IQWiG Reports – Commission No. A21-153

# Abemaciclib (breast cancer; combination with fulvestrant) –

## Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

**Extract**

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Abemaciclib (Mammakarzinom; Kombination mit Fulvestrant) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 25 February 2022). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

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**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 Quality of Life Questionnaire-Breast Cancer Module 23 |
| EORTC QLQ-C30 | European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 |
| 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 |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SOC | System Organ Class |
| VAS | visual analogue scale |
| WHO | World Health Organization |

# 2 Benefit assessment

## 2.1 Executive summary of the benefit assessment

### Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug abemaciclib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 2 December 2021.

The time limit was set because the MONARCH plus study lacked processing of the available evidence for the subpopulations A1 and B1. In addition, final results on overall survival from the MONARCH plus study were still pending. In accordance with the commission, the current benefit assessment refers exclusively to research questions A1 and B1.

### Research question

The aim of the present report is the assessment of the added benefit of abemaciclib in combination with fulvestrant in comparison with the appropriate comparator therapy (ACT) in patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.

Depending on the patients' lines of treatment, the G-BA distinguished between different treatment situations and specified different ACTs for each of them. In accordance with the G-BA's limitation of the decision, the present assessment refers exclusively to the 2 research questions A1 and B1 presented in Table 2 (designation according to the previous assessments).

Table 2: Research questions of the benefit assessment of abemaciclib

| Research question | Subindication | ACT[a] |
|---|---|---|
| **Women with HR-positive, HER2-negative locally advanced or metastatic breast cancer[b]** | | |
| A1 | Postmenopausal women, initial endocrine-based therapy | ▪ anastrozole or<br>▪ letrozole or<br>▪ **fulvestrant** or<br>▪ possibly tamoxifen if aromatase inhibitors are unsuitable or<br>▪ ribociclib in combination with an NSAI (anastrozole, letrozole)[c] or<br>▪ abemaciclib in combination with an NSAI (anastrozole, letrozole)[c] or<br>▪ palbociclib in combination with an NSAI (anastrozole, letrozole)[c] or<br>▪ ribociclib in combination with fulvestrant[c] or<br>▪ palbociclib in combination with fulvestrant[c] or |
| B1 | Postmenopausal women who have received prior endocrine therapy | ▪ tamoxifen or<br>▪ anastrozole or<br>▪ **fulvestrant** as monotherapy; only for patients with recurrence or progression following anti-oestrogen therapy[d]<br>▪ letrozole; only for patients with recurrence or progression following anti-oestrogen therapy, or<br>▪ exemestane; only for patients with progression following anti-oestrogen therapy, or<br>▪ everolimus in combination with exemestane; only for patients without symptomatic visceral metastases following progression after an NSAI or ribociclib in combination with an NSAI (anastrozole, letrozole)[c], or<br>▪ abemaciclib in combination with an NSAI (anastrozole, letrozole)[c] or<br>▪ palbociclib in combination with an NSAI (anastrozole, letrozole)[c] or<br>▪ ribociclib in combination with fulvestrant[c] or<br>▪ palbociclib in combination with fulvestrant[c] |

a. Presented is the respective ACT specified by the GBA. 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. It is assumed for the present therapeutic indication that (if applicable, another) endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
c. The ACT has changed as a result of a reassessment of the available evidence compared with the previous assessments and currently includes all approved combination therapies of an aromatase inhibitor or fulvestrant with CDK4/6 inhibitors.
d. In therapeutic indication, the approval of fulvestrant provides for use of the drug only after prior anti-oestrogen therapy. In this respect, there is a discrepancy with the use of fulvestrant recommended in guidelines and established in health care, which do not focus exclusively on previous therapy with anti-oestrogens, but also on previous therapy with aromatase inhibitors. In this special therapeutic and health care situation, the G-BA sees sufficient medical reason that, in the present case, justifies considering fulvestrant as a sufficiently suitable comparator despite remaining uncertainties. It is assumed that there has been a change in treatment with respect to the drugs used for initial endocrine-based therapy.

CDK: cyclin-dependent kinase; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; NSAI: nonsteroidal aromatase inhibitor

The company designated fulvestrant as ACT for research questions A1 and B1, thus following the G-BA's specification. However, fulvestrant is approved for postmenopausal women who have received prior endocrine therapy (B1) only after previous anti-oestrogen therapy. In

accordance with the note by the G-BA, studies in which patients had been pretreated with aromatase inhibitors are also used for the comparison with fulvestrant for research question B1.

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

**Results (research questions A1 and B1)**

***Study pool and study design***

The study pool includes the studies MONARCH 2 and MONARCH plus. For assessing research questions A1 and B1, a subpopulation of the studies was included in each case.

*Study MONARCH 2*

The MONARCH 2 study is a double-blind RCT in which abemaciclib in combination with fulvestrant is directly compared with fulvestrant (+ placebo). The study included women with locally advanced or metastatic HR-positive and HER2-negative breast cancer, regardless of their menopausal status, who either had or had not received prior endocrine therapy.

A total of 713 patients were included in the study and randomized in a 2:1 ratio to the 2 treatment arms. From among these patients, 374 patients are relevant to the assessment of research question A1 (postmenopausal women with initial endocrine-based therapy) and 210 patients to the assessment of research question B1 (postmenopausal women who have received prior endocrine therapy).

The primary outcome of the MONARCH 2 study is progression-free survival (PFS). Patient-relevant secondary outcomes are overall survival, symptoms, health status, health-related quality of life, and adverse events (AEs).

The MONARCH 2 study is an ongoing study (planned end of study: January 2024). So far, 3 data cut-offs are available.

*Study MONARCH plus*

The MONARCH plus study (cohort B) is a double-blind RCT in which abemaciclib in combination with fulvestrant is directly compared with fulvestrant (+ placebo). The study was conducted mainly in Asia.

The study included only 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.

A total of 157 patients were included in cohort B of the study, which was the cohort relevant to the benefit assessment, and randomized in a 2:1 ratio to the 2 treatment arms. From among these patients, 121 patients are relevant to the assessment of research question A1

(postmenopausal women with initial endocrine-based therapy) and 36 patients to the assessment of research question B1 (postmenopausal women who have received prior endocrine therapy).

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

The MONARCH plus study is an ongoing study. So far, 2 data cut-offs are available.

***Risk of bias and certainty of results (research question A1, research question B1)***

The risk of bias across outcomes for the studies MONARCH 2 and MONARCH plus is rated as low. The risk of bias of the results for the outcome of overall survival for the studies MONARCH 2 and MONARCH is rated as low. The certainty of results for the outcome of discontinuation due to AEs is limited despite a low risk of bias. For all other outcomes, the risk of bias of the results is rated as high.

***Usability of the analyses presented by the company on patient-reported outcomes on symptoms and health-related quality of life (EORTC scales and EQ-5D VAS)***

The company submitted event time analyses for the outcomes on symptoms and health-related quality of life (recorded with the scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30] and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module 23 [EORTC QLQ-BR23] and the EQ-5D visual analogue scale [VAS]). These were operationalized as time to so-called "definitive deterioration" by 10 points (EORTC) or 7, 10 or 15 points (EQ-5D VAS) without subsequent improvement.

On the one hand, there is the problem in the present data situation that the observation period of the patient-reported outcomes only covers a very small proportion of the entire observation period (discontinuation of observation with the end of treatment). It is therefore not appropriate to speak of a "definitive deterioration" in this situation. Rather, this is only a deterioration confirmed over the shortened observation period.

On the other hand, due to clear differences in observation periods between the treatment arms, the available analyses cannot be interpreted without further information. In order to be able to interpret the data on patient-reported outcomes in the present situation, additional analyses of the first-time deterioration or the once-confirmed first-time deterioration would be necessary.

