Abemaciclib (breast cancer; combination with an aromatase inhibitor)

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

EXTRACT

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Patient and family involvement

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

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer Breast Cancer 23
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Core 30
EQ-5D	European Quality of Life Questionnaire – 5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
mBPI-SF	modified Brief Pain Inventory–Short Form
PFS	progression-free survival
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
VAS	visual analogue scale

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug abemaciclib (in combination with an aromatase inhibitor). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 22 December 2022.

For the drug to be assessed, the company had already submitted a dossier for a previous benefit assessment. In this procedure, the G-BA issued a decision dated 2 May 2019, limiting its validity for postmenopausal women who have not yet received initial endocrine therapy to 31 December 2022. The time limit was imposed because the overall survival data available from the MONARCH 3 study were preliminary and based on a small number of events, and further results from interim analyses and final results were pending. For the new benefit assessment after expiry of the time limit, the dossier was to present the results of the interim analysis to be conducted after 252 deaths, which was expected to occur in 2022. According to the commission, the current benefit assessment refers exclusively to postmenopausal women who have not yet received initial endocrine therapy.

Research question

The aim of this report was to assess the added benefit of abemaciclib in combination with an aromatase inhibitor in comparison with the appropriate comparator therapy (ACT) in postmenopausal women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer. In accordance with the time limit imposed by the G-BA, the present evaluation is based exclusively on patients who have not yet received initial endocrine therapy.

According to the approval, abemaciclib is to be administered in combination with either an aromatase inhibitor or fulvestrant. The combination with an aromatase inhibitor is the subject of the present dossier assessment.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of abemaciclib in combination with an aromatase inhibitor

Therapeutic indication	**ACT**[a]
Postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy[b]	▪ **Anastrozole** or ▪ **letrozole** or ▪ fulvestrant or ▪ tamoxifen if aromatase inhibitors are not suitable or ▪ ribociclib in combination with an NSAI (anastrozole, letrozole)[c] or ▪ palbociclib in combination with an NSAI (anastrozole, letrozole)[c] or ▪ ribociclib in combination with fulvestrant[c] or ▪ abemaciclib in combination with fulvestrant[c] or ▪ palbociclib in combination with fulvestrant[c]
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold. b. Concerning the locally advanced or metastatic stage; for the present therapeutic indication, patients are presumed to be indicated for (further) endocrine therapy and not to be indicated for chemotherapy or (secondary) resection or curative radiotherapy. c. The ACT has changed from the prior assessment as a result of a reevaluation of the available evidence and additionally includes combination therapies of an NSAI or fulvestrant with CDK4/6 inhibitors. ACT: appropriate comparator therapy; CDK: cyclin-dependent kinase; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; NSAI: non-steroidal aromatase inhibitor	

The company followed the ACT and chose anastrozole and letrozole from the available options.

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 to derive added benefit. This concurs with the company's inclusion criteria.

Study pool and study design

The study pool includes the MONARCH 3 and MONARCH plus studies.

MONARCH 3 study

The MONARCH 3 study is a double-blind RCT comparing abemaciclib + anastrozole or letrozole with placebo + anastrozole or letrozole. The study enrolled postmenopausal women with locally advanced or metastatic HR-positive and HER2-negative breast cancer. Patients were not expected to be therapeutically indicated for chemotherapy or curative radiotherapy. Patients were to have received neither chemotherapy nor endocrine therapy for the locally advanced or metastatic stage.

A total of 493 patients were randomly assigned in a 2:1 ratio to treatment with either abemaciclib + anastrozole or letrozole (N = 328) or placebo + anastrozole or letrozole (N = 165). Randomization was stratified by type of disease (visceral metastases versus bone metastases only versus other) and prior (neo)adjuvant endocrine therapy (aromatase inhibitors versus other versus none).

Treatment with the study medication of abemaciclib, anastrozole, and letrozole was largely in accordance with the respective Summary of Product Characteristics (SPCs).

Treatment continues until disease progression, participation in another study, or discontinuation of therapy at the discretion of the physician, patient, or sponsor. After treatment discontinuation, patients were allowed to start subsequent therapy.

The primary outcome of the MONARCH 3 study is progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, morbidity outcomes, health-related quality of life, and adverse events (AEs).

The study is ongoing. The final analysis for overall survival, planned to occur after 315 deaths, is still pending. The present benefit assessment uses the most recent data cutoff of 2 July 2021, planned to occur after 252 deaths (4th interim analysis).

MONARCH plus study

The MONARCH plus study is a double-blind RCT. The study enrolled postmenopausal women with locally recurrent or metastatic HR-positive, HER2-negative breast cancer who either had or had not received prior endocrine therapy for the advanced disease stage. In addition, the patients had to have received no previous chemotherapy in the locally recurrent or metastatic stage. Patients were not expected to be therapeutically indicated for chemotherapy or curative radiotherapy. The MONARCH plus study's Cohort A comparing abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole is relevant for the present benefit assessment. This cohort included only patients without prior endocrine therapy in the locally recurrent or metastatic stage.

A total of 306 patients in Cohort A of the MONARCH plus study were randomly assigned in a 2:1 ratio to treatment with either abemaciclib + anastrozole or letrozole (N = 207) or placebo + anastrozole or letrozole (N = 99). Randomization was based on type of disease (visceral metastases versus nonvisceral metastases) and prior (neo)adjuvant endocrine therapy (prior therapy with > 12 months' disease-free interval after treatment end versus prior therapy with ≤ 12 months disease-free interval after end of therapy versus no prior therapy).

Treatment with the study medication of abemaciclib, anastrozole, and letrozole was largely in accordance with the respective SPCs.

Treatment continues until disease progression, participation in another study, or discontinuation of therapy at the discretion of the physician, patient, or sponsor.

The primary outcome of the MONARCH plus study is PFS. Patient-relevant secondary outcomes are overall survival and outcomes on morbidity, health-related quality of life, and AEs.

The present benefit assessment uses the data cutoff for the final analysis dated 18 May 2020.

Below, all descriptions of the MONARCH plus study refer to the study's Cohort A, which is relevant for the present benefit assessment.

Risk of bias

The risk of bias across outcomes for the studies MONARCH 3 and MONARCH plus was rated as low.

The risk of bias of the results for the outcome of overall survival is rated as low in both studies. For the outcome of discontinuation due to AEs, the certainty of results is reduced in both studies, despite a low risk of bias. For all other outcomes surveyed in the MONARCH 3 and MONARCH plus studies, the risk of bias of results is rated as high due to incomplete observations for potentially informative reasons, with treatment arms differing in treatment durations.

Results

Mortality

Overall survival

For the outcome of overall survival, the metaanalysis shows a statistically significant difference in favour of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. This results in proof of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. It should be noted that the benefit of abemaciclib in the MONARCH 3 study becomes apparent only approximately 30 months after randomization. Until then, the Kaplan-Meier curves of both treatment arms look similar. The observation duration in the MONARCH plus study is much shorter, but it suggests a similar picture as shown by the MONARCH 3 study.

Morbidity

For all outcomes surveyed with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30), the EORTC QLQ-Breast Cancer 23 (EORTC QLQ-BR23), and the European Quality of Life Questionnaire – 5 Dimensions (EQ-5D) visual analogue scale (VAS), the evaluations for time until first deterioration are used.

Symptoms (EORTC QLQ-C30)

Fatigue, nausea and vomiting, appetite loss

For each of the outcomes of fatigue, nausea and vomiting as well as appetite loss, the metaanalysis shows a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. For each of them, this results in an indication of lesser benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

Diarrhoea

For the outcome of diarrhoea, the metaanalysis shows a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole. Despite a high risk of bias of results, this outcome is associated with a high certainty of results due to the effect size already observed early in both studies. For this outcome, this results in proof of lesser benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

Dyspnoea

For the outcome of dyspnoea, the metaanalysis shows a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. The difference, however, is no more than marginal for this outcome in the category of non-serious/non-severe symptoms / late complications. Consequently, there is no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven for this outcome.

Pain, insomnia, and congestion

The metaanalysis does not show a statistically significant difference between treatment groups for any of the outcomes of pain, insomnia, or constipation. For each of these outcomes, this results in no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Symptoms (EORTC QLQ-BR23)

EORTC QLQ-BR23 was surveyed only in the MONARCH 3 study.

Side effects of systemic therapy

For the outcome of side effects of systemic therapy, a statistically significant difference was found to the disadvantage of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. This results in a hint of lesser benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

Arm symptoms and chest symptoms

No statistically significant difference between treatment groups was shown for the outcomes of arm symptoms or chest symptoms. For each of these outcomes, this results in no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Upset by hair loss

No suitable data are available for the outcome of upset by hair loss because the proportion of patients with missing values at baseline and during the course of the study was unclear. For this outcome, this results in no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Pain (modified Brief Pain Inventory–Short Form [mBPI-SF])

The outcome of pain (mBPI-SF), operationalized as pain at its worst in the last 24 hours, was surveyed only in the MONARCH plus study. No statistically significant difference between treatment arms was found for this outcome. For this outcome, this results in no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

The outcome of health status (EQ-5D VAS) was recorded only in the MONARCH 3 study. No statistically significant difference between treatment arms was found for this outcome. For this outcome, this results in no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Health-related quality of life

For all outcomes surveyed with the EORTC QLQ-C30 and the EORTC QLQ-BR23, the analyses of time to first deterioration are used.

EORTC QLQ-C30

Physical functioning, role functioning, emotional functioning, and cognitive functioning

The metaanalysis showed no statistically significant differences between treatment arms for any of the outcomes of physical functioning, role functioning, emotional functioning, or cognitive functioning. For each of these outcomes, this results in no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Global health status and social functioning

For the outcomes of global health status and social functioning, the metaanalysis does not show a statistically significant difference between treatment groups. However, both

outcomes exhibited an effect modification by the characteristic of age. In women ≥ 65 years of age, both outcomes are associated with an indication of lesser benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. For women < 65 years of age, both outcomes are associated with no hint of added benefit or lesser benefit of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven for these outcomes in women < 65 years of age.

EORTC QLQ-BR23

EORTC QLQ-BR23 was surveyed only in the MONARCH 3 study.

Body image

For the outcome of body image, there is a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole comparison with anastrozole or letrozole. This results in a hint of lesser benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

Sexual functioning and future perspective

No statistically significant difference between treatment groups was shown for the outcomes of sexual functioning or future perspective. For each of these outcomes, this results in no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Sexual enjoyment

No suitable data are available for the outcome of sexual enjoyment due to the unclear proportion of patients with missing values at baseline and during the course of the study. For this outcome, this results in no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Side effects

Serious adverse events (SAEs)

For the outcome of SAEs, the metaanalysis shows a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. However, there is an effect modification by the attribute of age. In women ≥ 65 years, this results in an indication of greater harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. For women < 65 years of age, there is no hint of greater or lesser harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; greater or lesser harm is therefore not proven for these outcomes in women < 65 years of age.

Severe AEs, discontinuation due to AEs

For each of the outcomes of severe AEs and discontinuation due to AEs, the metaanalysis shows a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. For each of these outcomes, this results in an indication of greater harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

Specific AEs

Neutropoenia, blood and lymphatic system disorders (each severe AEs)

For each of the outcomes of neutropoenia and blood and lymphatic system disorders (severe AEs), the metaanalysis shows a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. Despite a high risk of bias of results, these outcomes are associated with a high certainty of results due to the size of the effects which, particularly in MONARCH 3, were observed already early in the study and almost exclusively in the intervention arm. For each of these outcomes, this results in proof of greater harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

Diarrhoea, infections and infestations, metabolism and nutrition disorders, investigations (each severe AEs), gastrointestinal disorders, skin and subcutaneous tissue disorders, and eye disorders (each AEs)

For each of the outcomes of diarrhoea, infections and infestations, metabolism and nutrition disorders, investigations (each severe AEs), gastrointestinal disorders, skin and subcutaneous tissue disorders, and eye disorders (each AEs), the metaanalysis showed a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. For each of these outcomes, this results in an indication of greater harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

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 an aromatase inhibitor in comparison with the ACT are assessed as follows:

Overall, a favourable effect in overall survival is offset by numerous unfavourable effects in the outcome categories of morbidity, health-related quality of life, and side effects. Data across the entire observation period are available only for overall survival. All unfavourable effects are based exclusively on the shortened observation period.

For the outcome of overall survival, there is proof of minor added benefit. Disadvantages in the morbidity category are associated with 1 proof, 1 hint, and indications of lesser benefit, depending on the symptom, and are at most of considerable extent. In the outcome category of health-related quality of life, there are 1 hint of lesser benefit of minor extent as well as 2 indications of lesser benefit, with an extent of at most of major, in women ≥ 65 years of age. Because of their size and certainty of reporting, the effects concerning severe AEs are determinant for the derivation of harm. They are evident in the overall rate of severe AEs as well as in numerous specific severe AEs. They are largely blood and lymphatic system disorders, in particular, severe neutropenia (proof of greater harm of major extent). In addition, greater harm is found regarding severe diarrhoea, metabolism and nutrition disorders, and infections and infestations, among others (indications of greater harm, at most of major extent). Further, greater harm is found in the overall rates of SAEs (in this case restricted to women ≥ 65 years) and discontinuations due to AEs.

In summary, weighing the favourable effect of minor extent against the numerous unfavourable effects of at most major extent for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy, there is no hint of added benefit of abemaciclib + anastrozole or letrozole compared with anastrozole or letrozole; thus there is no proof of added benefit.

