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale

2.5.3.2 Overall conclusion on added benefit

Table 26 summarizes the results included in the overall conclusion on the extent of added benefit.

Table 26: Positive and negative effects from the assessment of abemaciclib + endocrine therapy in comparison with endocrine therapy (research question 2: postmenopausal women) (multipage table)

Positive effects	**Negative effects**
Serious/severe symptoms/late complications ▪ Recurrence: hint of an added benefit – extent: "minor"	
	Serious/severe side effects ▪ SAEs: indication of greater harm – extent "considerable" ▫ ILD/pneumonitis (SAEs): indication of greater harm – extent: "minor" ▪ Severe AEs: indication of greater harm – extent: "major" ▫ Neutropenia, diarrhoea, blood and lymphatic system disorders (in each case severe AEs): indication of greater harm – extent: "major" ▫ Hypokalaemia, fatigue, hepatic events (severe AEs): indication of greater harm – extent "considerable" ▫ Venous thromboembolism (severe AEs): - Age ≥ 65: indication of greater harm – extent: "minor"
Non-serious/non-severe side effects ▪ Arthralgia (PT, AEs): hint of an added benefit – extent: "considerable"	Non-serious/non-severe side effects ▪ Discontinuation due to AEs: hint of greater harm – extent: "considerable" ▪ Alopecia, dizziness, eye disorders, gastrointestinal disorders (in each case PT, AEs): hint of greater harm – extent: "considerable"
The data on symptoms and health-related quality of life are not usable.	
AE: adverse event; ILD: interstitial lung disease; PT: Preferred Term; SAE: serious adverse event	

Overall, there are positive and negative effects of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy. The positive effects are one hint of minor added benefit in serious/severe symptoms for the outcome of recurrence and one hint of a considerable added benefit in non-serious/non-severe side effects for one specific AE.

The negative effects are related exclusively to outcomes of the category of side effects. There are indications of greater harm of abemaciclib, partly with major extent, in particular for the overall rates of serious and severe AEs as well as for specific severe AEs.

No conclusions can be drawn about longer-term effects of therapy with abemaciclib in the present therapeutic indication, as the observation period in the MONARCH-E study was only 28 months at the time of the data cut-off used. Furthermore, no conclusions can be drawn on the patient-reported outcomes on symptoms and health-related quality of life, as no usable data are available.

Overall, the negative effects call into question the positive ones. Hence, there is no hint of added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine

therapy for postmenopausal patients with node-positive, HR-positive, HER2-negative early breast cancer at high risk of recurrence; an added benefit is therefore not proven.

The assessment described above deviates from that of the company, which derived an indication of considerable added benefit.

2.6 Research question 3: men

2.6.1 Study characteristics

The information on the study design, interventions used, data cut-offs and planned duration of follow-up of the outcomes is described in detail in Section 2.4.1.

Subpopulation relevant to the assessment of research question 3

Of the patients included in the MONARCH-E study, only the subpopulation of male subjects who were treated with the G-BA's ACT is relevant to the assessment of research question 3 (see Section 2.2). These were 22 patients in total, 11 of whom were treated with abemaciclib in combination with endocrine therapy and 11 with endocrine therapy alone. However, this population includes patients who, in the course of the study, switched to an endocrine therapy that, according to the company, does not correspond to the ACT or is not covered by a corresponding approval. For the benefit assessment, the company only used the results of those patients who received endocrine therapy corresponding to the ACT for the entire duration of the study. These were 19 patients in total, 10 of whom were treated with abemaciclib in combination with endocrine therapy and 9 with endocrine therapy alone. The company presented the data of this subpopulation in its dossier.

However, in the opinion of the company, statistical tests cannot be meaningfully performed on the basis of this small subpopulation and differences in the relative frequencies between the study arms cannot be meaningfully interpreted. The company did not calculate effect estimates and provided a descriptive presentation of the results. The data provided by the company are presented below.

Table 27: Characteristics of the study population – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 3: men) (multipage table)