***Results for research question A1: postmenopausal women, initial endocrine-based therapy***

*Mortality*

*Overall survival*

For the outcome of overall survival, the meta-analysis of the studies does not show any statistically significant differences between treatment groups. This results in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

*Morbidity*

*Pain*

For the outcome of pain (worst pain in the last 24 hours and increase in analgesic use), the studies showed no statistically significant difference between the treatment groups, neither for the composite outcome nor for its individual components. In each case, this results in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

*Symptoms, recorded using the EORTC QLQ-C30 and the EORTC QLQ-BR23 (symptom scales)*

There are no usable data for the outcome of symptoms, recorded with the EORTC QLQ-C30 and EORTC QLQ-BR23 symptom scales. In each case, this results in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

*Health status (EQ-5D VAS)*

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

*Health-related quality of life*

*Health-related quality of life, recorded using the EORTC QLQ-C30 (global health status and functional scales) and the EORTC QLQ-BR23 (functional scales)*

There are no usable data for the outcome of health-related quality of life, recorded using the scales of EORTC QLQ-C30 (global health status and functional scales) and EORTC QLQ-BR23 (functional scales). In each case, this results in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

*Side effects*

*Serious AEs (SAEs) and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3) as well as discontinuation due to AEs*

The meta-analysis shows a statistically significant difference to the disadvantage of abemaciclib + fulvestrant for each of the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3) as well as discontinuation due to AEs. This results in an indication of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for each of these outcomes.

*Specific AEs*

*Neutropenia (severe AEs)*

The meta-analysis shows a statistically significant difference to the disadvantage of abemaciclib + fulvestrant for the outcome of neutropenia (severe AEs). Due to the size of the

effect, which was already evident in both studies at an early point in the course of the studies and almost exclusively in the intervention arms, there is a high certainty of results for this outcome despite high risk of bias. This results in proof of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

*Diarrhoea (severe AEs)*

The MONARCH 2 study showed a statistically significant difference to the disadvantage of abemaciclib for the outcome of diarrhoea (severe AEs). As no events occurred in the control arm of the MONARCH plus study, the effect estimate cannot be calculated and a meta-analysis cannot be conducted in a meaningful way. This results in a hint of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

*Anaemia (severe AEs), eye disorders (AEs), gastrointestinal disorders (AEs), skin and subcutaneous tissue disorders (AEs) as well as renal and urinary disorders (AEs)*

For the specific AEs of anaemia (severe AEs), eye disorders (AEs), gastrointestinal disorders (AEs), skin and subcutaneous tissue disorders (AEs) as well as renal and urinary disorders (AEs), the meta-analysis shows a statistically significant difference to the disadvantage of abemaciclib + fulvestrant. This results in an indication of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for each of these outcomes.

***Results (research question B1): postmenopausal women who have received prior endocrine therapy***

*Mortality*

*Overall survival*

The meta-analysis shows a statistically significant difference in favour of abemaciclib + fulvestrant for the outcome of overall survival. However, there is an effect modification by the characteristic of type of disease. This results in proof of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for the outcome of overall survival in patients with visceral metastases. For patients with non-visceral metastases, there is no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

*Morbidity*

*Pain*

For the outcome of pain (worst pain in the last 24 hours and increase in analgesic use), the studies showed no statistically significant difference between the treatment groups, neither for the composite outcome nor for its individual components. However, there is an effect modification by the characteristic of age for the component of pain (worst pain in the last 24 hours), which was recorded in both studies. This results in an indication of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this component for patients ≥ 65 years of age. For patients < 65 years of age, there is no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this component; an added benefit

is therefore not proven. In each case, this results in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for the composite outcome as well as for the individual component of increase in analgesic use; an added benefit is therefore not proven.

*Symptoms, recorded using the EORTC QLQ-C30 and the EORTC QLQ-BR23 (symptom scales)*

There are no usable data for the outcome of symptoms, recorded with the EORTC QLQ-C30 and EORTC QLQ-BR23 symptom scales. In each case, this results in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

*Health status (EQ-5D VAS)*

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

*Health-related quality of life*

*Health-related quality of life, recorded using the EORTC QLQ-C30 (global health status and functional scales) and the EORTC QLQ-BR23 (functional scales)*

There are no usable data for the outcome of health-related quality of life, recorded using the scales of EORTC QLQ-C30 (global health status and functional scales) and EORTC QLQ-BR23 (functional scales). In each case, this results in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

*Side effects*

*SAEs*

For the outcome of SAEs, the meta-analysis does not show any statistically significant differences between treatment groups. This results in no hint of greater or lesser harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome; greater or lesser harm is therefore not proven.

*Severe AEs*

The meta-analysis shows a statistically significant difference to the disadvantage of abemaciclib + fulvestrant for the outcome of severe AEs (CTCAE grade ≥ 3). This results in an indication of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

*Discontinuation due to AEs*

The meta-analysis shows a statistically significant difference to the disadvantage of abemaciclib + fulvestrant for the outcome of discontinuation due to AEs. The extent of the effect in this non-serious/non-severe outcome was no more than marginal, however. This results

in no hint of greater or lesser harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome; greater or lesser harm is therefore not proven.

*Specific AEs*

*Neutropenia (severe AEs)*

The MONARCH 2 study showed a statistically significant difference to the disadvantage of abemaciclib for the outcome of neutropenia (severe AEs). As no events occurred in the control arm of the MONARCH plus study, the effect estimate cannot be calculated and a meta-analysis cannot be conducted in a meaningful way. However, the event rates in the intervention arm (7 events) of the MONARCH plus study support the result of MONARCH 2. This results overall in an indication of greater harm from abemaciclib + fulvestrant in comparison with fulvestrant.

*Diarrhoea (severe AEs)*

The MONARCH 2 study showed a statistically significant difference to the disadvantage of abemaciclib for the outcome of diarrhoea (severe AEs). As no events occurred in the control arm of the MONARCH plus study, the effect estimate cannot be calculated and a meta-analysis cannot be conducted in a meaningful way. This results overall in a hint of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

*Gastrointestinal disorders (AEs)*

The meta-analysis shows a statistically significant difference to the disadvantage of abemaciclib + fulvestrant for the outcome of gastrointestinal disorders (AEs). This results in an indication of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

*Skin and subcutaneous tissue disorders (AEs)*

The meta-analysis shows a statistically significant difference to the disadvantage of abemaciclib + fulvestrant for the outcome of skin and subcutaneous tissue disorders (AEs). There is an effect modification by the characteristic of age, however. As no events occurred in patients ≥ 65 years of age in the control arm of the MONARCH plus study, the effect estimate cannot be calculated and a meta-analysis cannot be conducted in a meaningful way. The MONARCH 2 study showed a statistically significant difference to the disadvantage of abemaciclib + fulvestrant for patients ≥ 65 years. Based on these data, there is a hint of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for the outcome of skin and subcutaneous tissue disorders (AEs) in patients ≥ 65 years. In patients < 65 years, based on the data of the meta-analysis of the 2 studies, there is no statistically significant difference between the treatment groups. This results in no hint of greater or lesser harm of abemaciclib + fulvestrant in comparison with fulvestrant for patients < 65 years; greater or lesser harm for these patients is therefore not proven.

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

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

***Research question A1 (postmenopausal women with initial endocrine-based therapy)***

In the overall consideration, there are only negative effects of abemaciclib + fulvestrant in comparison with fulvestrant on the basis of the results of the studies MONARCH 2 and MONARCH plus. These refer exclusively to the shortened period until the end of treatment. The analyses presented on morbidity (except pain) and health-related quality of life are not usable.

In the present data situation, there is particular uncertainty as to whether adequate analyses of the outcomes on morbidity and health-related quality of life would influence the overall weighing in favour of abemaciclib in combination with fulvestrant.

Taking into account this uncertainty and the narrowly not statistically significant result of overall survival, there is no hint of an added benefit of abemaciclib in combination with fulvestrant compared with fulvestrant alone for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer with initial endocrine-based therapy (research question A1); an added benefit is therefore not proven.

***Research question B1 (postmenopausal women who have received prior endocrine therapy)***

In the overall consideration, there are positive and negative effects of abemaciclib + fulvestrant in comparison with fulvestrant on the basis of the results of the studies MONARCH 2 and MONARCH plus. Data over the entire observation period are only available for all-cause mortality. The positive effect in the outcome of pain as well as the negative effects in severe and non-severe side effects refer exclusively to the shortened observation period. The analyses presented on morbidity (except pain) and health-related quality of life are not usable and are also only available for the shortened observation period.