Table 3 presents a summary of the probability and extent of added benefit of abemaciclib in combination with an aromatase inhibitor.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Abemaciclib in combination with an aromatase inhibitor – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy[b].	▪ **Anastrozole** or ▪ **letrozole** or ▪ fulvestrant or ▪ tamoxifen if aromatase inhibitors are not suitable or ▪ ribociclib in combination with an NSAI (anastrozole, letrozole)[c] or ▪ palbociclib in combination with an NSAI (anastrozole, letrozole)[c] or ▪ ribociclib in combination with fulvestrant[c] or ▪ abemaciclib in combination with fulvestrant[c] or ▪ palbociclib in combination with fulvestrant[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. Concerning the locally advanced or metastatic stage; for the present therapeutic indication, patients are presumed to be indicated for (further) endocrine therapy and not to be indicated for chemotherapy or (secondary) resection or curative radiotherapy.
c. The ACT has changed from the prior assessment as a result of a reevaluation of the available evidence and additionally includes combination therapies of an NSAI or fulvestrant with CDK4/6 inhibitors.

ACT: appropriate comparator therapy; CDK: cyclin-dependent kinase; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; NSAI: non-steroidal aromatase inhibitor

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

I 2 Research question

The aim of this report was to assess the added benefit of abemaciclib in combination with an aromatase inhibitor in comparison with the ACT in postmenopausal women with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative locally advanced or metastatic breast cancer. In accordance with the time limit imposed by the G-BA, the present evaluation is based exclusively on patients who have not yet received initial endocrine therapy.

According to the approval, abemaciclib is to be administered in combination with either an aromatase inhibitor or fulvestrant. The combination with an aromatase inhibitor is the subject of the present dossier assessment.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of abemaciclib in combination with an aromatase inhibitor

Therapeutic indication	**ACT**[a]
Postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy[b]	▪ **Anastrozole** or ▪ **letrozole** or ▪ fulvestrant or ▪ tamoxifen if aromatase inhibitors are not suitable or ▪ ribociclib in combination with an NSAI (anastrozole, letrozole)[c] or ▪ palbociclib in combination with an NSAI (anastrozole, letrozole)[c] or ▪ ribociclib in combination with fulvestrant[c] or ▪ abemaciclib in combination with fulvestrant[c] or ▪ palbociclib in combination with fulvestrant[c]
a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold. b. Concerning the locally advanced or metastatic stage; for the present therapeutic indication, patients are presumed to be indicated for (further) endocrine therapy and not to be indicated for chemotherapy or (secondary) resection or curative radiotherapy. c. The ACT has changed from the prior assessment as a result of a reevaluation of the available evidence and additionally includes combination therapies of an NSAI or fulvestrant with CDK4/6 inhibitors. ACT: appropriate comparator therapy; CDK: cyclin-dependent kinase; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; NSAI: non-steroidal aromatase inhibitor	

The company followed the ACT and chose anastrozole and letrozole from the available options.

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

I 3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on abemaciclib (status: 7 October 2022)
- bibliographical literature search on abemaciclib (last search on 7 October 2022)
- search in trial registries/ trial results databases for studies on abemaciclib (last search on 26 October 2022)
- search on the G-BA website for abemaciclib (last search on 26 October 2022)

To check the completeness of the study pool:

- search in trial registries for studies on abemaciclib (last search on 16 January 2023); for search strategies, see I Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

I 3.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCTs, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole

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])
3Y-MC-JPBM (MONARCH 3[d])	Yes	Yes	No	Yes [3,4]	Yes [5,6]	Yes [7-9]
I3Y-CR-JPBQ (MONARCH plus[d])	No	Yes	No	Yes [10,11]	Yes [12]	Yes [13,14]

a. Study sponsored by the company.
b. References of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to by this acronym.

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

The study pool for the benefit assessment concurs with that of the company. In accordance with the time limit imposed by the G-BA, the company took into account the MONARCH 3

study. In addition, the company took into account the MONARCH plus study. Both studies are known from previous benefit assessments of abemaciclib [7,8,13].

I 3.2 Study characteristics

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

Table 6: Characterization of the included studies – RCTs, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MONARCH 3	RCT, parallel, double-blind	Postmenopausal women with HR-positive, HER2-negative locally recurrent or metastatic breast cancer[b] who have not yet received prior therapy in the locally recurrent or metastatic stage[c], with ECOG-PS ≤ 1.	abemaciclib + anastrozole or letrozole (N = 328) placebo + anastrozole or letrozole (N = 165)	Screening: up to 28 days Treatment: until disease progression, participation in another study, or discontinuation of therapy at the discretion of the physician, patient, or sponsor Observation [d]: outcome-specific, at most until death or end of the study	A total of 158 centres in Australia, Austria, Belgium, Canada, France, Germany, Greece, Israel, Italy, Japan, Mexico, Netherlands, New Zealand, Republic of Korea, Russia, Slovakia, Spain, Sweden, Taiwan, Turkey, United Kingdom, United States 11/2014–ongoing Data cutoffs: ▪ 31 January 2017: 1st interim analysis, planned to take place after 189 PFS events ▪ 3 November2017: 2nd interim analysis, planned to take place after 240 PFS events. ▪ 3 February 2020: 3rd interim analysis, planned to take place after 189 deaths ▪ 2 July 2021: 4th interim analysis, planned to take place after 252 deaths[e] ▪ Pending: final analysis of overall survival, planned to take place after 315 deaths	Primary: PFS Secondary: overall survival, symptoms, health status, health-related quality of life, AEs

Table 6: Characterization of the included studies – RCTs, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MONARCH plus	RCT, parallel, double-blind	Postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer[b, f] as well as ECOG-PS ≤ 1	Cohort A[g]: abemaciclib + anastrozole or letrozole (N = 207) placebo + anastrozole or letrozole (N = 99)	Screening: up to 28 days Treatment: until disease progression, participation in another study, or discontinuation of therapy at the discretion of the physician, patient, or sponsor Observation[d]: outcome-specific, at most until death or end of the study	45 study centres in Brazil, China, India, and South Africa 12/2016–ongoing Data cutoffs: ▪ 29 March 2019: interim analysis, planned to take place after 119 PFS events in Cohort A ▪ 18 May 2020: final analysis, planned to take place after 170 PFS events in Cohort A[e]	Primary: PFS Secondary: overall survival, symptoms, health-related quality of life, AEs

a. Primary outcomes include information without taking into account relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Ineligible for resection or curative radiotherapy.
c. Patients with prior (neo)adjuvant endocrine therapy (e.g. antioestrogens or aromatase inhibitors) with a disease-free interval of ≤ 12 months after the end of treatment were excluded from the study.
d. Outcome-specific information is provided in Table 8.
e. Data cutoff relevant for the present benefit assessment.
f. Included were patients without prior endocrine therapy or after prior endocrine therapy (each for the advanced stage). The assessment-relevant Cohort A of the study (see footnote g) included only patients without prior endocrine therapy in the locally recurrent or metastatic stage. Unlike in the MONARCH 3 study (see footnote c), the protocol also allowed including patients with recurrence during the (neo)adjuvant therapy or with a disease-free interval ≤ 12 months after completion of treatment into Cohort A.
g. The MONARCH plus study investigates 2 different cohorts: cohort A (abemaciclib + anastrozole or letrozole vs. placebo + anastrozole or letrozole) and Cohort B (abemaciclib + fulvestrant vs. placebo + fulvestrant). Only Cohort A, which is relevant to this benefit assessment, is presented here (and in subsequent tables).

AE: adverse event; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; HER2: human epidermal growth factor receptor-2; HR: hormone receptor; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial

Table 7: Characterization of the intervention – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Study	Intervention	Comparison
MONARCH 3	Abemaciclib 150 mg orally, every 12 hours on Days 1–28 of each cycle (cycle duration: 28 days) + anastrozole 1 mg or letrozole 2.5 mg orally, every 24 hours on Days 1–28 of each cycle	Placebo orally, every 12 hours on Days 1–28 of each cycle (cycle duration: 28 days) + anastrozole 1 mg or letrozole 2.5 mg orally, every 24 hours on Days 1–28 of each cycle
	Dose adjustments: ▪ Abemaciclib / placebo: if toxicities[a] occurred, dose reductions (first to 100 mg and subsequently to 50 mg, each twice daily) or treatment interruptions for ≤ 14 days or treatment discontinuation with continuation of anastrozole or letrozole were possible ▪ Anastrozole or letrozole: no adjustment allowed, switch allowed, e.g. from anastrozole to letrozole after consultation with sponsor; treatment interruption ≤ 14 days or discontinuation possible while continuing abemaciclib/placebo	
	Allowed prior treatment ▪ Local radiotherapies up to ≥ 2 weeks before randomization ▪ (neo-)adjuvant endocrine therapy with a disease-free interval of ≥ 12 months after the end of treatment **Disallowed prior treatment** ▪ Endocrine therapy or chemotherapy for locally recurrent or metastatic stage[b] ▪ Everolimus, CDK4 or CDK6 inhibitors ▪ Autologous or allogeneic stem cell transplantation **Allowed concomitant treatment:** ▪ Dexamethasone, preferably ≤ 7 days ▪ Antidiarrheal agents (e.g. loperamide), in case of severe diarrhoea (infusion requirement and/or in combination with fever or severe neutropenia): broad-spectrum antibiotics (e.g. fluoroquinolone) ▪ Bisphosphates or approved RANK ligands (e.g. denosumab) for patients with bone metastases, provided treatment started ≥ 7 days prior to randomization ▪ Supportive therapy **Disallowed concomitant treatment:** ▪ Other cancer therapies (radiotherapy[c], hormone therapy, immunotherapy, or chemotherapy) ▪ Megestrol acetate (as an appetite stimulant)	

Table 7: Characterization of the intervention – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Study	Intervention	Comparison
MONARCH plus, Cohort A	Abemaciclib 150 mg orally, twice daily (every 12 hours); cycle duration: 28 days + Anastrozole 1 mg or letrozole 2.5 mg orally, every 24 hours on Days 1–28 of each cycle	Placebo orally, twice daily (every 12 hours); cycle duration: 28 days + Anastrozole 1 mg or letrozole 2.5 mg orally, every 24 hours on Days 1–28 of each cycle
	The dose adjustments as well as the allowed and disallowed prior and concomitant treatment in Cohort A of the MONARCH plus study do not differ in a relevant manner from the MONARCH 3 study, except for the following: ▪ The protocol allowed including patients with a recurrence during (neo)adjuvant therapy or with a disease-free interval of ≤ 12 months after completion of treatment. ▪ Everolimus was not mentioned as a disallowed prior treatment.	

a. Depending on severity (CTCAE grade ≥ 2) and type of toxicity.
b. Non-steroidal aromatase inhibitor therapy of ≤ 2 weeks immediately prior to randomization was allowed if the patient consented to discontinuation.
c. Surgery followed by radiotherapy was allowed in case of locally advanced breast cancer becoming operable as a result of study treatment.

CDK: cyclin-dependent kinase; CTCAE: Common Terminology Criteria for Adverse Events; RANK: receptor activator of nuclear factor kappa-B; RCT: randomized controlled trial

Study design

Study MONARCH 3

The MONARCH 3 study is a double-blind RCT comparing abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole. The study enrolled postmenopausal women with locally advanced or metastatic HR-positive and HER2-negative breast cancer. Patients were not expected to be therapeutically indicated for chemotherapy or curative radiotherapy. Patients were to have received neither chemotherapy nor endocrine therapy for the locally advanced or metastatic stage. Patients with prior (neo)adjuvant endocrine therapy (e.g. antioestrogens or aromatase inhibitors) with a disease-free interval of ≤ 12 months after the end of treatment were excluded from the study. Patients had to have a Cooperative Oncology Group - Performance Status (ECOG-PS) of 0 or 1 at the time they joined the study.

A total of 493 patients were randomly assigned in a 2:1 ratio to treatment with either abemaciclib + anastrozole or letrozole (N = 328) or placebo + anastrozole or letrozole (N = 165). Randomization was stratified by type of disease (visceral metastases versus bone metastases only versus other) and prior (neo)adjuvant endocrine therapy (aromatase inhibitors versus other versus none). The aromatase inhibitor was chosen by the physician. In both study arms, approximately 20% of patients received anastrozole, and approximately 80% of patients received letrozole.

Treatment with the study medication of abemaciclib, anastrozole, and letrozole was largely in accordance with the respective SPCs [15-17].

Treatment continues until disease progression, participation in another study, or discontinuation of therapy at the discretion of the physician, patient, or sponsor. After treatment discontinuation, patients were allowed to start subsequent therapy. The choice of subsequent therapies is not limited. Switching patient treatment from the comparator arm to the intervention arm is not allowed.

The primary outcome of the MONARCH 3 study is PFS. Patient-relevant secondary outcomes are overall survival, morbidity outcomes, health-related quality of life, and AEs.

Data cutoffs

In the MONARCH 3 study, 4 planned interim analyses have already been conducted. The final analysis for overall survival, planned to occur after 315 deaths, is still pending. The present benefit assessment uses the most recent data cutoff of 2 July 2021, planned to occur after 252 deaths (4th interim analysis).

Study MONARCH plus

The MONARCH plus study is a double-blind RCT. The study enrolled postmenopausal women with locally recurrent or metastatic HR-positive, HER2-negative breast cancer who either had or had not received prior endocrine therapy for the advanced disease stage. In addition, the patients had to have received no previous chemotherapy in the locally recurrent or metastatic stage. Patients were not expected to be therapeutically indicated for chemotherapy or curative radiotherapy. Patients had to have an ECOG-PS of 0 or 1 at enrolment. The study consists of 2 different cohorts: Cohort A comparing abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole and Cohort B comparing abemaciclib + fulvestrant versus placebo + fulvestrant. Cohort A of the MONARCH plus study is relevant for the present benefit assessment. This is described below.