Study Characteristic Category	Abemaciclib + endocrine therapy N[a] = 10	Endocrine therapy N[a] = 9
MONARCH-E		
Sex [F/M], %	0/100	0/100
Age [years], mean (SD)	63 (6)	65 (10)
Median (min–max)	62 (56–72)	63 (54–82)
Family origin 1, n (%)		
Asian	2 (20.0)	2 (22.2)
White/Caucasian	7 (70.0)	7 (77.8)
Other[b]	1 (10.0)	0 (0)
Region, n (%)		
North America/Europe	6 (60.0)	7 (77.8)
Asia	0 (0)	2 (22.2)
Other	4 (40.0)	0 (0)
ECOG PS, n (%)		
0	8 (80.0)	8 (88.9)
1	2 (20.0)	1 (11.1)
≥ 2	0 (0)	0 (0)
Primary tumour size by radiology prior to any systemic treatment, n (%)		
< 20 mm	3 (30.0)	5 (55.6)
≥ 20 to < 50 mm	5 (50.0)	4 (44.4)
≥ 50 mm	1 (10.0)	0 (0)
Missing	1 (10.0)	0 (0)
Primary tumour size by pathology following definitive surgery, n (%)		
< 20 mm	2 (20.0)	2 (22.2)
≥ 20 to < 50 mm	6 (60.0)	7 (77.8)
≥ 50 mm	2 (20.0)	0 (0)
Missing	0 (0)	0 (0)
Number of positive lymph nodes, n (%)		
0	0 (0)	0 (0)
1–3	2 (20.0)	2 (22.2)
4–9	4 (40.0)	3 (33.3)
≥ 10	4 (40.0)	4 (44.4)

Table 27: Characteristics of the study population – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 3: men) (multipage table)

Study **Characteristic** **Category**	**Abemaciclib + endocrine therapy** **N[a] = 10**	**Endocrine therapy** **N[a] = 9**
Histopathological grading at diagnosis, n (%)		
G1 – favourable	0 (0)	0 (0)
G2 – moderately favourable	7 (70.0)	4 (44.4)
G3 – unfavourable	3 (30.0)	5 (55.6)
Gx – cannot be assessed	0 (0)	0 (0)
Missing	0 (0)	0 (0)
Tumour stage at first diagnosis, n (%)		
Stage IA	0 (0)	0 (0)
Stage IIA	0 (0)	0 (0)
Stage IIB	0 (0)	0 (0)
Stage IIIA	4 (40.0)	1 (11.1)
Stage IIIB	0 (0)	2 (22.2)
Stage IIIC	6 (60.0)	6 (66.7)
Missing	0 (0)	0 (0)
Oestrogen receptor status, n (%)		
Positive	10 (100)	9 (100)
Negative	0 (0)	0 (0)
Unknown	0 (0)	0 (0)
Missing	0 (0)	0 (0)
Progesterone receptor status, n (%)		
Positive	7 (70.0)	8 (88.9)
Negative	2 (20.0)	0 (0)
Unknown	1 (10.0)	0 (0)
Missing	0 (0)	1 (11.1)
HER2 status at time of first diagnosis, n (%)		
Positive	0 (0)	0 (0)
Negative	10 (100)	9 (100)
Missing	0 (0)	0 (0)
Prior chemotherapy, n (%)		
Adjuvant chemotherapy	6 (60.0)	5 (55.6)
Neoadjuvant chemotherapy	2 (20.0)	3 (33.3)
No chemotherapy	2 (20.0)	1 (11.1)
Endocrine therapy at baseline, n (%)		
Aromatase inhibitor	0 (0)	0 (0)
Tamoxifen	10 (100)	9 (100)
Treatment discontinuation, n (%)	ND[c]	ND[c]
Study discontinuation, n (%)	ND[d]	ND[d]

Table 27: Characteristics of the study population – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 3: men) (multipage table)

Study Characteristic Category	Abemaciclib + endocrine therapy N[a] = 10	Endocrine therapy N[a] = 9
a. Number of patients who received ACT-compliant endocrine therapy during the entire study period. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant. b. Other includes Native American/Native Alaskan, African American, Native Hawaiian or Pacific Islander, multiple and missing data. c. Data on treatment discontinuations are only available in relation to AEs. d. Data on study discontinuations of the intervention or comparator arm are only available at study level. Of the randomized patients, 18.0% in the intervention arm and 17.5% in the comparator arm discontinued the study prematurely. ACT: appropriate comparator therapy; AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; HER2: human epidermal growth factor receptor 2; M: male; n: number of patients in the category; N: number of patients who received ACT-compliant endocrine therapy during the entire study period; ND: no data; RCT: randomized controlled trial; SD: standard deviation		

Table 28: Information on the course of the study – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 3: men)