Decisive for patients with visceral metastases is proof of a positive effect with major extent for the outcome of overall survival. The clearly negative effects in severe side effects do not completely call into question the positive effect in overall survival. Overall, there is proof of

[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].

considerable added benefit of abemaciclib in combination with fulvestrant compared with fulvestrant alone for patients with visceral metastases.

For patients with non-visceral metastases, besides a positive effect in the outcome of pain (limited to older patients), mainly negative effects remain, especially in severe side effects. This results in an indication of lesser benefit of abemaciclib in combination with fulvestrant compared with fulvestrant alone.

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

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

| Research question | Sub-indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|---|
| **Women with HR-positive, HER2-negative locally advanced or metastatic breast cancer[b]** | | | |
| A1 | Post-meno-pausal women, initial endocrine-based therapy | ▪ anastrozole or<br>▪ letrozole or<br>▪ **fulvestrant** or<br>▪ possibly tamoxifen if aromatase inhibitors are unsuitable<br>▪ ribociclib in combination with an NSAI (anastrozole, letrozole) or<br>▪ abemaciclib in combination with an NSAI (anastrozole, letrozole) or<br>▪ palbociclib in combination with an NSAI (anastrozole, letrozole) or<br>▪ ribociclib in combination with fulvestrant or<br>▪ palbociclib in combination with fulvestrant | Added benefit not proven |
| B1 | Post-meno-pausal women who have received prior endocrine therapy | ▪ tamoxifen or<br>▪ anastrozole or<br>▪ **fulvestrant** as monotherapy; only for patients with recurrence or progression following anti-oestrogen therapy, or<br>▪ letrozole; only for patients with recurrence or progression following anti-oestrogen therapy, or<br>▪ exemestane; only for patients with progression following anti-oestrogen therapy, or<br>▪ everolimus in combination with exemestane; only for patients without symptomatic visceral metastases who have progressed after an NSAI, or<br>▪ ribociclib in combination with an NSAI (anastrozole, letrozole) or<br>▪ abemaciclib in combination with an NSAI (anastrozole, letrozole) or<br>▪ palbociclib in combination with an NSAI (anastrozole, letrozole) or<br>▪ ribociclib in combination with fulvestrant or<br>▪ palbociclib in combination with fulvestrant | Patients with visceral metastases: proof of considerable added benefit[c, d]<br>Patients with non-visceral metastases: indication of lesser benefit[c, d] |

a. Presented is the respective ACT specified by the GBA. 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. It is assumed for the present therapeutic indication that further endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
c. Only patients with an ECOG PS of 0 or 1 were included in the studies MONARCH 2 and MONARCH plus. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
d. The added benefit or lesser benefit exists only in comparison with fulvestrant, which is assessed as sufficiently suitable comparator by the G-BA.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; NSAI: nonsteroidal aromatase inhibitor

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

## 2.2 Research question

The aim of the present report is the assessment of the added benefit of abemaciclib in combination with fulvestrant in comparison with the ACT in patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer.

According to the approval, administration of abemaciclib has to be in combination either with an aromatase inhibitor or with fulvestrant. The present dossier assessment deals with the combination with fulvestrant.

Depending on the patients' lines of treatment, the G-BA distinguished between different treatment situations and specified different ACTs for each of them. In accordance with the G-BA's limitation of the decision, the present assessment refers exclusively to the 2 research questions A1 and B1 presented in Table 4 (designation according to the previous assessments [3,4]).

Table 4: Research questions of the benefit assessment of abemaciclib

| Research question | Subindication | ACT[a] |
|---|---|---|
| **Women with HR-positive, HER2-negative locally advanced or metastatic breast cancer[b]** | | |
| A1 | Postmenopausal women, initial endocrine-based therapy | ▪ anastrozole or<br>▪ letrozole or<br>▪ **fulvestrant** or<br>▪ possibly tamoxifen if aromatase inhibitors are unsuitable or<br>▪ ribociclib in combination with an NSAI (anastrozole, letrozole)[c] or<br>▪ abemaciclib in combination with an NSAI (anastrozole, letrozole)[c] or<br>▪ palbociclib in combination with an NSAI (anastrozole, letrozole)[c] or<br>▪ ribociclib in combination with fulvestrant[c] or<br>▪ palbociclib in combination with fulvestrant[c] |
| B1 | Postmenopausal women who have received prior endocrine therapy | ▪ tamoxifen or<br>▪ anastrozole or<br>▪ **fulvestrant** as monotherapy; only for patients with recurrence or progression following anti-oestrogen therapy[d], or<br>▪ letrozole; only for patients with recurrence or progression following anti-oestrogen therapy, or<br>▪ exemestane; only for patients with progression following anti-oestrogen therapy, or<br>▪ everolimus in combination with exemestane; only for patients without symptomatic visceral metastases who have progressed after an NSAI, or<br>▪ ribociclib in combination with an NSAI (anastrozole, letrozole)[c] or<br>▪ abemaciclib in combination with an NSAI (anastrozole, letrozole)[c] or<br>▪ palbociclib in combination with an NSAI (anastrozole, letrozole)[c] or<br>▪ ribociclib in combination with fulvestrant[c] or<br>▪ palbociclib in combination with fulvestrant[c] |

a. Presented is the respective ACT specified by the GBA. 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. It is assumed for the present therapeutic indication that (if applicable, another) endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
c. The ACT has changed as a result of a reassessment of the available evidence compared with the previous assessments and currently includes all approved combination therapies of an aromatase inhibitor or fulvestrant with CDK4/6 inhibitors.
d. In therapeutic indication, the approval of fulvestrant provides for use of the drug only after prior anti-oestrogen therapy [5]. In this respect, there is a discrepancy with the use of fulvestrant recommended in guidelines and established in health care, which do not focus exclusively on previous therapy with anti-oestrogens, but also on previous therapy with aromatase inhibitors. In this special therapeutic and health care situation, the G-BA sees sufficient medical reason that, in the present case, justifies considering fulvestrant as a sufficiently suitable comparator despite remaining uncertainties. It is assumed that there has been a change in treatment with respect to the drugs used for initial endocrine-based therapy.

CDK: cyclin-dependent kinase; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; NSAI: nonsteroidal aromatase inhibitor

The company designated fulvestrant as ACT for research questions A1 and B1, thus following the G-BA's specification. However, fulvestrant is approved for postmenopausal women who have received prior endocrine therapy (B1) only after previous anti-oestrogen therapy [5]. In

accordance with the note by the G-BA, studies in which patients had been pretreated with aromatase inhibitors are also used for the comparison with fulvestrant for research question B1 (see also dossier assessment A20-32, Section 2.5.1 [4] and the G-BA justification on benefit assessment A18-73 [6]).

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

## 2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on abemaciclib (status: 1 September 2021)
- bibliographical literature search on abemaciclib (last search on 1 September 2021)
- search in trial registries/trial results databases for studies on abemaciclib (last search on 1 September 2021)
- search on the G-BA website for abemaciclib (last search on 1 September 2021)

To check the completeness of the study pool:

- search in trial registries for studies on abemaciclib (last search on 10 December 2021); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any additional relevant study.

### 2.3.1 Studies included

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

Table 5: Study pool – direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant

| Study | Study category | | | Available sources | | |
|---|---|---|---|---|---|---|
| | Study for the approval of the drug to be assessed (yes/no) | Sponsored study[a] (yes/no) | Third-party study (yes/no) | CSR (yes/no [citation]) | Registry entries[b] (yes/no [citation]) | Publication and other sources[c] (yes/no [citation]) |
| I3Y-MC-JPBL (MONARCH 2[d]) | Yes | Yes | No | Yes [7] | Yes [8-10] | Yes [3,4,11-23] |
| I3Y-CR-JPBQ (MONARCH plus[d]) | No | Yes | No | Yes [24][e] | Yes [25] | Yes [4,26] |

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Other sources: documents from the search on the G-BA website and further publicly available documents on the studies MONARCH 2 and MONARCH plus.
d. In the following tables, the study is referred to by this acronym.
e. The citation refers to the CSR on the first data cut-off (29 March 2019). The CSR on the data cut-off relevant to the present benefit assessment (18 May 2020) was not yet available in English at the time of the assessment.