Cohort A

Cohort A included only patients who had not received any prior endocrine therapy in the locally recurrent or metastatic stage. Patients additionally had to meet at least 1 of the following criteria:

- recurrence ≤ 12 months after completion of adjuvant endocrine therapy or during adjuvant endocrine therapy (except with letrozole or anastrozole).
- recurrence > 12 months after completion of adjuvant endocrine therapy or no adjuvant endocrine therapy
- de novo metastatic disease without any prior endocrine therapy

A total of 306 patients in Cohort A of the MONARCH plus study were randomly assigned in a 2:1 ratio to treatment with either abemaciclib + anastrozole or letrozole (N = 207) or placebo + anastrozole or letrozole (N = 99). Randomization was based on type of disease (visceral metastases versus nonvisceral metastases) and prior (neo)adjuvant endocrine therapy (prior therapy with > 12 months' disease-free interval after treatment end versus prior therapy with ≤ 12 months disease-free interval after end of therapy versus no prior therapy). The aromatase inhibitor was chosen by the physician. In both study arms, approximately 25% of patients received anastrozole, and approximately 75% of patients received letrozole.

Treatment with the study medication of abemaciclib, anastrozole, and letrozole was largely in accordance with the respective SPCs [15-17].

Treatment continues until disease progression, participation in another study, or discontinuation of therapy at the discretion of the physician, patient, or sponsor. After treatment discontinuation, patients were allowed to start subsequent therapy. The choice of subsequent therapies is not limited. Patients were allowed to switch treatment from the comparator arm to the intervention arm only after the final data cutoff used in the present dossier assessment.

The primary outcome of the MONARCH plus study is PFS. Patient-relevant secondary outcomes are overall survival and outcomes on morbidity, health-related quality of life, and AEs.

Below, all descriptions of the MONARCH plus study refer to the study's Cohort A, which is relevant for the present benefit assessment.

Data cutoffs

For Cohort A of the MONARCH plus study, results are available from the interim analysis, planned to occur after 119 PFS events, and from the final analysis, planned to occur after 170 PFS events. The present benefit assessment uses the data cutoff for the final analysis dated 18 May 2020.

Planned duration of follow-up observation

Table 8 shows the prespecified duration of participant follow-up observation for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole

Study **Outcome category** **Outcome**	**Predefined follow-up observation**
MONARCH 3	
Mortality	
overall survival	Until death or study end
Morbidity	
symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23), health status (EQ-5D VAS)	Until 30 days after treatment end[a]
Health-related quality of life	
EORTC QLQ-C30 and EORTC QLQ-BR23	Until 30 days after treatment end[a]
Side effects	
all outcomes in the side effects category	Until 30 days after treatment end[a]
MONARCH plus	
Mortality	
overall survival	Until death or study end
Morbidity	
symptoms (EORTC QLQ-C30, mBPI-SF)	Up to 30 days after treatment end[a]
Health-related quality of life	
EORTC QLQ-C30	Until 30 days after treatment end[a]
Side effects	
all outcomes in the side effects category	Until 30 days after treatment end[a]

a. Treatment end was defined as discontinuation of abemaciclib/placebo and anastrozole/letrozole in the MONARCH 3 study, and as discontinuation of abemaciclib/placebo in MONARCH plus.

EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; mBPI-SF: modified Brief Pain Inventory-Short Form; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale

The observation durations for the outcomes of morbidity, health-related quality of life, and side effects are systematically shortened in both studies because these outcomes were surveyed only for the period of treatment with the study drug (plus 30 days). However, drawing a reliable conclusion on the total study period or the time until patient death would require obtaining data regarding these outcomes throughout the entire period, as was done for survival.

Characterization of the patients in the included studies

Table 9 shows the characteristics of the patients in the studies included.

Table 9: Characterization of the study populations as well as study/treatment discontinuation – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Study	**MONARCH 3**		**MONARCH plus**	
Characteristic **Category**	**Abemaciclib + anastrozole or letrozole**	**Placebo + anastrozole or letrozole**	**Abemaciclib + anastrozole or letrozole**	**Placebo + anastrozole or letrozole**
	N[a] = 328	**N[a] = 165**	**N[a] = 207**	**N[a] = 99**
Age [years], mean (SD)	63 (10)	63 (10)	56 (11)	56 (10)
Age group, n (%)				
< 65 years	180 (55)	91 (55)	157 (76)	83 (84)
≥ 65 years	148 (45)	74 (45)	50 (24)	16 (16)
Ancestry, n (%)				
White	186 (57)	102 (62)	24 (12)	8 (8)
Asian	103 (31)	45 (27)	182 (88)	89 (90)
Other	11 (3)[b]	7 (4)[b]	1 (< 1)[c]	2 (2)
Not reported	28 (9)	11 (7)	0 (0)	0 (0)
Region, n (%)				
Europe	166 (51)	93 (56)	0 (0)	0 (0)
Asia	102 (31)	42 (26)	182 (88)	89 (90)
North America	60 (18)	30 (18)	21 (10)	8 (8)
Africa	0 (0)	0 (0)	4 (2)	2 (2)
South America	0 (0)	0 (0)	0 (0)	0 (0)
ECOG-PS, n (%)				
0	192 (59)	104 (63)	70 (34)	43 (43)
1	136 (42)	61 (37)	137 (66)	56 (57)
Disease duration [months][d]				
Mean (SD)	79.6 (92.3)	74.5 (77.6)	78.1 (69.7)	67.1 (59.6)
Median [Q1; Q3]	53.5 [1.4; 132.0]	63.1 [2.2; 120.6]	65.1 [18.4; 115.7]	51.7 [17.7; 105.7]
Disease stage at study start, n (%)				
De novo metastatic	135 (41)	61 (37)	41 (20)	22 (22)
Recurrent metastatic	182 (56)	99 (60)	157 (76)	70 (71)
Locoregional recurrent	11 (3)	5 (3)	8 (4)	7 (7)
Missing	0 (0)	0 (0)	1 (< 1)	0 (0)
Type of disease, n (%)				
Visceral metastases	172 (52)	89 (54)	126 (61)	59 (60)
Nonvisceral metastases	156 (48)	76 (46)	81 (39)	40 (40)
Bone metastases only	70 (21)	39 (24)	ND	ND
Other	86 (26)	37 (22)	ND	ND
Patients with neoadjuvant endocrine therapy, n (%)	2 (< 1)	7 (4)	0 (0)	0 (0)

Table 9: Characterization of the study populations as well as study/treatment discontinuation – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Study	MONARCH 3		MONARCH plus	
Characteristic Category	Abemaciclib + anastrozole or letrozole	Placebo + anastrozole or letrozole	Abemaciclib + anastrozole or letrozole	Placebo + anastrozole or letrozole
	N[a] = 328	N[a] = 165	N[a] = 207	N[a] = 99
Patients with adjuvant endocrine therapy, n (%)	140 (43)	72 (44)	122 (59)	62 (63)
Disease-free interval, n (%)				
Recurrence during adjuvant endocrine therapy	ND	ND	24 (20[e])	17 (27[e])
≤ 12 months after the end of adjuvant endocrine therapy	9[f] (6[e])	6[f] (8[e])	11 (9[e])	3 (5[e])
> 12 months after the end of adjuvant endocrine therapy	ND	ND	87 (71[e])	41 (66[e])
≤ 24 months after the end of adjuvant endocrine therapy	22 (16[e])	19 (26[e])	ND	ND
> 24 months after the end of adjuvant endocrine therapy	115 (82[e])	53 (74[e])	ND	ND
Duration of disease-free interval [months], mean [min; max]	50.4 [0.0; 271.1]	37.4 [0.0; 186.2]	ND	ND
Prior (neo)adjuvant endocrine therapy, n (%)				
Aromatase inhibitor[g]	85 (26)	50 (30)	20 (10)	13 (13)
Anastrozole	46 (14)	26 (16)	6 (3)	3 (3)
Letrozole	29 (9)	23 (14)	11 (5)	5 (5)
Exemestane	14 (4)	8 (5)	9 (4)	9 (9)
Other[h]				
Tamoxifen	87 (27)	43 (26)	92 (44)	49 (50)
Toremifene	3 (1)	1 (< 1)	14 (7)	5 (5)
Goserelin	4 (1)	1 (< 1)	2 (1)	2 (2)
No (neo)adjuvant endocrine therapy	178 (54)	85 (52)	85 (41)	38 (38)
Treatment discontinuation, n (%)[i]	285 (87)[j]	157 (95)[j]	137 (66)[k]	85 (86)[k]
Study discontinuation, n (%)[i]	175 (53)[l]	108 (66)[l]	60 (29)[m]	37 (37)[m]

Table 9: Characterization of the study populations as well as study/treatment discontinuation – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Study	MONARCH 3		MONARCH plus	
Characteristic Category	Abemaciclib + anastrozole or letrozole	Placebo + anastrozole or letrozole	Abemaciclib + anastrozole or letrozole	Placebo + anastrozole or letrozole
	N[a] = 328	N[a] = 165	N[a] = 207	N[a] = 99

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Native American or Alaska Native, Black/African American, Native Hawaiian or Other Pacific Islander, multiple.
c. Black / African American.
d. Time from initial diagnosis to randomization.
e. Related to patients with adjuvant therapy.
f. Patients who were enrolled in the study despite the exclusion criterion "disease-free interval of ≤ 12 months after the end of (neo)adjuvant endocrine therapy" (protocol violators).
g. Patients with at least 1 drug in the category of aromatase inhibitors.
h. Listed were only drugs taken by ≥ 1% of patients in one of the studies; no summary analysis possible due to multiple entries.
i. Information for the data cutoffs 2 July 2021 (MONARCH 3) or 18 May 2020 (MONARCH plus).
j. Common reasons for treatment discontinuation in the intervention arm versus the control arm were disease progression (53% vs. 84%), AEs (16% vs. 2%), and patient decision (8% vs. 3%). Two patients in the intervention arm and 3 in the control arm were randomized but not treated.
k. Common reasons for treatment discontinuation in the intervention arm versus the control arm were disease progression (41% vs. 69%), AEs (18% vs. 3%), and patient decision (4% vs. 11%). Two patients in the intervention arm were randomized but not treated.
l. Common reasons for study discontinuation in the intervention arm versus control arm were death (44% vs. 57%) and patient decision (8% vs. 6%).
m. Common reason for study discontinuation in the intervention arm vs. control arm was death (23% vs. 25%).

ECOG-PS: Eastern Cooperative Oncology Group - Performance Status; max: maximum; min: minimum; n: number of patients in category; N: number of randomized patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation.

The characteristics of postmenopausal patients who have not yet received initial endocrine therapy in the locally advanced or metastatic stage are largely comparable between the study arms of the MONARCH 3 study and the MONARCH plus study (Cohort A).

The mean patient age at enrolment in the MONARCH 3 study was about 63 years. About 60% of the patients were White. Approximately 60% of patients had an ECOG-PS of 0, and about half had visceral metastases. The median disease duration was 80 months in the intervention arm and 75 months in the comparator arm.

The mean patient age at the start of the MONARCH plus study was 56 years. The study was conducted exclusively in non-European centres (see Table 6), with the vast majority of the patients being Asian. Approximately 60% of patients had an ECOG-PS of 1, and about 60% had

visceral metastases. The mean disease duration was 78 months in the intervention arm and 67 months in the comparator arm.

Differences between the studies are particularly evident for (1) age (patients in the MONARCH plus study were on average approximately 7 years younger), (2) the proportion of patients with de novo metastasis (approximately 40% of patients in the MONARCH 3 study and approximately 20% in the MONARCH plus study), and (3) ancestry (while the MONARCH 3 study included a majority of White patients, MONARCH plus participants were almost exclusively of Asian ancestry). In addition, the MONARCH plus study allowed including patients with ≤ 12 months' disease-free interval after the end of adjuvant endocrine therapy or during adjuvant therapy (a total of 18% of patients in the MONARCH plus study). In contrast, the MONARCH 3 study excluded patients with a disease-free interval ≤ 12 months after the end of adjuvant endocrine therapy (but contrary to protocol requirements, 3% of enrolled patients exhibited a disease-free interval ≤ 12 months).

The differences between the analysed study populations do not call into question the feasibility of a metaanalysis. The studies and the relevant study populations are deemed sufficiently comparable. For the benefit assessment, a fixed-effect model is therefore used to calculate metaanalyses.

Information on the course of the study

Table 10 shows patients' median and mean treatment durations and the median observation durations for individual outcomes. No information is available on the mean observation duration.