Study **Duration of the study phase** **Outcome category**	**Abemaciclib + endocrine therapy** **N = 10**	**Endocrine therapy** **N = 9**
MONARCH-E		
Duration of treatment with abemaciclib [months]		
Median [Q1; Q3]	23.4 [12.8; 23.8]	-
Duration of treatment with endocrine therapy [months]		
Median [Q1; Q3]	23.6 [15.5; 23.9]	23.6 [23.5; 23.9]
Observation period [months]		
Overall survival[a]		
Median [Q1; Q3]	25.8 [24.1; 31.8]	24.9 [22.9; 26.9]
Morbidity (IDFS)		
Median [Q1; Q3]	25.8 [24.1; 31.8]	24.9 [24.8; 31.3]
Morbidity (EQ-5D VAS)		
Median [Q1; Q3]	20.9 [16.8; 25.12]	24.8 [23.6; 27.6]
Morbidity (FACIT-Fatigue)		
Median [Q1; Q3]	20.9 [16.8; 25.1]	24.8 [23.6; 27.6]
Health-related quality of life (FACT-B)		
Median [Q1; Q3]	20.9 [16.8; 25.1]	24.8 [23.6; 27.6]
Health-related quality of life (FACT-ES)		
Median [Q1; Q3]	20.9 [16.8; 25.1]	24.8 [23.6; 27.6]
Side effects		
Median [Q1; Q3]	24.6 [16.0; 24.9]	24.6 [23.5; 24.9]

a. The company did not provide any information on the methods used to determine observation periods in the subpopulation.

FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; IDFS: invasive disease-free survival; max.: maximum; min: minimum; N: number of analysed patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; VAS: visual analogue scale

Table 29: Results (mortality, morbidity and side effects) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 3: men) (multipage table)

Study Outcome category Outcome	Abemaciclib + endocrine therapy		Endocrine therapy		Abemaciclib + endocrine therapy vs. endocrine therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
MONARCH-E					
Mortality					
Overall survival	10	2 (20.0) Median time to event: NA [15.95; NC]	9	0 (0) Median time to event: NA [NC; NC]	–
Morbidity					–
Recurrence					–
Recurrence rate[a]	10	2 (20.0)	9	1 (11.1)	–
Local breast cancer recurrence	10	0 (0)	9	1 (11.1)	–
Regional invasive breast cancer recurrence	10	0 (0)	9	0 (0)	–
Distant recurrence	10	2 (20.0)	9	0 (0)	–
Contralateral invasive breast cancer	10	0 (0)	9	0 (0)	–
Second primary carcinoma (no breast cancer)	10	0 (0)	9	0 (0)	–
Death without recurrence	10	0 (0)	9	0 (0)	–
Disease-free survival[b]	10	2 (20.0) Median time to event: NA [9.93; NC]	9	1 (11.1) Median time to event: NA [21.76; NC]	–
Symptoms (FACIT-Fatigue)				No usable data[c]	
Health status (EQ-5D VAS)				No usable data[c]	
Health-related quality of life					
FACT-B, FACT-ES				No usable data[c]	
Side effects					
AEs (supplementary information)	10	10 (100.0)	9	9 (100.0)	–
SAEs	10	3 (30.0)	9	1 (11.1)	–
Severe AEs[d]	10	4 (40.0)	9	2 (22.2)	–
Discontinuation due to AEs	10	2 (20.0)	9	0 (0)	–
Neutropenia (PTs, severe AEs[d])	10	2 (20.0)	9	0 (0)	–
Diarrhoea (PT, severe AEs[d])	10	0 (0)	9	0 (0)	–

Table 29: Results (mortality, morbidity and side effects) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 3: men) (multipage table)

Study Outcome category Outcome	Abemaciclib + endocrine therapy		Endocrine therapy		Abemaciclib + endocrine therapy vs. endocrine therapy
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value

a. Operationalization according to IDFS; the individual components are presented in the lines below.
b. For individual components, see recurrence (IDFS).
c. No usable data; see Section 2.4.2.1 for reasons.
d. Operationalized as CTCAE grade ≥ 3.

CTCAE: Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; IDFS: invasive disease-free survival; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Overall, data on only few patients are available for male patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence. The available data provide no hint of an added benefit; an added benefit is therefore not proven.

2.6.2 Probability and extent

For male patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence, the added benefit is not proven.

The assessment described above concurs with that of the company.

2.7 Probability and extent of added benefit – summary

Table 30 shows a summary of the probability and extent of added benefit of abemaciclib in combination with endocrine therapy for research questions 1 (premenopausal women), 2 (postmenopausal women) and 3 (men).

Table 30: Abemaciclib in combination with endocrine therapy – probability and extent of added benefit

Research question	Subindication	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	▪ Tamoxifen (possibly in addition to suppression of the ovarian function)	▪ Hint of minor added benefit
2	Postmenopausal women	▪ anastrozole or ▪ letrozole or ▪ possibly tamoxifen if aromatase inhibitors are unsuitable or ▪ anastrozole or ▪ exemestane ▪ in sequence after tamoxifen	▪ Added benefit not proven
3	Men	▪ Tamoxifen	▪ Added benefit not proven

a. Presented is the respective ACT specified by the GBA.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor

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

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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