CSR: clinical study report; G-BA: Federal Joint Committee

The study pool for the benefit assessment concurs with that of the company. In accordance with the G-BA's condition of the limitation, the company also considered the MONARCH plus study in addition to the MONARCH 2 study in its assessment and, in connection with the resubmission, examined the possibility of a meta-analytical summary of the studies, provided that there were no decisive reasons to the contrary. Both studies are known from previous assessments [3,4].

Table 6 shows the overall evidence base resulting for the benefit assessment on the basis of the relevant studies MONARCH 2 and MONARCH plus.

Table 6: Evidence base in the benefit assessment

| Research question | Subindication | Relevant data for the benefit assessment | Section in the benefit assessment |
|---|---|---|---|
| **Women with HR-positive, HER2-negative locally advanced or metastatic breast cancer** | | | |
| A1 | Postmenopausal women, initial endocrine-based therapy | ▪ Subpopulation of the MONARCH 2 study<br>▪ Subpopulation of the MONARCH plus study | Assessment in Section 2.4 |
| B1 | Postmenopausal women who have received prior endocrine therapy | ▪ Subpopulation of the MONARCH 2 study[a]<br>▪ Subpopulation of the MONARCH plus study[a] | Assessment in Section 2.5 |

a. In the special therapeutic and health care situation, the G-BA assesses fulvestrant as a sufficiently suitable comparator (see the G-BA justification on benefit assessment A18-73 [6]).

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

## 2.4 Research question A1: postmenopausal women, initial endocrine-based therapy

Details on the information retrieval and on the study pool relevant to this research question A1 can be found in Section 2.3.

### 2.4.1 Study characteristics

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

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

| Study | Study design | Population | Interventions (number of randomized patients) | Study duration | Location and period of study | Primary outcome; secondary outcomes[a] |
|---|---|---|---|---|---|---|
| MONARCH 2 | RCT, parallel, double-blind | Women with HR-positive, HER2-negative locally advanced or metastatic breast cancer[b] and ECOG PS ≤ 1 | Abemaciclib + fulvestrant (N = 446)[c]<br>placebo + fulvestrant (N = 223)[c]<br><br>Relevant subpopulations thereof:<br>▪ Postmenopausal, initial endocrine-based therapy (A1)<br>▫ abemaciclib + fulvestrant (n = 246)<br>▫ placebo + fulvestrant (n = 128)<br>▪ Postmenopausal, after progression under endocrine therapy (B1)<br>▫ abemaciclib + fulvestrant (n = 144)<br>▫ placebo + fulvestrant (n = 66) | ▪ Screening: up to 28 days<br>▪ Treatment: until disease progression, participation in another study or treatment discontinuation following decision by physician, patient or sponsor<br>▪ Observation[d]: outcome-specific, at most until death, discontinuation of participation in the study or end of study | 145 centres in Australia, Belgium, Canada, Denmark, Finland, France, Germany, Greece, Italy, Japan, Mexico, Poland, Puerto Rico, Republic of Korea, Romania, Russia, Spain, Switzerland, Taiwan, USA<br><br>8/2014–ongoing<br>▪ 14 February 2017: interim analysis, planned after 378 PFS events<br>▪ 20 June 2019: interim analysis (referred to by the company as final data cut-off), planned after 331 deaths[c] | ▪ Primary: PFS<br>▪ Secondary: overall survival, symptoms, health status, health-related quality of life, AEs |

Table 7: Characteristics of the study included – RCT, direct comparison: abemaciclib + fulvestrant vs. fulvestrant (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] and ECOG PS ≤ 1 | Abemaciclib + fulvestrant (N = 104)[f]<br>placebo + fulvestrant (N = 53)[f]<br><br>Relevant subpopulations thereof:<br>▪ Postmenopausal, initial endocrine-based therapy (A1)<br>▫ abemaciclib + fulvestrant (n = 81)<br>▫ placebo + fulvestrant (n = 40)<br>▪ Postmenopausal, after progression under endocrine therapy (B1)<br>▫ abemaciclib + fulvestrant (n = 23)<br>▫ placebo + fulvestrant (n = 13) | ▪ Screening: up to 28 days<br>▪ Treatment: until disease progression, participation in another study or treatment discontinuation following decision by physician, patient or sponsor<br>▪ Observation[d]: outcome-specific, at most until death, discontinuation of participation in the study or end of study | 45 study centres in Brazil, China, India and South Africa<br><br>12/2016–ongoing<br>▪ 29 March 2019: interim analysis<br>▪ 18 May 2020: final analysis[g] | ▪ Primary: PFS<br>▪ Secondary: overall survival, symptoms, health-related quality of life, AEs |

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes include only information on relevant available outcomes for this benefit assessment.
b. Patients with initial endocrine-based therapy or after prior endocrine therapy (each for the advanced stage) were included. Their tumours had to be not amenable to resection or radiotherapy with curative intent.
c. The patient numbers refer to the ITT population (44 endocrine-naive patients are not included in the ITT population). The study initially included women who either had not received prior endocrine therapy or who had already received prior endocrine therapy. As a result of the protocol change dated 30 March 2015, women who had not received endocrine therapy at any prior time (endocrine-naive patients) were excluded from participation in the study. Before this protocol change, 44 endocrine-naive patients had already been included, who can mostly be assigned to research question A1. Based on the G-BA decision on the first benefit assessment of abemaciclib, the company took these patients into account in the present dossier when analysing the subpopulations [15].
d. Outcome-specific information is provided in Table 9.
e. Data cut-off relevant to the present benefit assessment (identical to the data cut-off for dossier assessment A20-32 [4]). This is the final data cut-off on overall survival planned according to the study documents. The company did not provide any information on whether further analyses are planned for the ongoing study.
f. 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 B, the cohort relevant to the present benefit assessment, is listed here.
g. Data cut-off relevant to the present benefit assessment.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; ITT: intention to treat; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial

Table 8: Characteristics of the intervention – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (multipage table)

| Study | Intervention | Comparison |
|---|---|---|
| MONARCH 2 | Abemaciclib 150 mg[a] orally, twice daily (every 12 hours), cycle duration: 28 days<br>+<br>fulvestrant 500 mg IM on days 1 and 15 of the first cycle, then on day 1 of each following cycle | Placebo[a] orally, twice daily (every 12 hours), cycle duration: 28 days<br>+<br>fulvestrant 500 mg IM on days 1 and 15 of the first cycle, then on day 1 of each following cycle |
| | **Dose adjustments:**<br>▪ Abemaciclib/placebo:<br>▫ in case of toxicity, dose reductions (first to 100 mg and then to 50 mg, each twice daily) or discontinuation of treatment with continuation of fulvestrant were possible[b]<br>▪ Fulvestrant:<br>▫ reduction to 250 mg for patients with moderate hepatic impairment (defined as Child-Pugh Class B)<br>▫ in case of toxicity delay of administration (or of the cycle) of up to 14 daysc or treatment discontinuation with continuation of abemaciclib/placebo possible | |
| | **Permitted pretreatment:**<br>▪ neoadjuvant or adjuvant chemotherapy<br>▪ prior anticancer therapies (including specifically aromatase inhibitors, anti-oestrogens, chemotherapy, radiotherapy, and immunotherapy) had to be discontinued (≥ 21 days for myelosuppressive therapies or 14 days for non-myelosuppressive therapies), and acute effects had to have subsided (except for alopecia and peripheral neuropathy)<br>**Non-permitted pretreatment:**<br>▪ prior chemotherapy (except for adjuvant/neoadjuvant) or treatment with fulvestrant, everolimus, or a CDK4 or CDK6 inhibitor<br>▪ autologous or allogeneic stem cell transplantation<br>**Permitted concomitant treatment:**<br>▪ any supportive care to maximize quality of life<br>▪ dexamethasone (if possible ≤ 7 days)<br>▪ supportive measures and instructions on the treatment of diarrhoea<br>▪ bisphosphonates or approved RANK ligands (e.g. denosumab) for patients with bone metastases if treatment started at least 7 days prior to randomization<br>**Non-permitted concomitant treatment**<br>▪ other anticancer therapies (including aromatase inhibitors, anti-oestrogens [besides fulvestrant], chemotherapy, radiotherapy[d], and immunotherapy)<br>▪ megestrol acetate (as an appetite stimulant)<br>▪ inducers and strong inhibitors of CYP3A | |
| MONARCH plus | Abemaciclib 150 mg orally, twice daily (every 12 hours), cycle duration: 28 days<br>+<br>fulvestrant 500 mg IM on days 1 and 15 of the first cycle, then on day 1 of each following cycle | Placebo orally, twice daily (every 12 hours), cycle duration: 28 days<br>+<br>fulvestrant 500 mg IM on days 1 and 15 of the first cycle, then on day 1 of each following cycle |
| | See MONARCH 2[e] | |