Table 10: Characterization of the course of the study – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Study **Duration of the study phase** **Outcome category**	**MONARCH 3 (data cutoff: 2/7/2021)**		**MONARCH plus (data cutoff: 18/05/2020)**	
	Abemaciclib + anastrozole or letrozole	**Placebo + anastrozole or letrozole**	**Abemaciclib + anastrozole or letrozole**	**Placebo + anastrozole or letrozole**
	N[a] = 328	N[a] = 165	N[a] = 207	N[a] = 99
Treatment duration [months[b]]				
Abemaciclib vs. placebo				
Median [Q1; Q3]	15.3 [4.5; 38.2]	13.9 [5.3; 27.4]	20.4 [6.7; 29.2]	12.4 [3.8; 22.3]
Mean (SD)	24.6 (24.0)	19.1 (18.3)	18.9 (11.9)	13.9 (10.7)
Anastrozole				
Median [Q1; Q3]	18.5 [ND]	10.2 [ND]	18.4 [10.8; 29.0]	14.7 [5.6; 22.3]
Mean (SD)	ND	ND	18.3 (11.5)	14.0 (9.2)
Letrozole				
Median [Q1; Q3]	17.0 [ND]	14.7 [ND]	21.1 [7.3; 29.4]	11.8 [3.7; 22.6]
Mean (SD)	ND	ND	19.0 (11.7)	14.0 (11.2)
Observation duration [months]				
Overall survival[c]				
Median [Q1; Q3]	70.2 [68.0; 73.0]	70.0 [68.1; 72.3]	30.1 [28.5; 33.5]	30.2 [28.2; 33.8]
Mean (SD)	ND	ND	ND	ND
Morbidity[d] (EORTC QLQ-C30)				
Median [Q1; Q3]	18.3 [6.5; 43.3]	13.4 [5.2; 26.0]	19.6 [7.4; 27.8]	11.7 [3.8; 23.1]
Mean (SD)	ND	ND	ND	ND
Morbidity[d] (EORTC QLQ-BR23, EQ-5D VAS)				
Median [Q1; Q3]	18.3 [6.5; 43.3]	13.4 [5.2; 26.0]	Outcome not recorded	
Mean (SD)	ND	ND	Outcome not recorded	
Morbidity (mBPI)[d]				
Median [Q1; Q3]	Outcome not recorded		19.6 [7.4; 27.8]	11.7 [3.8; 23.1]
Mean (SD)	Outcome not recorded		ND	ND
Health-related quality of life (EORTC QLQ-C30)[d]				
Median [Q1; Q3]	18.3 [6.5; 43.3]	13.4 [5.2; 26.0]	19.6 [7.4; 27.8]	11.7 [3.8; 23.1]
Mean (SD)	ND	ND	ND	ND
Health-related quality of life (EORTC QLQ-BR23)[d]				
Median [Q1; Q3]	18.3 [6.5; 43.3]	13.4 [5.2; 26.0]	Outcome not recorded	
Mean (SD)	ND	ND	Outcome not recorded	
Side effects[e]				
Median [Q1; Q3]	19.2 [6.8; 42.4]	14.9 [6.3; 28.4]	21.6 [8.5; 28.9]	13.4 [4.8; 23.3]
Mean (SD)	ND	ND	ND	ND

Table 10: Characterization of the course of the study – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Study **Duration of the study phase** **Outcome category**	**MONARCH 3 (data cutoff: 2/7/2021)**		**MONARCH plus (data cutoff: 18/05/2020)**	
	Abemaciclib + anastrozole or letrozole	**Placebo + anastrozole or letrozole**	**Abemaciclib + anastrozole or letrozole**	**Placebo + anastrozole or letrozole**
a. Number of analysed patients. d. Converted by IQWiG from data reported in weeks. c. Calculated using Kaplan-Meier method and inverse censoring based on ITT population. d. Calculated from the day of the first dose to the last analysable measurement. e. Calculated from date of first dose to earliest date out of last treatment day +30, death, lost to follow-up, date of data cut-off. EORTC: European Organisation for Research and Treatment of Cancer; mBPI-SF: modified Brief Pain Inventory-Short Form; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; VAS: visual analogue scale				

In both studies, the treatment durations are longer in the intervention arms than in the control arms. The observation duration for the outcome of overall survival was more than twice as long in the MONARCH 3 study, at about 70 months, than in the MONARCH plus study, at about 30 months. For the other outcomes, whose observation period was linked to treatment end (see Table 8), the observation periods were markedly shorter. For these outcomes, conclusions can therefore be drawn only about the time under treatment, which for the MONARCH 3 study, for example, represents a median of approximately 1/4 (intervention arm) and 1/5 (comparator arm) of the observation period for overall survival. It should be noted that for the MONARCH 3 study, time under treatment was defined as the time until discontinuation of the entire study medication, whereas for the MONARCH plus study, it was defined as the time until discontinuation of abemaciclib or placebo. Data for the entire observation period are missing for these outcomes.

In addition, the differences in treatment durations between the arms of the 2 studies result in differences in the observation periods for the outcomes. This evidence scenario has consequences regarding the interpretability of the outcomes which were observed for a shorter period (see Section I 4.1).

Subsequent therapies

Table 11 and Table 12 show the subsequent therapies patients received after discontinuation of the study medication in the MONARCH 3 and MONARCH plus studies.

Table 11: Information on subsequent antineoplastic therapies – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (MONARCH 3)

Study **Treatment type** **Drug**	**Patients with subsequent therapy n (%)**	
	Abemaciclib + anastrozole or letrozole **N = 328**	**Placebo + anastrozole or letrozole** **N = 165**
MONARCH 3 (data cutoff: 2/07/2021)		
Total	ND	ND
Systemic therapy[a]	218 (66.5)	142 (86.1)
Chemotherapy	122 (37.2)	98 (59.4)
Capecitabine	72 (22.0)	53 (32.1)
Cisplatin	4 (1.2)	9 (5.5)
Cyclophosphamide	25 (7.6)	18 (10.9)
Doxorubicin	25 (7.6)	16 (9.7)
Epirubicin	13 (4.0)	10 (6.1)
Eribulin	21 (6.4)	17 (10.3)
Fluorouracil	4 (1.2)	9 (5.5)
Gemcitabine	15 (4.6)	13 (7.9)
Paclitaxel	73 (22.3)	59 (35.8)
Vinorelbine	27 (8.2)	15 (9.1)
Endocrine therapy	181 (55.2)	121 (73.3)
Anastrozole	16 (4.9)	9 (5.5)
Exemestane	68 (20.7)	51 (30.9)
Fulvestrant	107 (32.6)	86 (52.1)
Letrozole	54 (16.5)	22 (13.3)
Tamoxifen	29 (8.8)	25 (15.2)
Other systemic therapy	34 (10.4)	26 (15.8)
Experimental therapy[b]	12 (3.7)	11 (6.7)
Targeted therapy	83 (25.3)	80 (48.5)
Everolimus	47 (14.3)	37 (22.4)
Palbociclib	26 (7.9)	42 (25.5)
Surgical procedure	13 (4.0)	11 (6.7)
Radiotherapy	51 (15.5)	43 (26.1)

a. ≥ 5% of patients in 1 treatment arm.
b. No information provided as to which therapies fall under this; abemaciclib falls under targeted therapies.

n: number of patients with subsequent therapy; N: number of analysed patients; ND: no data;
RCT: randomized controlled trial

Table 12: Information on subsequent antineoplastic therapies – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (MONARCH plus)

Study **Treatment type** **Drug**	**Patients with subsequent therapy n (%)**	
	Abemaciclib + anastrozole or letrozole **N = 205**	**Placebo + anastrozole or letrozole** **N = 99**
MONARCH plus (data cut-off: 18/05/2020)		
Total	ND	ND
Systemic therapy[a]	89 (43.4)	58 (58.6)
Chemotherapy	43 (21.0)	35 (35.4)
Capecitabine	24 (11.7)	27 (27.3)
Docetaxel	9 (4.4)	11 (11.1)
Gemcitabine	7 (3.4)	7 (7.1)
Paclitaxel	24 (11.7)	15 (15.2)
Vinorelbine	7 (3.4)	6 (6.1)
Endocrine therapy	56 (27.3)	40 (40.4)
Exemestane	14 (6.8)	14 (14.1)
Fulvestrant	22 (10.7)	26 (26.3)
Letrozole	18 (8.8)	1 (1.0)
Other systemic therapy	ND	ND
Experimental therapy[b]	7 (3.4)	8 (8.1)
Targeted therapy	8 (3.9)	7 (7.1)
Palbociclib	3 (1.5)	6 (6.1)
Surgical procedure	0 (0)	0 (0)
Radiotherapy	6 (2.9)	4 (4.0)

a. ≥ 5% of patients in 1 treatment arm.
b. No information provided as to which therapies fall under this; abemaciclib falls under targeted therapies.

n: number of patients with subsequent therapy; N: number of analysed patients; ND: no data;
RCT: randomized controlled trial

The company has not provided any information on the total number of patients who received subsequent therapy. In the MONARCH 3 study, 67% of patients in the intervention arm and 86% of patients in the comparator arm had received at least 1 subsequent systemic therapy. Within systemic therapies, the most common subsequent therapies were endocrine therapies followed by chemotherapies and targeted therapies. Targeted therapy was received by 25% of patients in the intervention arm and 49% of patients in the comparison arm.

In the MONARCH plus study, 43% of patients in the intervention arm and 59% of patients in the comparator arm had received at least 1 subsequent systemic therapy. In this study as well,

endocrine therapies were the most common subsequent therapies, followed by chemotherapies and targeted therapies. Targeted therapies were used significantly less frequently compared to the MONARCH 3 study (4% in the comparator arm and 7% in the intervention arm).

According to information provided in both studies' reports, endocrine therapies were more commonly used as the first subsequent therapy, while chemotherapies were more commonly used in later lines of therapy.

Overall, the subsequent therapies used in both studies largely correspond to the therapy recommendations stated in national guidelines [18,19].

Risk of bias across outcomes (study level)

Table 13 shows the risk of bias across outcomes (risk of bias at study level).

Table 13: Risk of bias across outcomes (study level) – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole

Study	Adequate random sequence generation	Allocation concealment	Blinding		Nonselective reporting	Absence of other aspects	Risk of bias at study level
			Patients	Treatment providers			
MONARCH 3	Yes	Yes	Yes	Yes	Yes	Yes	Low
MONARCH plus	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes is rated as low for both studies.

Transferability of the study results to the German health care context

MONARCH 3 study

The company argues that the results of the MONARCH 3 study can be transferred to the German health care context. It reports that the characteristics of study participants (e.g. in terms of age, family origin, and prognosis) are comparable to those of breast cancer patients in the locally advanced or metastatic stage in the German health care context. According to the company, the study treatment also complied with German and international treatment standards.

MONARCH plus study

The company presumes the study results of the MONARCH plus study to be transferable to the German healthcare context. It concedes that there are differences in terms of the ancestry of enrolled patients (predominantly Asian women) and the younger participant age compared to European patients. However, the company explains the comparatively younger participant age by the fact that breast cancer tends to occur earlier in Chinese patients than in Western patients. Nevertheless, it assesses the patient characteristics as sufficiently similar to the corresponding population in Germany. The company characterizes the study population as consisting of patients with a poor prognosis, citing, for example, the high proportion of patients with prognostically unfavourable visceral metastases and the fact that almost all patients had metastatic disease. Furthermore, the company cites the information provided by a current Chinese guideline [20] being largely in line with the recommendations by the German and European guidelines.

The company did not provide any further information on the transferability of MONARCH 3 and MONARCH plus study results to the German health care context.

I 4 Results on added benefit

I 4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms surveyed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30 (EORTC QLQ-C30) and the EORTC QLQ – Breast Cancer 23 (EORTC QLQ-BR23)
  - pain (measured using the modified questionnaire Brief Pain Inventory–Short Form [mBPI-SF])
  - health status measured using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - surveyed using the EORTC QLQ-C30 and the EORTC QLQ-BR23
- Side effects
  - SAEs
  - severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - discontinuation due to AEs
  - neutropoenia (company's Preferred Term [PT] collection, severe AEs)
  - diarrhoea (PT, severe AEs)
  - further specific AEs, if any

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

Table 14 shows the outcomes for which data were available from the included studies.

Table 14: Matrix of outcomes – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole

Study	Outcomes												
	Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-BR23)	Pain (mBPI-SF)[a]	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-BR23)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Neutropoenia (PT collection[d], severe AEs[b])	Diarrhoea (PT, severe AEs[b])	Further specific AEs[e]
MONARCH 3	Yes	Yes	Yes	No[f]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
MONARCH plus	Yes	Yes	No[f]	Yes	No[f]	Yes	No[f]	Yes	Yes	Yes	Yes	Yes	Yes

a. Measured using the symptom scale “pain at its worst in the last 24 hours".
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Discontinuation of 1 or more treatment components.
d. The company’s Module 4 A states that the events neutropenia (PT) and febrile neutropenia (PT) were analysed jointly; for a more detailed description of the outcome, see body of text below.
e. The following events were taken into account (coded according to MedDRA): blood and lymphatic system disorders (SOC, serious AEs), infections and infestations (SOC, serious AEs), metabolism and nutrition disorders (SOC, serious AEs), investigations (SOC, serious AEs), gastrointestinal tract disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), and eye disorders (SOC, AEs).
f. Outcome not recorded.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; MedDRA: Medical Dictionary for Regulatory Activities; mBPI-SF: modified Brief Pain Inventory – Short Form; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire – Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire – Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

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

For the patient-reported outcomes on symptoms, health status, and health-related quality of life, surveyed with the scales of the EORTC QLQ-C30, EORTC QLQ-BR23, and EQ-5D VAS, the company presents time-to-event analyses for time to first deterioration as well as for time to "sustained" deterioration by ≥ 10 points (EORTC QLQ instruments) or ≥ 15 points (EQ-5D VAS). Sustained deterioration was operationalized as deterioration by ≥ 10 or ≥ 15 points without subsequent improvement to a score below that level. The survey of patient-reported outcomes was discontinued 30 days after treatment end in each case (see Table 8). The median observation durations for the morbidity and health-related quality of life outcomes show that the observation durations for these outcomes are significantly shorter than the median observation duration for overall survival (see Table 10). For example, the median observation time for overall survival among patients in the MONARCH 3 study was 70 months

in both study arms. In contrast, the median observation times for patient-reported outcomes in the MONARCH 3 study was 18 months in the intervention arm and 13 months in the comparator arm (see Table 10). In the MONARCH plus study, observation durations for patient-reported outcomes were likewise longer in the intervention arm than in the comparator arm and shorter overall than observation durations for overall survival. As already described in detail in benefit assessment A21-153 on abemaciclib in combination with fulvestrant [13], this results, firstly, in the problem of the observation period for patient-reported outcomes covering only a very small proportion of the total observation time. In this situation, it is therefore not appropriate to speak of a permanent deterioration (as in previous dossiers on abemaciclib, e.g. [21,22]) or a sustained deterioration (as in the dossier for the present assessment). Rather, the deterioration is confirmed merely over the shortened observation period. Secondly, the substantial between-arm differences in observation periods mean that the available analyses cannot be interpreted. Confirmed deterioration across all subsequent values is potentially more difficult to achieve in the longer-observed intervention arm (abemaciclib treatment). In addition, it is unclear how many (if any) patients were included in the analysis who had deteriorated once at the last survey time point and for whom no confirmatory value was available at all.

Overall, in the present situation with markedly different observation durations between treatment arms, the analyses of "sustained" deterioration are not usable. In each case, the analyses of time until the first deterioration are used.

Documentation of AEs in the MONARCH 3 study

According to the statistical analysis plan (SAP) of the MONARCH 3 study, PTs and System Organ Classes (SOCs) were not consistently documented according to the classification prescribed by the Medical Dictionary for Regulatory Activities (MedDRA); instead, some PTs were combined for joint analysis into consolidated PTs. In some cases, this consolidation involved PTs from different SOCs. This also affects the AE outcomes used in the present benefit assessment, specifically blood and lymphatic system disorders, investigations, metabolism and nutrition disorders (each SOCs, severe AEs) and the outcome of neutropenia (severe AEs). In Module 4 A, the company does not specify whether any consolidated PTs were included in the AE analyses presented according to SOC or PT. However, based on the comparison with the study report data, some of the presented PTs for the frequent AEs in Module 4 A of the MONARCH 3 study were presumably also consolidated.

The AE analyses including the consolidated PTs from the MONARCH 3 study are used in the present benefit assessment despite the documentation deviating from the MedDRA classification based on the prespecified information as well as the substantial and numerous disadvantages of the intervention. Individual AE outcomes affected by the survey of consolidated PTs are discussed below.

Outcome of neutropenia (severe AEs)

According to information provided in the company's Module 4 A, the outcome neutropenia (severe AEs) was operationalized for the MONARCH 3 and MONARCH plus studies by jointly analysing the events of neutropenia (PT) and febrile neutropenia (PT). Contrary to the definition in Module 4 A, however, the SAP shows that the MONARCH 3 study predefined neutropenia as the consolidated PT of neutropenia via the 2 PTs neutropenia and neutrophil count decreased. In contrast to the MedDRA classification, the PT neutrophil count decreased was not documented under the SOC investigations but under the SOC blood and lymphatic system disorders via the consolidated PT of neutropenia. This predefined operationalization was also used in the initial evaluation of abemaciclib in combination with an aromatase inhibitor [7]. For the MONARCH plus study, neither a precise operationalization of neutropenia nor an analysis as a consolidated PT as in the MONARCH 3 study was predefined. However, it is evident from the study documents that the documentation differed from that in the MONARCH 3 study: rather than documenting the PT neutropenia of SOC blood and lymphatic system disorders at all (0 events), only the PT neutrophil count decreased of the SOC investigations was recorded. The PT febrile neutropenia, which the company additionally included in Module 4 A, was documented only very rarely according to both study reports (MONARCH 3: 3 versus 0 events; MONARCH plus: 1 versus 0 events); therefore, this PT does not substantially contribute to the total number of patients with neutropenia.

For both studies, it is generally unclear which PTs the dossier's Module 4 A included in the analyses of severe neutropenia. For the MONARCH 3 study, however, they are assumed to be the consolidated PT neutropenia and the PT febrile neutropenia. For the MONARCH plus study, in contrast, and contrary to the information provided by the company, the analysis presumably included the PT neutrophil count decreased and the PT febrile neutropenia. For the outcome of neutropenia (severe AEs), substantial harm is found according to the company's operationalization in Module 4 A (see Table 18). The presentation of other operationalizations or operationalizations which are shared by both studies would presumably not relevantly change the results for this outcome. Therefore, the company's analyses from Module 4 A for neutropenia (severe AEs) – in the form of a PT collection – were used.

Outcomes of blood and lymphatic system disorders as well as investigations (each SOCs, severe AEs)

In the MONARCH 3 study, consolidated PTs were likewise defined for other PTs from the SOC blood and lymphatic system disorders, and they included PTs from the SOC investigations. This applies, e.g. to the consolidated PT lymphopenia (joint analysis of the PTs lymphopenia and lymphocyte count decreased) or the consolidated PT leukopenia (joint analysis of the PTs leukopenia and leukocyte count decreased). As was the case for the outcome of neutropenia, the documentation in the MONARCH plus study differed from that in the MONARCH 3 study:

e.g. rather than documenting the PT lymphopenia or the PT leukopenia from the SOC blood and lymphatic system disorders at all, only the PT lymphocyte count decreased or leukocyte count decreased was surveyed from the SOC investigations. Thus, several PTs from the 2 SOCs, e.g. leukopenia / leukocyte count decreased or lymphopenia / lymphocyte count decreased, are documented only in the SOC blood and lymphatic system disorders in the MONARCH 3 study and only in SOC Investigations in the MONARCH plus study. For each of the outcomes diseases of the blood and lymphatic system as well as investigations (each SOC, severe AEs), significant harm is shown according to the company's operationalization in Module 4 A (see Table 18). These results would not be expected to change in a relevant manner if the AE events were documented in the same way in both studies. For the two specific AEs SOC blood and lymphatic system disorders (severe AEs) and SOC Investigations (severe AEs), the company's analyses in Module 4 A are therefore used.

Outcome of metabolism and nutrition disorders (SOC, severe AEs)

The MONARCH 3 study likewise defined consolidated PTs for the SOC metabolism and nutrition disorders which included PTs from the SOC investigations but documented them in the SOC metabolism and nutrition disorders. In addition to the SOC investigations (severe AEs), the SOC metabolism and nutrition disorders (severe AEs) was selected as a specific AE.

I 4.2 Risk of bias

Table 15 describes the risk of bias for the results of the relevant outcomes.

Table 15: Risk of bias across outcomes and risk of bias at the outcome level – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole

Study	Study level	Outcomes												
		Overall survival	Symptoms (EORTC QLQ-C30)	Symptoms (EORTC QLQ-BR23)	Pain (mBPI-SF)[a]	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30)	Health-related quality of life (EORTC QLQ-BR23)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Neutropoenia (PT collection[d], severe AEs[b])	Diarrhoea (PT, severe AEs[b])	Further specific AEs[e]
MONARCH 3	L	L	H[f]	H[f]	–[g]	H[f]	H[f]	H[f]	H[f]	H[f]	L[h]	H[f]	H[f]	H[f]
MONARCH plus	L	L	H[f]	–[g]	H[f]	–[g]	H[f]	–[g]	H[f]	H[f]	L[h]	H[f]	H[f]	H[f]

a. Measured using the symptom scale "pain at its worst in the last 24 hours".
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Discontinuation of 1 or more treatment components.
d. As stated by the company in Module 4 A, joint analysis of the events neutropenia (PT) and febrile neutropenia (PT); for a more detailed description of the outcome, see Section I 4.1.
e. The following events are taken into account (coded according to MedDRA): blood and lymphatic system disorders (SOC, serious AEs), infections and infestations (SOC, serious AEs), metabolism and nutrition disorders (SOC, serious AEs), investigations (SOC, serious AEs), gastrointestinal tract disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), and eye disorders (SOC, AEs).
d. High percentage of potentially informative censoring or incomplete observation with different treatment durations between treatment arms.
g. Outcome not surveyed.
h. Despite low risk of bias, the certainty of results for the outcome of discontinuation due to AEs is assumed to be limited (see running text below).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; EQ-5D: European Quality of Life Questionnaire – 5 Dimensions; H: high; MedDRA: Medical Dictionary for Regulatory Activities; mBPI-SF: modified Brief Pain Inventory – Short Form; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire – Breast Cancer 23; QLQ – C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias of the results for the outcome of overall survival is rated as low in both studies.

For the outcome of discontinuation due to AEs, the certainty of results is reduced in both studies, despite a low risk of bias. Premature treatment discontinuation for reasons other than AEs represents a competing event for the outcome to be recorded, discontinuation due to AEs. This means that while AEs that would have led to treatment discontinuation might occur after discontinuation for other reasons, it is no longer possible to survey the criterion of "discontinuation" for them. It is impossible to estimate how many AEs are affected by this issue.

For all other outcomes in the MONARCH 3 and MONARCH plus studies, the risk of bias of results due to incomplete observations for potentially informative reasons is rated as high, with treatment durations differing between treatment arms.

I 4.3 Results

Table 16 summarizes the results comparing abemaciclib + anastrozole or letrozole with placebo + anastrozole or letrozole in postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves for the time-to-event analyses of the outcomes in the included studies are shown in I Appendix B of the full dossier assessment. No Kaplan-Meier curves by the subgroup characteristic of age are available for the outcome global health status (first deterioration) regarding the MONARCH 3 study. For the MONARCH plus study, no Kaplan-Meier curves by the subgroup characteristic of age are available for the outcomes of global health status, social functioning (first deterioration each), or the outcome of SAEs. Results on common AEs can be found in I Appendix C of the full dossier assessment.

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Outcome category Outcome Study	Abemaciclib + anastrozole or letrozole		Placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Mortality					
Overall survival					
MONARCH 3	328	67.1 [59.3; NC] 158 (48.2)	165	54.5 [44.8; 62.6] 97 (58.8)	0.75 [0.58; 0.97]; 0.030
MONARCH plus	207	40.0 [40.0; NC] 49 (23.7)	99	NR [32.8; NC] 26 (26.3)	0.89 [0.55; 1.44]; 0.645
Total					0.78 [0.63; 0.98]; 0.034
Morbidity					
Symptoms (EORTC QLQ-C30 – first deterioration)[b]					
Fatigue					
MONARCH 3	327	3.7 [2.3; 4.0] 220 (67.3)	161	7.4 [4.7; 13.4] 83 (51.6)	1.50 [1.16; 1.93]; 0.001
MONARCH plus	205	1.9 [1.1; 3.7] 138 (67.3)	99	3.7 [1.9; 11.0] 59 (59.6)	1.19 [0.88; 1.61]; 0.278
Total					1.36 [1.12; 1.66]; 0.002
Nausea and vomiting					
MONARCH 3	327	7.4 [4.6; 9.2] 195 (59.6)	161	19.4 [9.2; 32.9] 74 (46.0)	1.51 [1.16; 1.98]; 0.002
MONARCH plus	205	22.6 [7.7; NC] 94 (45.9)	99	NR [11.4; NC] 35 (35.4)	1.25 [0.85; 1.85]; 0.280
Total					1.42 [1.14; 1.78]; 0.002
Pain					
MONARCH 3	327	11.1 [7.6; 15.8] 172 (52.6)	161	12.8 [7.5; 19.8] 78 (48.4)	1.08 [0.83; 1.41]; 0.564
MONARCH plus	205	14.9 [6.5; NC] 94 (45.9)	99	9.1 [5.6; NC] 46 (46.5)	0.94 [0.66; 1.33]; 0.693
Total					1.03 [0.83; 1.27]; 0.817

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Outcome category Outcome Study	Abemaciclib + anastrozole or letrozole		Placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Dyspnoea					
MONARCH 3	327	14.8 [11.5; 29.0] 153 (46.8)	161	37.4 [14.3; 54.4] 60 (37.3)	1.25 [0.92; 1.68]; 0.150
MONARCH plus	205	13.9 [7.6; NC] 96 (46.8)	99	27.8 [12.9; NC] 35 (35.4)	1.31 [0.89; 1.93]; 0.178
Total					1.27 [1.00; 1.61]; 0.048
Insomnia					
MONARCH 3	327	9.5 [7.6; 13.3] 170 (52.0)	161	14.9 [9.2; 37.8] 69 (42.9)	1.22 [0.92; 1.61]; 0.162
MONARCH plus	205	7.6 [5.8; 23.4] 106 (51.7)	99	11.1 [7.4; NC] 43 (43.4)	1.25 [0.87; 1.78]; 0.233
Total					1.23 [0.99; 1.53]; 0.068
Appetite loss					
MONARCH 3	327	5.7 [3.8; 9.4] 187 (57.2)	161	30.1 [11.1; 39.4] 64 (39.8)	1.69 [1.27; 2.25]; < 0.001
MONARCH plus	205	5.6 [1.9; 14.9] 113 (55.1)	99	19.7 [10.5; NC] 39 (39.4)	1.61 [1.12; 2.31]; 0.015
Total					1.66 [1.33; 2.08]; < 0.001
Constipation					
MONARCH 3	327	15.1 [11.5; 25.1] 151 (46.2)	161	13.9 [9.5; 62.7] 69 (42.9)	0.97 [0.73; 1.30]; 0.888
MONARCH plus	205	NR [30.9; NC] 70 (34.1)	99	NR [13.8; NC] 31 (31.3)	0.96 [0.63; 1.46]; 0.839
Total					0.97 [0.77; 1.23]; 0.792
Diarrhoea					
MONARCH 3	327	2.0 [1.9; 2.1] 240 (73.4)	161	22.1 [13.2; 33.2] 63 (39.1)	3.34 [2.52; 4.42]; < 0.001
MONARCH plus	205	1.0 [0.95; 1.05] 161 (78.5)	99	NR 20 (20.2)	7.67 [4.80; 12.27]; < 0.001
Total					4.16 [3.27; 5.29]; < 0.001[c]