Table 8: Characteristics of the intervention – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (multipage table)

| Study | Intervention | Comparison |
|---|---|---|
| a. According to the initial study protocol, the starting dose of abemaciclib/placebo was 200 mg. With a protocol change dated 12 January 2015, the starting dose for all study participants was reduced to 150 mg. Patients who were receiving 200 mg abemaciclib at this time point (178 patients) reduced their dose to 150 mg.<br>b. The decision was based on the severity grade and type of toxicity (haematological, non-haematological, diarrhoea, ALT increased) according to the study protocol.<br>c. In exceptional situations, a delay > 14 days was possible upon request to the sponsor.<br>d. Surgery with subsequent radiotherapy was allowed if study treatment had rendered the locally advanced breast cancer operable.<br>e. The dose adjustments as well as permitted and non-permitted pre- and concomitant treatments in the MONARCH plus study do not show any relevant differences compared with the specifications in the MONARCH 2 study.<br>ALT: alanine aminotransferase; CDK: cyclin-dependent kinase; CYP: cytochrome P450; RANK: receptor activator of nuclear factor kappa-B; RCT: randomized controlled trial | | |

**Study MONARCH 2**

The MONARCH 2 study is a double-blind RCT in which abemaciclib in combination with fulvestrant is directly compared with fulvestrant. Women with locally advanced or metastatic HR-positive and HER2-negative breast cancer, regardless of their menopausal status, were included in the study. The patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 on study entry.

A total of 713 patients were included in the study and randomized in a 2:1 ratio to the 2 treatment arms. Randomization was stratified by type of disease (visceral metastases, bone only metastases, other) and sensitivity to endocrine therapy (primary, secondary and, before ending enrolment of endocrine-naive patients additionally: endocrine-naive).

The use of abemaciclib and fulvestrant in the MONARCH 2 study is largely in compliance with the recommendations of the respective Summaries of Product Characteristics (SPCs) [5,27]. Although there are deviations with regard to the starting dose of abemaciclib provided for in the initial study protocol (200 mg instead of 150 mg) and the pretreatment when using fulvestrant, which was partly not in compliance with the approval, analogous to the previous procedures, this has no consequences for the present benefit assessment (for details see Section 2.4.1 in dossier assessment A20-32 [4] and the G-BA justification on benefit assessment procedure A18-73 [6].

Treatment with the study medication is continued until disease progression or discontinuation for other reasons (e.g. AEs or patient request). After treatment discontinuation, patients in both study arms can start subsequent therapy. Treatment switching from placebo to abemaciclib is not allowed.

The primary outcome of the MONARCH 2 study is PFS. Patient-relevant secondary outcomes are overall survival, symptoms, health status, health-related quality of life, and AEs.

***Subpopulation relevant to the assessment of research question A1***

Among the patients included in the MONARCH 2 study, only the subpopulation of postmenopausal women who have not received prior endocrine therapy for the advanced disease stage are relevant to the assessment of research question A1 (see Section 2.2). Out of the total of 713 patients, this applies to 374 (52.5%) patients, of which 246 patients were treated with abemaciclib in combination with fulvestrant and 128 patients were treated with fulvestrant (+ placebo). Analogous to the previous benefit assessment, the company presented analyses of this subpopulation in its dossier. These are used for the benefit assessment.

***Data cut-offs***

According to the information provided by the company in the dossier, the final data cut-off for the MONARCH 2 study has already been carried out. Overall, the 3 data cut-offs known from the previous benefit assessment are available.

- First data cut-off: planned interim analysis after 265 PFS events
- Second data cut-off (14 February 2017): planned interim analysis after 378 PFS events, subject of the first assessment
- Third data cut-off (20 June 2019): analysis after 331 deaths, planned as final analysis (if the result on overall survival was statistically significant) The data cut-off is identical to the relevant data cut-off in dossier assessment A20-32 [4].

The study is still ongoing [8]. Analogous to the previous benefit assessment, the results of the third data cut-off are relevant to the present benefit assessment. This is the final data cut-off on overall survival planned according to the study documents. The company did not provide any information on whether further analyses are planned for the ongoing study.

**Study MONARCH plus**

The MONARCH plus study (cohort B) is a double-blind RCT in which abemaciclib in combination with fulvestrant is directly compared with fulvestrant (+ placebo). The study was conducted mainly in Asia and is the study on which approval in China was based.

The study included only 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. The patients had to have an ECOG PS of 0 or 1 on study entry.

A total of 157 patients were included in cohort B of the study, which was the cohort relevant to the benefit assessment, and randomized in a 2:1 ratio to the 2 treatment arms. 104 patients were allocated to the intervention arm and 53 patients to the control arm. Randomization was stratified by type of disease (visceral metastases versus non-visceral metastases) and sensitivity to endocrine therapy (primary versus secondary).

The use of abemaciclib and fulvestrant in the MONARCH plus study is in compliance with the recommendations of the respective SPCs [5,27]. Although there are deviations with regard to the pretreatment when using fulvestrant, which was partly not in compliance with the approval (see Table 10, prior anti-oestrogen therapy), analogous to the previous procedures, this has no consequences for the present benefit assessment because the G-BA cited fulvestrant as ACT without limitation in this treatment situation (see, for example, the G-BA justification on benefit assessment procedure A18-73 [6]).

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

***Subpopulation relevant to the assessment of research question A1***

Among the patients included in the MONARCH plus study, only the subpopulation of postmenopausal women who have not received prior endocrine therapy are relevant to the assessment of research question A1 (see Section 2.2). In the current dossier, the company presented for the first time analyses for the subpopulations relevant to the assessment. Out of the total of 157 patients, 121 (77.1%) patients are relevant to research question A1, of which 81 patients were treated with abemaciclib in combination with fulvestrant and 40 patients were treated with fulvestrant (+ placebo).

***Data cut-offs***

Two data cut-offs are available for the MONARCH plus study.

- First data cut-off (29 March 2019): planned interim analysis after 119 PFS events (in cohort A of the study)
- Second data cut-off (18 May 2020): final analysis (further data cut-offs are not planned)

The study is still ongoing [25]. The results of the second data cut-off (final analysis) are relevant to the present assessment.

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

Table 9: Planned duration of follow-up observation – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant

| **Study**<br>**Outcome category**<br>**Outcome** | **Planned follow-up observation** |
|---|---|
| **MONARCH 2** | |
| Mortality | |
| Overall survival | Until death, discontinuation of participation in the study or end of study |
| Morbidity | |
| Symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23) | Until 30 days after the end of treatment |
| Pain (mBPI-SF) | Until 30 days after the end of treatment |
| Health status (EQ-5D-5L VAS) | Until 30 days after the end of treatment |
| Health-related quality of life | |
| EORTC QLQ-C30 and EORTC QLQ-BR23 | Until 30 days after the end of treatment |
| Side effects | |
| All outcomes in the category of side effects | Until 30 days after the end of treatment[a] |
| **MONARCH plus** | |
| Mortality | |
| Overall survival | Until death, discontinuation of participation in the study or end of study |
| Morbidity | |
| Symptoms (EORTC QLQ-C30) | Until 30 days after the end of treatment |
| Pain (mBPI-SF) | Until 30 days after the end of treatment |
| Health-related quality of life | |
| EORTC QLQ-C30 | Until 30 days after the end of treatment |
| Side effects | |
| All outcomes in the category of side effects | Until 30 days after the end of treatment[a] |

a. SAEs that are related to study drugs or protocol procedures are observed until death or end of study (long-term follow-up).