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Outcome category Outcome Study	Abemaciclib + anastrozole or letrozole		Placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Symptoms (EORTC QLQ-BR23 – first deterioration)[b]					
Side effects of systemic therapy					
MONARCH 3	327	4.0 [3.7; 5.5] 213 (65.1)	161	13.2 [7.4; NC] 67 (41.6)	1.95 [1.48; 2.56]; < 0.001
MONARCH plus				Not recorded	
Arm symptoms					
MONARCH 3	327	9.2 [7.2; 11.3] 191 (58.4)	161	9.3 [5.8; 12.9] 84 (52.2)	1.08 [0.84; 1.40]; 0.529
MONARCH plus				Not recorded	
Chest symptoms					
MONARCH 3	327	61.9 [39.1; NC] 102 (31.2)	161	47.1 [28.5; NC] 44 (27.3)	1.03 [0.72; 1.46]; 0.883
MONARCH plus				Not recorded	
Upset by hair loss					
MONARCH 3				No suitable data[d]	
MONARCH plus				Not recorded	
Pain at its worst in the last 24 hours (mBPI-SF – first deterioration)[e]					
MONARCH 3				Not recorded	
MONARCH plus	205	NR [30.5; NC] 58 (28.3)	99	NR [18.9; NC] 32 (32.3)	0.77 [0.50; 1.19]; 0.249
Health status (EQ-5D VAS – first deterioration)[f]					
MONARCH 3	327	22.2 [13.0; 33.6] 142 (43.4)	161	30.4 [14.9; NC] 56 (34.8)	1.17 [0.86; 1.59]; 0.325
MONARCH plus				Not recorded	

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Outcome category Outcome Study	Abemaciclib + anastrozole or letrozole		Placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Health-related quality of life					
EORTC QLQ-C30 – first deterioration[g]					
Global health status					
MONARCH 3	327	7.6 [6.5; 11.0] 194 (59.3)	161	14.9 [7.9; 31.7] 74 (46.0)	1.32 [1.01; 1.73]; 0.038
MONARCH plus	205	8.5 [3.8; 16.7] 117 (57.1)	99	9.9 [5.8; 17.3] 51 (51.5)	1.04 [0.75; 1.45]; 0.804
Total					1.20 [0.98; 1.48]; 0.082
Physical functioning					
MONARCH 3	327	11.4 [9.3; 20.9] 170 (52.0)	161	19.4 [12.0; 43.3] 71 (44.1)	1.23 [0.93; 1.62]; 0.140
MONARCH plus	205	10.3 [5.6; 23.8] 108 (52.7)	99	11.6 [5.6; NC] 45 (45.5)	1.12 [0.79; 1.58]; 0.533
Total					1.18 [0.95; 1.47]; 0.127
Role functioning					
MONARCH 3	327	5.6 [4.0; 8.4] 202 (61.8)	161	11.1 [7.4; 16.0] 82 (50.9)	1.26 [0.98; 1.64]; 0.072
MONARCH plus	205	11.5 [3.9; 23.6] 105 (51.2)	99	11.8 [5.5; NC] 44 (44.4)	1.13 [0.80; 1.61]; 0.493
Total					1.22 [0.99; 1.50]; 0.065
Emotional functioning					
MONARCH 3	327	24.8 [14.4; 42.6] 137 (41.9)	161	16.9 [11.1; NC] 64 (39.8)	0.97 [0.72; 1.30]; 0.840
MONARCH plus	205	28.0 [14.1; NC] 86 (42.0)	99	20.3 [6.6; NC] 43 (43.4)	0.80 [0.56; 1.16]; 0.260
Total					0.90 [0.71; 1.13]; 0.370
Cognitive functioning					
MONARCH 3	327	7.4 [5.6; 10.7] 204 (62.4)	161	5.6 [3.7; 9.2] 92 (57.1)	0.93 [0.72; 1.19]; 0.612
MONARCH plus	205	3.7 [3.0; 6.5] 125 (61.0)	99	6.4 [3.3; 17.5] 51 (51.5)	1.19 [0.86; 1.65]; 0.298
Total					1.02 [0.83; 1.24]; 0.885

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Outcome category **Outcome** **Study**	**Abemaciclib + anastrozole or letrozole**		**Placebo + anastrozole or letrozole**		**Abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
Social functioning					
MONARCH 3	327	10.4 [5.8; 13.8] 184 (56.3)	161	12.7 [8.3; 27.6] 76 (47.2)	1.18 [0.90; 1.55]; 0.220
MONARCH plus	205	5.7 [3.7; 10.3] 116 (56.6)	99	11.8 [4.0; NC] 46 (46.5)	1.24 [0.88; 1.74]; 0.222
Total					1.20 [0.97; 1.49]; 0.086
EORTC QLQ-BR23 – first deterioration[g]					
Body image					
MONARCH 3	327	9.2 [7.4; 13.0] 158 (48.3)	161	60.8 [16.3; NC] 57 (35.4)	1.48 [1.09; 2.01]; 0.010
MONARCH plus				Not recorded	
Sexual functioning					
MONARCH 3	327	NR 74 (22.6)	161	NR 22 (13.7)	1.52 [0.94; 2.45]; 0.081
MONARCH plus				Not recorded	
Sexual enjoyment					
MONARCH 3				No suitable data[d]	
MONARCH plus				Not recorded	
Future perspective					
MONARCH 3	327	NR [47.9; NC] 108 (33.0)	161	NR [31.1; NC] 52 (32.3)	0.92 [0.66; 1.28]; 0.672
MONARCH plus				Not recorded	
Side effects					
AEs (supplementary information)					
MONARCH 3	327	0.2 [0.1; 0.2] 323 (98.8)	161	0.9 [0.5; 1.0] 152 (94.4)	–
MONARCH plus	205	0.2 [0.1; 0.2] 204 (99.5)	99	0.8 [0.4; 1.1] 89 (89.9)	–

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Outcome category Outcome Study	Abemaciclib + anastrozole or letrozole		Placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
SAEs					
MONARCH 3	327	50.3 [38.4; 65.9] 122 (37.3)	161	NR 29 (18.0)	1.95 [1.30; 2.93]; 0.001
MONARCH plus	205	NR 56 (27.3)	99	NR 11 (11.1)	2.17 [1.13; 4.14]; 0.016
Total					2.01 [1.42; 2.83]; < 0.001
Severe AEs[h]					
MONARCH 3	327	7.9 [4.8; 11.1] 224 (68.5)	161	NR [32.5; NC] 46 (28.6)	3.13 [2.28; 4.30]; < 0.001
MONARCH plus	205	7.4 [4.8; 11.1] 141 (68.8)	99	NR [22.7; NC] 29 (29.3)	2.96 [1.99; 4.42]; < 0.001
Total					3.07 [2.39; 3.93]; < 0.001
Discontinuation due to AEs[i]					
MONARCH 3	327	NR [63.0; NC] 98 (30.0)	161	NR 7 (4.3)	6.06 [2.81; 13.06]; < 0.001
MONARCH plus	205	NR 40 (19.5)	99	NR 4 (4.0)	3.42 [1.22; 9.58]; 0.013
Total					4.94 [2.67; 9.14]; < 0.001
Neutropoenia (PT collection, severe AEs[h,j])					
MONARCH 3	327	NR [60.6; NC] 89 (27.2)	161	NR 2 (1.2)	22.86 [5.63; 92.84]; < 0.001
MONARCH plus	205	NR 64 (31.2)	99	NR 8 (8.1)	4.01 [1.92; 8.37]; < 0.001
Total					5.84 [3.05; 11.21]; < 0.001[c]
Diarrhoea (PT, severe AEs[h])					
MONARCH 3	327	NR 32 (9.8)	161	NR 2 (1.2)	7.85 [1.88; 32.78]; < 0.001
MONARCH plus	205	NR 9 (4.4)	99	NR 1 (1.0)	3.73 [0.47; 29.46]; 0.181
Total					6.17 [1.90; 19.99]; 0.002

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Outcome category Outcome Study	Abemaciclib + anastrozole or letrozole		Placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Blood and lymphatic system disorders (SOC, severe AEs[h])					
MONARCH 3	327	46.3 [32.4; NR] 119 (36.4)	161	NR 5 (3.1)	12.97 [5.30; 31.74]; < 0.001
MONARCH plus	205	NR 27 (13.2)	99	NR 3 (3.0)	3.73 [1.13; 12.32]; 0.020
Total					8.29 [4.05; 16.96]; < 0.001
Infections and infestations (SOC, severe AEs[h])					
MONARCH 3	327	NR 33 (10.1)	161	NR 7 (4.3)	1.91 [0.84; 4.33]; 0.114
MONARCH plus	205	NR 12 (5.9)	99	NR 1 (1.0)	4.42 [0.57; 34.07]; 0.119
Total					2.15 [1.00; 4.59]; 0.049
Metabolism and nutrition disorders (SOC, severe AEs[h])					
MONARCH 3	327	NR 42 (12.8)	161	NR 5 (3.1)	3.78 [1.49; 9.57]; 0.003
MONARCH plus	205	NR 28 (13.7)	99	NR 1 (1.0)	11.93 [1.62; 87.70]; 0.002
Total					4.64 [2.0; 10.77]; < 0.001
Investigations[k] (SOC, severe AEs[h])					
MONARCH 3	327	NR 47 (14.4)	161	NR 8 (5.0)	2.66 [1.25; 5.64]; 0.008
MONARCH plus	205	21.5 [13.7; 27.0] 102 (49.8)	99	NR 16 (16.2)	3.40 [2.01; 5.76]; < 0.001
Total					3.13 [2.04; 4.83]; < 0.001
Gastrointestinal disorders (SOC, AEs)					
MONARCH 3	327	0.2 [0.2; 0.3] 297 (90.8)	161	4.2 [3.0; 8.9] 104 (64.6)	3.12 [2.48; 3.94]; < 0.001
MONARCH plus	205	0.2 [0.2; 0.3] 176 (85.9)	99	16.2 [5.6; NC] 48 (48.5)	3.48 [2.52; 4.81]; < 0.001
Total					3.24 [2.68; 3.91]; < 0.001

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Outcome category Outcome Study	Abemaciclib + anastrozole or letrozole		Placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Skin and subcutaneous tissue disorders (SOC, AEs)					
MONARCH 3	327	6.8 [5.7; 8.8] 182 (55.7)	161	43.3 [23.0; NC] 54 (33.5)	2.04 [1.50; 2.76]; < 0.001
MONARCH plus	205	NR [29.1; NC] 71 (34.6)	99	NR 18 (18.2)	1.84 [1.09; 3.08]; 0.019
Total					1.98 [1.53; 2.58]; < 0.001
Eye disorders (SOC, AEs)					
MONARCH 3	327	NR [65.4; NC] 71 (21.7)	161	NR 9 (5.6)	3.77 [1.88; 7.55]; < 0.001
MONARCH plus	205	NR 27 (13.2)	99	NR 4 (4.0)	3.01 [1.05; 8.61]; 0.031
Total					3.52 [1.97; 6.28]; < 0.001

a. Overall survival: Cox model with the stratification variables of prior endocrine therapy, type of disease, and with treatment as a covariate; p-value: stratified log-rank test (stratified analysis was prespecified for overall survival); all other outcomes: unstratified Cox model; p-value: log-rank test; metaanalysis: fixed-effect model.
b. A score increase by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).
c. IQWiG calculation: metaanalysis with fixed effect.
d. Unclear proportion of patients with missing values at baseline and during the course of the study.
e. Measured by the symptom scale "pain at its worst in the last 24 hours"; an increase of ≥ 2 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 10).
f. A score decrease by ≥ 15 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 100).
g. A score decrease by ≥ 10 points from baseline is deemed a clinically relevant deterioration (scale range 0 to 100).
h. Operationalized as CTCAE grade ≥ 3.
i. Discontinuation of 1 or more treatment components.
j. As stated by the company in Module 4 A, the events neutropenia (PT) and febrile neutropenia (PT) were analysed jointly; for more detailed description of the outcome, see Section I 4.1.
k. Among them, particularly in the MONARCH 3 study: alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased (see Table 23 of the full dossier assessment); in the MONARCH plus study: neutrophil count decreased, leukocyte count decreased, alanine aminotransferase increased, aspartate aminotransferase increased, platelet count decreased, lymphocyte count decreased (see Table 27 of the full dossier assessment).

Table 16: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Outcome category Outcome Study	Abemaciclib + anastrozole or letrozole		Placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; mBPI-SF: modified Brief Pain Inventory – Short Form; MedDRA: Medical Dictionary for Regulatory Activities; N: number of analysed patients; n: number of patients with (at least 1) event; NC: not calculable; NR: not reached; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire – Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale					

On the basis of the data available from the MONARCH 3 and MONARCH plus studies, a maximum of 1 proof, e.g. of added benefit, can be derived for the outcome overall survival and a maximum of indications for the other outcomes due to the high risk of bias or the limited certainty of results (discontinuation due to AEs). Despite the high risk of bias, the certainty of conclusions for results might not be downgraded for certain outcomes (see description of results below). For outcomes whose results were classified as highly biased and for which only results based on 1 study are available, at most hints can be derived.

Mortality

Overall survival

For the outcome of overall survival, the predefined stratified analysis (referred to as sensitivity analysis in the company's Module 4 A) is used. The results of the unstratified analysis, which was primarily used by the company, differ only minimally and have no impact on the extent or statistical significance in the metaanalysis.

For the outcome of overall survival, the metaanalysis shows a statistically significant difference in favour of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. This results in proof of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. It should be noted that the benefit of abemaciclib in the MONARCH 3 study does not become apparent until approximately 30 months after randomization (see Figure 1). Until then, the Kaplan-Meier curves of both treatment arms look

similar. The observation duration in the MONARCH plus study is much shorter, but the picture is similar to that in the MONARCH 3 study (see Figure 39 of the full report).

Morbidity

Symptoms (EORTC QLQ-C30)

Fatigue, nausea and vomiting, appetite loss

For each of the outcomes of fatigue, nausea and vomiting as well as appetite loss, the metaanalysis shows a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. For each of them, this results in an indication of lesser benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

Diarrhoea

For the outcome of diarrhoea, the metaanalysis shows a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole. Despite a high risk of bias, this outcome is associated with a high certainty of results due to the effect size observed already early in both studies (see Figure 9 and Figure 47 of the full report). For this outcome, this results in proof of lesser benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

Dyspnoea

For the outcome of dyspnoea, the metaanalysis shows a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. The difference, however, is no more than marginal for this outcome in the category of non-serious/non-severe symptoms / late complications. Consequently, there is no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven for this outcome.

Pain, insomnia, and congestion

The metaanalysis does not show a statistically significant difference between treatment groups for any of the outcomes of pain, insomnia, or constipation. For each of these outcomes, this results in no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Symptoms (EORTC QLQ-BR23)

EORTC QLQ-BR23 was surveyed only in the MONARCH 3 study.

Side effects of systemic therapy

For the outcome of side effects of systemic therapy, a statistically significant difference was found to the disadvantage of abemaciclib + anastrozole or letrozole in comparison with

anastrozole or letrozole. This results in a hint of lesser benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

Arm symptoms and chest symptoms

No statistically significant difference between treatment groups was shown for the outcomes of arm symptoms or chest symptoms. For each of these outcomes, this results in no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Upset by hair loss

No suitable data are available for the outcome of upset by hair loss because the proportion of patients with missing values at baseline and during the course of the study was unclear. For this outcome, this results in no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Pain (mBPI-SF)

The outcome of pain (mBPI-SF), operationalized as pain at its worst in the last 24 hours, was surveyed only in the MONARCH plus study. No statistically significant difference between treatment arms was found for this outcome. For this outcome, this results in no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

The outcome of health status (EQ-5D VAS) was recorded only in the MONARCH 3 study. No statistically significant difference between treatment arms was found for this outcome. For this outcome, this results in no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Health-related quality of life

EORTC QLQ-C30

Physical functioning, role functioning, emotional functioning, and cognitive functioning

The metaanalysis showed no statistically significant differences between treatment arms for any of the outcomes of physical functioning, role functioning, emotional functioning, or cognitive functioning. For each of these outcomes, this results in no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Global health status and social functioning

For the outcomes of global health status and social functioning, the metaanalysis does not show a statistically significant difference between treatment groups. However, both

outcomes exhibited an effect modification by the characteristic of age. In women ≥ 65 years of age, both outcomes are associated with an indication of lesser benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. For women < 65 years of age, both outcomes are associated with no hint of added benefit or lesser benefit of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven for these outcomes in women < 65 years of age.

EORTC QLQ-BR23

EORTC QLQ-BR23 was surveyed only in the MONARCH 3 study.

Body image

For the outcome of body image, there is a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole comparison with anastrozole or letrozole. This results in a hint of lesser benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

Sexual functioning and future perspective

No statistically significant difference between treatment groups was shown for the outcomes of sexual functioning or future perspective. For each of these outcomes, this results in no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Sexual enjoyment

No suitable data are available for the outcome of sexual enjoyment due to the unclear proportion of patients with missing values at baseline and during the course of the study. For this outcome, this results in no hint of added benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, the metaanalysis shows a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. However, there is an effect modification by the attribute of age. In women ≥ 65 years, this results in an indication of greater harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. For women < 65 years of age, there is no hint of greater or lesser harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; greater or lesser harm is therefore not proven for these outcomes in women < 65 years of age.

Severe AEs, discontinuation due to AEs

For each of the outcomes of severe AEs and discontinuation due to AEs, the metaanalysis shows a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. For each of these outcomes, this results in an indication of greater harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

Specific AEs

Neutropoenia, blood and lymphatic system disorders (each severe AEs)

For each of the outcomes of neutropoenia and blood and lymphatic system disorders (severe AEs), the metaanalysis shows a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. Despite a high risk of bias, these outcomes are associated with a high certainty of results due to the size of the effects observed already early in the MONARCH 3 study and almost exclusively in the intervention arm (see Figure 26, Figure 28, Figure 58, and Figure 60 of the full report). For each of these outcomes, this results in proof of greater harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

Diarrhoea, infections and infestations, metabolism and nutrition disorders, investigations (each severe AEs), gastrointestinal disorders, skin and subcutaneous tissue disorders, and eye disorders (each AEs)

For each of the outcomes of diarrhoea, infections and infestations, metabolism and nutrition disorders, investigations (each severe AEs), gastrointestinal disorders, skin and subcutaneous tissue disorders, and eye disorders (each AEs), the metaanalysis showed a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. For each of these outcomes, this results in an indication of greater harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

I 4.4 Subgroups and other effect modifiers

The present benefit assessment accounts for the following subgroup characteristics:

- age (< 65 years, ≥ 65 years)
- type of disease (visceral metastases versus non-visceral metastases)

The above characteristics were defined a priori. For the MONARCH 3 study, the categories visceral metastases versus bone metastases only versus other were predefined for the characteristic of type of disease; for the MONARCH plus study, the categories visceral metastases versus non-visceral metastases were predefined. For the MONARCH plus study, no information is available on the subgroup with 3 interventions (as in the MONARCH 3 study).

Interaction tests are performed when 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 1 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 presented only if there is a statistically significant and relevant effect in at least one subgroup. Subgroup results where the extent did not differ between subgroups are not presented.

Table 17: Subgroups (health-related quality of life, side effects) – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Outcome Characteristic Study Subgroup	Abemaciclib + anastrozole or letrozole		Placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole	
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]	p-value[b]
Health-related quality of life						
EORTC QLQ-C30 – global health status, first deterioration[c]						
Age						
MONARCH 3						
< 65 years	179	9.2 [5.69; 12.46] 107 (59.8)	89	14.9 [5.16; 31.73] 43 (48.3)	1.09 [0.77; 1.56]	0.619
≥ 65 years	148	7.4 [5.56; 12.89] 87 (58.8)	72	24.0 [9.24; NC] 31 (43.1)	1.67 [1.11; 2.51]	0.013
MONARCH plus						
< 65 years	156	11.3 [5.59; 24.00] 86 (55.1)	83	9.7 [2.99; 16.83] 42 (50.6)	0.92 [0.63; 1.33]	0.640
≥ 65 years	49	1.9 [1.84; 9.37] 31 (63.3)	16	17.3 [0.95; NC] 9 (56.3)	1.69 [0.78; 3.65]	0.173
Total					Interaction:	0.025
< 65 years					1.00 [0.78; 1.30]	0.974
≥ 65 years					1.67 [1.16; 2.40]	0.005
EORTC QLQ-C30 – Social functioning, first deterioration[c]						
Age						
MONARCH 3						
< 65 years	179	14.8 [9.90; 29.49] 94 (52.5)	89	9.3 [5.56; 27.58] 46 (51.7)	0.82 [0.58; 1.17]	0.276
≥ 65 years	148	5.6 [3.72; 10.16] 90 (60.8)	72	24.9 [9.24; NC] 30 (41.7)	1.87 [1.24; 2.83]	0.002
MONARCH plus						
< 65 years	156	6.5 [2.83; 12.23] 88 (56.4)	83	11.1 [1.91; NC] 40 (48.2)	1.09 [0.75; 1.58]	0.668
≥ 65 years	49	3.7 [1.41; 11.15] 28 (57.1)	16	NR [7.36; NC] 6 (37.5)	2.36 [0.96; 5.82]	0.054
Total					Interaction:	0.002
< 65 years					0.94 [0.73; 1.22]	0.634
≥ 65 years					1.95 [1.34; 2.84]	< 0.001

Table 17: Subgroups (health-related quality of life, side effects) – RCT, direct comparison: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Outcome Characteristic Study Subgroup	Abemaciclib + anastrozole or letrozole		Placebo + anastrozole or letrozole		Abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole	
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]	p-value[b]
Side effects						
SAEs						
Age						
MONARCH 3						
< 65 years	179	65.9 [46.45; NC] 49 (27.4)	89	NR [36.56; NC] 16 (18.0)	1.15 [0.65; 2.04]	0.622
≥ 65 years	148	27.2 [14.27; 48.33] 73 (49.3)	72	NR 13 (18.1)	3.17 [1.76; 5.73]	< 0.001
MONARCH plus						
< 65 years	156	NR 34 (21.8)	83	NR 7 (8.4)	1.92 [0.85; 4.36]	0.112
≥ 65 years	49	20.4 [7.63; NC] 22 (44.9)	16	NR [17.06; NC] 4 (25.0)	2.70 [0.93; 7.88]	0.058
Total					Interaction:	0.023
< 65 years					1.36 [0.85; 2.17]	0.196
≥ 65 years					3.06 [1.82; 5.12]	< 0.001

a. HR: unstratified Cox model; meta-analysis: fixed effect model.
b. p-value: log-rank test; interaction p-value from metaanalysis (Cochran`s Q-test for heterogeneity).
c. A decrease by ≥ 10 points from baseline is defined as a clinically relevant deterioration (scale range 0 to 100).

CI: confidence interval; EORTC: European Organization for Research and Treatment of Cancer; HR: hazard ratio; N: number of analysed patients; n: number of patients with (at least 1) event; NC: not calculable; NR: not reached; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event

Health-related quality of life

EORTC QLQ-C30

Global health status and social functioning

For the outcomes of global health status and social functioning, there is an effect modification by the characteristic of age. For patients ≥ 65 years, the metaanalysis shows a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole, while for

patients < 65 years of age, the metaanalysis shows no statistically significant difference. For patients ≥ 65 years of age, this results in an indication of lesser benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. For patients < 65 years of age, there is no hint of added benefit or lesser benefit for abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

Side effects

SAEs

For the outcome of SAEs, there was an effect modification by the attribute of age. For patients ≥ 65 years of age, the metaanalysis shows a statistically significant difference to the disadvantage of abemaciclib + anastrozole or letrozole, while for patients < 65 years, the metaanalysis shows no statistically significant difference. For patients ≥ 65years of age, this results in an indication of greater harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole. For patients < 65 years of age, there is no hint of greater or lesser harm from abemaciclib + anastrozole or letrozole in comparison with anastrozole or letrozole; greater or lesser harm is therefore not proven patients < 65 years of age.

I 5 Probability and extent of added benefit

The probability and extent of added benefit 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 IQWiG General Methods [1].

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

I 5.1 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 I 4 (see Table 18).

Determination of the outcome category for symptoms outcomes and for the outcome of discontinuation due to AEs

For the below symptoms outcomes and for the outcome of discontinuation due to AEs, it is impossible to infer from the dossier whether they are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Symptoms outcomes (EORTC QLQ-C30, EORTC QLQ-BR23)

For the symptoms outcomes collected with the EORTC QLQ-C30 and EORTC QLQ-B23 instruments, no information is available to justify their classification as serious/severe. These outcomes were therefore assigned to the outcome category of non-serious/non-severe symptoms / late complications.

Outcome of discontinuations due to AEs

For the MONARCH 3 study, no information is available on severity as per CTCAE or on the proportion of discontinuations of at least 1 treatment component due to AEs which involved SAEs. In the MONARCH plus study, the proportion of SAEs was 25% in the intervention arm (10 of 40 events) and 100% in the comparator arm (4 of 4 events). Again, information on severity as per CTCAE is missing. Therefore, the outcome of discontinuation due to AEs is generally allocated to the category of non-serious/non-severe side effects. Due to the missing information, however, it is impossible to rule out that it actually belongs in the category of serious / severe side effects.