AE: adverse event; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module 23; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; mBPI-SF: modified Brief Pain Inventory-Short Form; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

The planned duration of follow-up observation is identical in the studies MONARCH 2 and MONARCH plus and is therefore described together below.

Only overall survival is recorded until the end of the studies. In each case, the observation periods for the outcomes of morbidity, health-related quality of life and side effects are

systematically shortened because they were only recorded for the time period of treatment with the study medication (plus 30 days). For these outcomes, data are therefore available only for the shortened observation period. Data on the entire study duration or until death are missing.

Table 10 shows the characteristics of the patients (research question A1) in the studies included.

Table 10: Characteristics of the study populations – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine-based therapy) (multipage table)

| **Study Characteristic Category** | **MONARCH 2** | | **MONARCH plus** | |
|---|---|---|---|---|
| | **Abemaciclib + fulvestrant N[a] = 246** | **Placebo + fulvestrant N[a] = 128** | **Abemaciclib + fulvestrant N[a] = 81** | **Placebo + fulvestrant N[a] = 40** |
| Sex [F/M],% | 100/0 | 100/0 | 100/0 | 100/0 |
| Age [years], mean (SD) | 62 (10) | 64 (9) | 59 (8) | 59 (10) |
| Age group, n (%) | | | | |
| < 65 years | 147 (60) | 72 (56) | 62 (77) | 30 (75) |
| ≥ 65 years | 99 (40) | 56 (44) | 19 (23) | 10 (25) |
| Family origin n (%) | | | | |
| Caucasian | 155 (63) | 80 (63) | 6 (7) | 4 (10) |
| Asian | 58 (24) | 32 (25) | 73 (90) | 35 (88) |
| Other | 33 (13)[b, c] | 16 (13)[b, c] | 2 (2)[c, d] | 1 (3)[d] |
| Region, n (%) | | | | |
| Europe | 97 (39) | 57 (45) | – | – |
| North America | 93 (38) | 39 (30) | – | – |
| South America | – | – | 8 (10) | 5 (13) |
| Asia | 56 (23) | 32 (25) | 73 (90) | 34 (85) |
| Africa | – | – | 0 (0) | 1 (3) |
| Starting dose, n (%) | | | | |
| 150 mg abemaciclib per dose | 170 (69) | 87 (68) | 81 (100) | 40 (100) |
| 200 mg abemaciclib per dose | 76 (31) | 41 (32) | – | – |
| ECOG PS, n (%) | | | | |
| 0 | 136 (55) | 74 (58) | 27 (33) | 14 (35) |
| 1 | 110 (45) | 54 (42) | 54 (67) | 26 (65) |
| Type of disease, n (%) | | | | |
| Visceral metastases | 131 (53) | 80 (63) | 47 (58) | 21 (53) |
| Non-visceral metastases | 115 (47)[e] | 48 (38)[e] | 34 (42) | 19 (48) |

Table 10: Characteristics of the study populations – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine-based therapy) (multipage table)

| Study Characteristic Category | MONARCH 2 | | MONARCH plus | |
|---|---|---|---|---|
| | Abemaciclib + fulvestrant N[a] = 246 | Placebo + fulvestrant N[a] = 128 | Abemaciclib + fulvestrant N[a] = 81 | Placebo + fulvestrant N[a] = 40 |
| Sensitivity to endocrine therapy, n (%) | | | | |
| Primary resistance | 57 (23) | 35 (27) | 30 (37) | 17 (43) |
| Secondary resistance | 169 (69) | 79 (62) | 51 (63) | 23 (58) |
| No prior therapy | 20 (8) | 14 (11) | – | – |
| Previous anti-oestrogen therapy, n (%) | | | | |
| Yes | 109 (44) | 52 (41) | 17 (21) | 10 (25) |
| No | 137 (56) | 76 (59) | 64 (79) | 30 (75) |
| Disease duration (time between first diagnosis and randomization) [months], mean (SD) | 72.2 (65.6) | 68.8 (63.4) | 49.5 (32.5) | 49.4 (45.1) |
| Treatment discontinuation, n (%) | ND[f] | ND[f] | ND[g] | ND[g] |
| Study discontinuation, n (%) | ND | ND | ND | ND |

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. Including Native American, Native Alaskan, Black/African American, multiple, and patients with missing information on family history.
c. Institute's calculation.
d. Including Black/African American and multiple.
e. Institute's calculation: totalled from the categories of bone metastases and other.
f. Data on the most common reasons for discontinuation are only available for the ITT population (446 vs. 223 patients), in which 364 (intervention arm) vs. 215 (control arm) patients discontinued therapy: Here, the most common reason for discontinuing therapy was disease progression in 269 (74%) vs. 187 (87%) patients who discontinued therapy.
g. Data on the most common reasons for discontinuation are only available for the ITT population (104 vs. 53 patients), in which 50 (intervention arm) vs. 40 (control arm) patients discontinued therapy: The most common reason for discontinuing therapy was disease progression in 40 (80%) vs. 33 (83%) patients who discontinued therapy.

ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the postmenopausal patients with initial endocrine-based therapy (research question A1) are largely comparable between the study arms of the MONARCH 2 study and of the MONARCH plus study.

The mean age of the patients in the MONARCH 2 study on study entry was about 63 years. Two thirds of the patients were of Caucasian family origin. A little more than half of the patients had an ECOG PS of 0, and about 56% of the patients had visceral metastases. The mean disease duration was approximately 71 months.

The mean age of the patients in the MONARCH plus study on study entry was about 59 years. The study was conducted exclusively in non-European centres (see Table 7), the vast majority of the patients were Asian. Two thirds of the patients had an ECOG PS of 1, and about 56% of the patients had visceral metastases. The mean disease duration was approximately 50 months.

Differences between the studies existed especially in terms of age (patients in the MONARCH plus study were about 4 years younger on average), disease duration (about 71 months in the MONARCH 2 study and about 49 months in the MONARCH plus study) and family origin (whereas the MONARCH 2 study included mainly Caucasian patients, almost all patients in the MONARCH plus study were of Asian family origin).

However, the differences do not fundamentally call into question the feasibility of a meta-analysis, as the studies are considered sufficiently comparable for the research question investigated. For the benefit assessment, before using or calculating meta-analyses, heterogeneity tests are used to check whether the 2 studies are sufficiently homogeneous for statistical pooling [1].

**Median treatment duration**

Table 11 shows the median treatment duration of the patients and the median observation period for individual outcomes in the studies MONARCH 2 and MONARCH plus.

Table 11: Information on the course of the study – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine-based therapy)

| **Study**<br>**Duration of the study phase**<br>**Outcome category** | **Abemaciclib + fulvestrant** | **Placebo + fulvestrant** |
|---|---|---|
| **MONARCH 2 (data cut-off: 20 June 2019)** | N = 245 | N = 128 |
| Treatment duration [months] | | |
| Median [Q1; Q3] | 10.4 [3.2; 27.9] | 8.9 [2.9; 20.4] |
| Observation period [months] | | |
| Overall survival[a] | | |
| Median [95% CI] | 48.4 [46.3; 49.6] | 47.6 [44.9; 48.9] |
| Morbidity (EORTC QLQ-C30, EORTC QLQ-BR23) | | |
| Median [min; max] | 12.1 [< 0.1; 55.6] | 8.8 [< 0.1; 54.7] |
| Morbidity pain (mBPI-SF) | ND | ND |
| Morbidity (EQ-5D VAS) | | |
| Median [min; max] | 12.1 [< 0.1; 55.6] | 8.9 [< 0.1; 54.7] |
| Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23) | | |
| Median [min; max] | 12.1 [< 0.1; 55.6] | 8.8 [< 0.1; 54.7] |
| Side effects | | |
| Median [min; max] | 13.2 [0.8; 56.1] | 9.9 [1.2; 54.8] |
| **MONARCH plus (data cut-off: 18 May 2020)** | N = 81 | N = 40 |
| Treatment duration [months] | | |
| Median [Q1; Q3] | 9.9 [5.7; 22.1] | 5.6 [2.3; 17.2] |
| Observation period [months] | | |
| Overall survival[a] | | |
| Median [95% CI] | 25.9 [25.1; 26.4] | 24.8 [23.2; 26.8] |
| Morbidity (EORTC QLQ-C30) | | |
| Median [min; max] | 10.6 [< 0.1; 28.4] | 5.3 [< 0.1; 28.9] |
| Morbidity pain (mBPI-SF) | ND | ND |
| Health-related quality of life (EORTC QLQ-C30) | | |
| Median [min; max] | 10.6 [< 0.1; 28.4] | 5.3 [< 0.1; 28.9] |
| Side effects | | |
| Median [min; max] | 10.9 [1.5; 29.9] | 6.5 [1.7; 29.1] |

a. The company did not provide any information on the methods used to determine observation periods in the subpopulation. However, it can be assumed that the observation period is calculated using the Kaplan-Meier method as indicated in the statistical analysis plan for the total population.

AE: adverse event; CI: confidence interval; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module 23; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; max: maximum; mBPI-SF: modified Brief Pain Inventory-Short Form; min: minimum; N: number of analysed patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; VAS: visual analogue scale

With the present benefit assessment, the company presented for the first time information on the median treatment durations and observation periods for the relevant subpopulations of the studies MONARCH 2 and MONARCH plus. In both studies, the treatment durations are longer in the intervention arms than in the control arms. However, the difference between the study arms is even more pronounced in the MONARCH plus study (9.9 versus 5.6 months) than in the MONARCH 2 study (10.4 versus 8.9 months). The observation period for the outcome of overall survival was similar in the arms of the studies, but at about 48 months markedly longer overall in the MONARCH 2 study than in the MONARCH plus study at about 25 months. For the other outcomes, whose observation period was linked to treatment end (see Table 9), the observation periods were markedly shorter. For these outcomes, it is therefore only possible to draw conclusions about the time under treatment, which, for example, only comprises about a quarter of the median survival time for each arm in the MONARCH 2 study (Table 15). Data for the entire observation period are missing for these outcomes.

In addition, there are also differences in the observation periods of the outcomes corresponding to the differences in the treatment durations between the study arms of both studies. This data situation influences the interpretability of the outcomes with shorter observation period (see Section 2.4.2.1).

**Subsequent therapies**

After treatment discontinuation, patients could start subsequent therapy. The data on the subsequent therapies used in the studies are available for the first time for the respective subpopulations and are presented in Appendix B.3 of the full dossier assessment (Table 39 and Table 40).

In the MONARCH 2 study, a large proportion (about 75%) of patients with progression had received at least one subsequent systemic therapy by the final data cut-off. The various subsequent therapies (chemotherapy, endocrine therapy, targeted therapy, other systemic therapies) were used in approximately equal proportions in both study arms. About one third of patients with progression had received targeted therapy in both arms.

In the MONARCH plus study, a large proportion (about 72%) of patients with progression had also received at least one subsequent systemic therapy by the relevant data cut-off. The various subsequent therapies (chemotherapy, endocrine therapy, targeted therapy, other systemic therapies) were used in largely equal proportions in both study arms. Use of targeted therapies was markedly less frequent than in the MONARCH 2-study (6.2% and 15.2%, respectively).

**Risk of bias across outcomes (study level)**

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

Table 12: Risk of bias across outcomes (study level) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine-based therapy)

| Study | Adequate random sequence generation | Allocation concealment | Blinding | | Reporting independent of the results | No additional aspects | Risk of bias at study level |
|---|---|---|---|---|---|---|---|
| | | | Patients | Treating staff | | | |
| MONARCH 2 | 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 2***

The company described that the results of the MONARCH 2 study can be transferred to the German health care context. It stated that the characteristics of the patients included in the study (e.g. in terms of age, family origin and prognosis) were comparable to those of breast cancer patients in the locally advanced or metastatic stage in the German health care context. The study treatment also complied with German and international treatment standards, according to the company.

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

***MONARCH plus***

The company stated that it assumed transferability of the study results to the German health care context. There were differences in the family origin of the patients included (mainly Asian) and their younger age in the MONARCH plus study compared with European patients, according to the company. However, it explained the comparatively younger age of the patients by the fact that breast cancer tends to occur earlier in Chinese patients than in Western countries. Nevertheless, it assessed the patient characteristics as sufficiently similar to the corresponding population in Germany. The company characterized the population in the study as patients with poor prognosis, citing for example the high proportion of patients with prognostically unfavourable visceral metastases and the fact that all patients had metastatic disease. Besides, the information in a current Chinese guideline were largely in line with the recommendations of the German and European guidelines [28].

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

### 2.4.2 Results on added benefit

#### 2.4.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the symptom scales of the questionnaires EORTC QLQ-C30 and EORTC QLQ-BR23
  - pain (measured with the modified Brief Pain Inventory-Short Form [mBPI-SF] and based on the increase in analgesic use by ≥ 1 step)
  - health status measured using the EQ-5D VAS
- Health-related quality of life
  - measured with the functional scales of the EORTC QLQ-C30 and of the EORTC QLQ-BR23
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - neutropenia, Preferred Term (PT) collection of the company (severe AEs [CTCAE grade ≥ 3])
  - diarrhoea, PT (severe AEs [CTCAE grade ≥ 3])
  - further specific AEs, if any

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

Table 13 shows for which outcomes data for research question A1 (postmenopausal women with initial endocrine-based therapy) are available in the included studies MONARCH 2 and MONARCH plus.

Table 13: Matrix of outcomes – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine-based therapy)

| Study | Outcomes | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overall survival | Symptoms (EORTC QLQ-C30)[a] | Symptoms (EORTC QLQ-BR23)[a] | Pain[b] | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30)[c] | Health-related quality of life (EORTC QLQ-BR23)[c] | SAEs | Severe AEs[d] | Discontinuation due to AEs[e] | Neutropenia[f] (severe AEs)[d] | Diarrhoea PT (severe AEs)[d] | Further specific AEs[g] |
| MONARCH 2 | Yes | No[h] | No[h] | Yes | No[h] | No[h] | No[h] | Yes | Yes | Yes | Yes | Yes | Yes |
| MONARCH plus | Yes | No[h] | No[i] | Yes[j] | No[i] | No[h] | No[i] | Yes | Yes | Yes | Yes | Yes | Yes |

a. Measured with the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-BR23.
b. Measured with the mBPI-SF symptom scale "worst pain in the last 24 hours" and the increase in analgesic use by ≥ 1 step according to the WHO 3-step system for the management of cancer pain [29], combined and separate analysis.
c. Measured with the functional scales of the EORTC QLQ-C30 and EORTC QLQ-BR23 as well as with the global health status of the EORTC QLQ-C30.
d. Severe AEs are operationalized as CTCAE grade ≥ 3.
e. Discontinuation of at least one of both drugs.
f. PT collection of the company, operationalized using the PTs neutropenia, febrile neutropenia and neutrophil count decreased.
g. The following events are considered (MedDRA coding): anaemia (PT, severe AEs), eye disorders (SOC, AEs), gastrointestinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), renal and urinary disorders (SOC, AEs).
h. No usable data (for explanation see running text below, Section 2.4.2.1).
i. Outcome not recorded.
j. In the MONARCH plus study, only the subcomponent "worst pain in the last 24 hours" of the mBPI-SF was recorded for the outcome of pain.