Table 18: Extent of added benefit at outcome level: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Outcomes with observation throughout the study		
Mortality		
Overall survival	40.0–67.1 vs. NR –54.5[c] HR: 0.78 [0.63; 0.98] p = 0.034 Probability: proof	Outcome category: mortality $0.95 \leq CI_u < 1.00$ Added benefit; extent: minor
Outcomes with shortened observation period		
Morbidity		
Symptoms, (EORTC QLQ-C30 – first deterioration by ≥ 10 points)		
Fatigue	1.9–3.7 vs. 3.7–7.4[c] HR: 1.36 [1.12; 1.66] HR: 0.74 [0.60; 0.89][d] p = 0.002 Probability: indication	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Lesser benefit; extent: minor
Nausea and vomiting	7.4–22.6 vs. NR –19.4[c] HR: 1.42 [1.14; 1.78] HR: 0.70 [0.56; 0.87][d] p = 0.002 Probability: indication	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Lesser benefit; extent: minor
Pain	11.1–14.9 vs. 9.1–12.8[c] HR: 1.03 [0.83; 1.27]; p = 0.817	Lesser/added benefit not proven
Dyspnoea	13.9–14.8 vs. 27.8–37.4[c] HR: 1.27 [1.002; 1.61] HR: 0.79 [0.62; 0.998][d] p = 0.048 Probability: indication	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser/added benefit not proven[e]
Insomnia	7.6–9.5 vs. 11.1–14.9[c] HR: 1.23 [0.99; 1.53] p = 0.068	Lesser/added benefit not proven
Appetite loss	5.6–5.7 vs. 19.7–30.1[c] HR: 1.66 [1.33; 2.08] HR: 0.60 [0.48; 0.75][d] p < 0.001 Probability: indication	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.80$ Lesser benefit, extent: considerable

Table 18: Extent of added benefit at outcome level: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Constipation	NR–15.1 vs. NR–13.9[c] HR: 0.97 [0.77; 1.23] p = 0.792	Lesser/added benefit not proven
Diarrhoea	1.0–2.0 vs. NR–22.1[c] HR: 4.16 [3.27; 5.29] HR: 0.24 [0.19; 0.30][d] p < 0.001 Probability: proof	Outcome category: non-serious/non-severe symptoms / late complications CI_u < 0.80 Lesser benefit, extent: considerable
Symptoms, (EORTC QLQ-BR23 – first deterioration by ≥ 10 points)[f]		
Side effects of systemic therapy	4.0 vs.13.2 HR: 1.95 [1.48; 2.56] HR: 0.51 [0.39; 0.68][d] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications CI_u < 0.80 Lesser benefit, extent: considerable
Arm symptoms	9.2 vs. 9.3 HR: 1.08 [0.84; 1.40] p = 0.529	Lesser/added benefit not proven
Chest symptoms	61.9 vs. 47.1 HR: 1.03 [0.72; 1.46] p = 0.883	Lesser/added benefit not proven
Upset by hair loss	No suitable data	Lesser/added benefit not proven
Pain (mBPI-SF) – first deterioration by ≥ 2 points		
Pain at its worst in the last 24 hours[g]	NR vs. NR HR: 0.77 [0.50; 1.19] p = 0.249	Lesser/added benefit not proven

Table 18: Extent of added benefit at outcome level: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Health status (EQ-5D VAS – first deterioration by ≥ 15)		
EQ-5D VAS[f]	22.2 vs. 30.4 HR: 1.17 [0.86; 1.59] p = 0.325	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 – first deterioration by ≥ 10 points		
Global health status		
Age		
< 65 years	9.2– 11.3 vs. 9.7–14.9[c] HR: 1.00 [0.78; 1.30] p = 0.974	Lesser/added benefit not proven
≥ 65 years	1.9–7.4 vs. 17.3–24.0[c] HR: 1.67 [1.16; 2.40] HR: 0.60 [0.42; 0.86][d] p = 0.005 Probability: indication	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Lesser benefit; extent: considerable
Physical functioning	10.3–11.4 vs. 11.6–19.4[c] HR: 1.18 [0.95; 1.47] p = 0.127	Lesser/added benefit not proven
Role functioning	5.6–11.5 vs. 11.1–11.8[c] HR: 1.22 [0.99; 1.50] p = 0.065	Lesser/added benefit not proven
Emotional functioning	24.8–28.0 vs. 16.9–20.3[c] HR: 0.90 [0.71; 1.13] p = 0.370	Lesser/added benefit not proven
Cognitive functioning	3.7–7.4 vs. 5.6–6.4[c] HR: 1.02 [0.83; 1.24] p = 0.885	Lesser/added benefit not proven

Table 18: Extent of added benefit at outcome level: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Social functioning		
Age		
< 65 years	6.5–14.8 vs. 9.3–11.1[c] HR: 0.94 [0.73; 1.22] p = 0.634	Lesser/added benefit not proven
≥ 65 years	3.7–5.6 vs. NR –24.9[c] HR: 1.95 [1.337; 2.84] HR: 0.51 [0.35; 0.748][d] p < 0.001 Probability: indication	Outcome category: health-related quality of life CI_u < 0.75, risk ≥ 5% Lesser benefit, extent: major
EORTC QLQ-BR23 – first deterioration by ≥ 10 points[f]		
Body image	9.2 vs. 60.8 HR: 1.48 [1.09; 2.01] HR: 0.68 [0.50; 0.92][d] p = 0.010 Probability: hint	Outcome category: health-related quality of life 0.90 ≤ CI_u < 1.00 Lesser benefit; extent: minor
Sexual functioning	NR vs. NR HR: 1.52 [0.94; 2.45] p = 0.081	Lesser/added benefit not proven
Sexual enjoyment	No suitable data	Lesser/added benefit not proven
Future perspective	NR vs. NR HR: 0.92 [0.66; 1.28] p = 0.672	Lesser/added benefit not proven
Side effects		
SAEs		
Age		
< 65 years	NR–65.9 vs. NR–NR [c] HR: 1.36 [0.85; 2.17] p = 0.196	Lesser/added benefit not proven
≥ 65 years	20.4–27.2 vs. NR–NR[c] HR: 3.06 [1.82; 5.12] HR: 0.33 [0.20; 0.55][d] p < 0.001 Probability: indication	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Greater harm; extent: major

Table 18: Extent of added benefit at outcome level: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Severe AEs	7.4–7.9 vs. NR–NR[c] HR: 3.07 [2.39; 3.93] HR: 0.33 [0.25; 0.42][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	NR– NR vs. NR–NR HR: 4.94 [2.67; 9.14] HR: 0.20 [0.11; 0.37][d] p < 0.001 Probability: indication	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm, extent: considerable
Neutropenia (severe AEs)	NR–NR vs. NR–NR HR: 5.84 [3.05; 11.21] HR: 0.17 [0.09; 0.33][d] p < 0.001 Probability: proof	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Greater harm; extent: major
Diarrhoea (severe AEs)	NR–NR vs. NR–NR HR: 6.17 [1.90; 19.99] HR: 0.16 [0.05; 0.53][d] p = 0.002 Probability: indication	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Greater harm; extent: major
Blood and lymphatic system disorders (severe AEs)	NR–46.3 vs. NR-NR [c] HR: 8.29 [4.05; 16.96] HR: 0.12 [0.06; 0.25][d] p < 0.001 Probability: proof	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Greater harm; extent: major
Infections and infestations (severe AEs)	NR– NR vs. NR–NR HR: 2.15 [1.004; 4.59] HR: 0.47 [0.22; 0.996][d] P =0.049 Probability: indication	Outcome category: serious/severe side effects 0.90 ≤ CI_u < 1.00 Greater harm; extent: minor
Metabolism and nutrition disorders (severe AEs)	NR– NR vs. NR–NR HR: 4.64 [2.0; 10.77] HR: 0.22 [0.09; 0.5][d] p < 0.001 Probability: indication	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Greater harm; extent: major

Table 18: Extent of added benefit at outcome level: abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole (multipage table)

Observation period **Outcome category** **Outcome** **Effect modifier** **Subgroup**	**Abemaciclib + anastrozole or letrozole versus placebo + anastrozole or letrozole** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Investigations (severe AEs)	NR–21.5 vs. NR–NR[c] HR: 3.13 [2.04; 4.83] HR: 0.32 [0.21; 0.49][d] p < 0.001 Probability: indication	Outcome category: serious/severe side effects CI_u < 0.75; risk ≥ 5% Greater harm; extent: major
Gastrointestinal disorders (AEs)	0.2–0.2 vs. 4.2–16.2[c] HR: 3.24 [2.68; 3.91] HR: 0.31 [0.26; 0.37][d] p < 0.001 Probability: indication	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm; extent: considerable
Skin and subcutaneous tissue disorders (AEs)	NR–6.8 vs. NR–43.3[c] HR: 1.98 [1.53; 2.58] HR: 0.51 [0.39; 0.65][d] p < 0.001 Probability: indication	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm; extent: considerable
Eye disorders (AEs)	NR–NR vs. NR–NR HR: 3.52 [1.97; 6.28] HR: 0.28 [0.16; 0.51][d] p < 0.001 Probability: indication	Outcome category: non-serious/non-severe side effects CI_u < 0.80 Greater harm; extent: considerable

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Minimum and maximum quantiles of time to event per treatment arm in the included studies.
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.
e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
f. Surveyed only in the MONARCH 3 study.
g. Surveyed only in the MONARCH plus study.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; HR: hazard ratio; mBPI-SF: modified Brief Pain Inventory – Short Form; NR: not reached; QLQ-BR23: Quality of Life Questionnaire – Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire– Core 30; SAE: serious adverse event; VAS: visual analogue scale

I 5.2 Overall conclusion on added benefit

Table 19 summarizes the results taken into account in the overall conclusion on the extent of added benefit.

Table 19: Favourable and unfavourable effects from the assessment abemaciclib + anastrozole or in comparison with anastrozole or letrozole (multipage table)

Favourable effects	Unfavourable effects
Outcomes with observation throughout the study	
Mortality ▪ Overall survival: proof of added benefit – extent: minor	–
Outcomes with shortened observation period	
–	Non-serious/non-severe symptoms / late complications ▪ Fatigue, nausea and vomiting: indication of lesser benefit – extent: minor ▪ Appetite loss: indication of lesser benefit – extent: considerable ▪ Diarrhoea: hint of lesser benefit – extent: considerable ▪ Side effects of systemic therapy: hint of lesser benefit – extent: considerable
–	Health-related quality of life ▪ Global health status, social functioning: ▫ Age ≥ 65 years: indication of lesser benefit – extent: considerable (global health status) to major (social functioning) ▪ Body image: hint of lesser benefit – extent: minor
–	Serious/severe side effects ▪ SAEs: ▫ Age (≥ 65 years): indication of greater harm – extent: major ▪ Severe AEs: indication of greater harm – extent: major, including ▫ neutropoenia, blood and lymphatic system disorders (severe AEs each): proof of greater harm – extent: major ▫ Further specific AEs: indication of greater harm – extent: minor or major (including diarrhoea, metabolism and nutrition disorders, investigations [severe AEs each] – extent: major; infections and infestations [severe AEs] – extent: minor)

Table 19: Favourable and unfavourable effects from the assessment abemaciclib + anastrozole or in comparison with anastrozole or letrozole (multipage table)

Favourable effects	Unfavourable effects
–	Non-serious/non-severe side effects ▪ Discontinuation due to AEs: indication of greater harm – extent: considerable ▪ Specific AEs: indication of greater harm – extent: considerable (including gastrointestinal disorders, skin and subcutaneous tissue disorders, eye disorders [each AEs])
AE: adverse event; SAE: serious adverse event	

Overall, a favourable effect in overall survival is offset by numerous unfavourable effects in the outcome categories of morbidity, health-related quality of life, and side effects. Data across the entire observation period are available only for overall survival. All unfavourable effects are based exclusively on the shortened observation period.

For the outcome of overall survival, there is proof of minor added benefit. Disadvantages in the morbidity category are associated with 1 proof, 1 hint, and indications of lesser benefit, depending on the symptom, and are at most of considerable extent. In the outcome category of health-related quality of life, there are 1 hint of lesser benefit of minor extent as well as 2 indications of lesser benefit, with an extent of at most of major, in women ≥ 65 years of age. Because of their size and certainty of reporting, the effects concerning severe AEs are determinant for the derivation of harm. They are evident in the overall rate of severe AEs as well as in numerous specific severe AEs. They are largely blood and lymphatic system disorders, in particular severe neutropenia (proof of greater harm of major extent). In addition, greater harm is found regarding severe diarrhoea, metabolism and nutrition disorders, and infections and infestations, among others (indications of greater harm, at most of major extent). Further, greater harm is found in the overall rates of SAEs (in this case restricted to women ≥ 65 years) and discontinuations due to AEs.

In summary, weighing the favourable effect of minor extent against the numerous unfavourable effects of at most major extent for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy, there is no hint of added benefit of abemaciclib + anastrozole or letrozole compared with anastrozole or letrozole; thus there is no proof of added benefit.

Table 20 summarizes the result of the assessment of added benefit of abemaciclib in combination with an aromatase inhibitor in comparison with the ACT.

Table 20: Abemaciclib in combination with an aromatase inhibitor – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have not yet received initial endocrine therapy[b]	▪ **Anastrozole** or ▪ **letrozole** or ▪ fulvestrant or ▪ tamoxifen if aromatase inhibitors are not suitable or ▪ ribociclib in combination with an NSAI (anastrozole, letrozole)[c] or ▪ palbociclib in combination with an NSAI (anastrozole, letrozole)[c] or ▪ ribociclib in combination with fulvestrant[c] or ▪ abemaciclib in combination with fulvestrant[c] or ▪ palbociclib in combination with fulvestrant[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. Concerning the locally advanced or metastatic stage; for the present therapeutic indication, patients are presumed to be indicated for (further) endocrine therapy and not to be indicated for chemotherapy or (secondary) resection or curative radiotherapy.
c. The ACT has changed from the prior assessment as a result of a reevaluation of the available evidence and additionally includes combination therapies of an NSAI or fulvestrant with CDK4/6 inhibitors.

ACT: appropriate comparator therapy; CDK: cyclin-dependent kinase; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; NSAI: non-steroidal aromatase inhibitor

The assessment described above deviates from the assessment by the company, which derived proof of considerable added benefit for abemaciclib in combination with an aromatase inhibitor.

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

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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