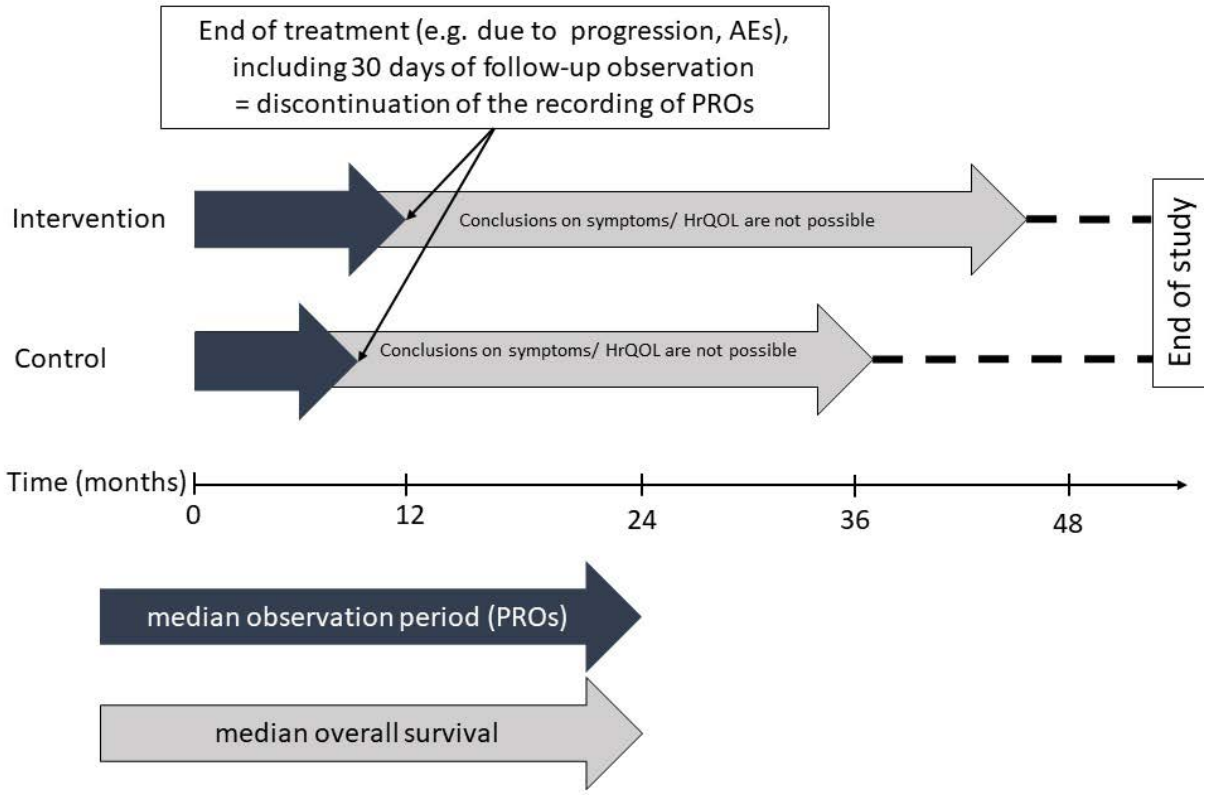
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer-Breast Cancer Module 23; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; mBPI-SF: modified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

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

***Scales of the EORTC and EQ-5D VAS***

The company submitted event time analyses for the outcomes on symptoms and health-related quality of life (recorded with the scales of the EORTC QLQ-C30 and the EORTC QLQ-BR23 and the EQ-5D VAS). These were operationalized as time to so-called "definitive deterioration"

by 10 points (EORTC) or 7, 10 or 15 points (EQ-5D VAS) without subsequent improvement. The recording of patient-reported outcomes was discontinued 30 days after treatment end in each case (see Table 9). The data on median observation periods for the symptom and health-related quality of life outcomes, presented for the first time with this dossier, show that the observation period for these outcomes is markedly shorter compared with median overall survival. For example, depending on the study arm, the median overall survival for patients in the MONARCH 2 study was 44.0 months (intervention arm) and 37.3 months (control arm). In contrast, the observation period for the patient-reported outcomes in the EORTC, for example, was only 12.1 months (intervention arm) and 8.8 months (control arm), see also Table 11 in Section 2.4.1 and Figure 1 below.




AE: adverse event; HRQoL: health-related quality of life; PRO: patient-reported outcome

Figure 1: Schematic representation of the systematically shortened observation period for the patient-reported outcomes (prepared as an example based on data from the MONARCH 2 study (research question A1, data cut-off from 20 June 2019)

On the one hand, this leads to the problem that the observation period of the patient-reported outcomes only covers a very small proportion of the entire observation period. It is therefore

not appropriate to speak of a "definitive deterioration" in this situation. Rather, this is only a deterioration confirmed over the shortened observation period.

On the other hand, due to clear differences in observation periods between the treatment arms, the available analyses cannot be interpreted without further information. This is because sustained deterioration across all subsequent values is potentially more difficult to achieve in the intervention arm with longer observation (treatment with abemaciclib). In addition, it can be assumed that the analysis also included patients who had deteriorated once at the last documentation time and for whom no confirmatory value was available at all. It is unclear how many patients in each of the study arms this affects.

In order to be able to interpret the data on patient-reported outcomes in the present situation, additional analyses of the first-time deterioration or the once-confirmed first-time deterioration would be necessary.

The data presented by the company (referred to by the company as "definitive deterioration" and in the benefit assessment as "confirmed deterioration under treatment") on these outcomes are presented as supplementary information in Appendix B.4 of the full dossier assessment.

*Note on the response criteria used*

*Scales of the EORTC*

As explained in the *General Methods* of the Institute [1,30], for a response criterion to reflect with sufficient certainty a change noticeable for the patient, it should correspond to a predefined value of at least 15% of the scale range of an instrument (in post hoc analyses, exactly 15% of the scale range). For the EORTC QLQ-C30 and its additional modules, the analysis with a previously accepted response threshold of 10 points is considered a sufficient approximation to an analysis with a 15% threshold (15 points) in certain constellations and is used for the benefit assessment (for explanation see [31]). Regardless of this, for a transitional period until the adjusted module templates for the dossier come into force (see FAQs of the G-BA [32]), analyses with the previously accepted response threshold of 10 points for the EORTC QLQ-C30 as well as all additional modules of the EORTC will be used primarily.

*EQ-5D VAS*

Of the response criteria presented by the company (deterioration by 7, 10 or 15 points), the response criterion of 15 points is relevant to the benefit assessment (for explanation see above).

***Pain***

For the outcome of pain (recorded using the mBPI-SF and analgesic use), the company presented event time analyses for the time from randomization to first deterioration. It rated as deterioration either an increase by ≥ 2 points from baseline (on the symptom scale "worst pain in the last 24 hours") or an increase in analgesic use by more than one step (according to the WHO 3-step system for the management of cancer pain [29]). For this purpose, the company also presented for the first time separate analyses for both response criteria for the

MONARCH 2 study. Here, the increase of at least 2 points (prespecified response criterion) corresponds to a threshold of > 15% of the total scale range of 0-11 points [1]. The analyses presented are suitable for deriving conclusions on the added benefit. The different observation periods in the 2 arms are addressed accordingly in the assessment of the risk of bias (see Section 2.4.2.2)

However, it is also true for this outcome that the observation period only covers a small proportion of the total observation period. On the basis of the available data, conclusions can therefore be drawn only for the shortened time period under treatment. No data are available on the entire observation period.

#### 2.4.2.2 Risk of bias

Table 14 describes the risk of bias for the results of the relevant outcomes in the included studies MONARCH 2 and MONARCH plus in research question A1 (postmenopausal women with initial endocrine-based therapy).

Table 14: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine-based therapy)

| Study | Study level | Outcomes | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Overall survival | Symptoms (EORTC QLQ-C30)[a] | Symptoms (EORTC QLQ-BR23)[a] | Pain[b] | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30)[c] | Health-related quality of life (EORTC QLQ-BR23)[c] | SAEs | Severe AEs[d] | Discontinuation due to AEs[e] | Neutropenia[f] (severe AEs)[d] | Diarrhoea PT (severe AEs)[d] | Further specific AEs[g] |
| MONARCH 2 | L | L | –[h] | –[h] | H[i] | –[h] | –[h] | –[h] | H[i] | H[i] | L[j] | H[i] | H[i] | H[i] |
| MONARCH plus | L | L | –[h] | –[k] | H[i, l] | –[k] | –[h] | –[k] | H[i] | H[i] | L[j] | H[i] | H[i] | H[i] |

a. Measured with the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-BR23.
b. Measured with the mBPI-SF symptom scale "worst pain in the last 24 hours" and the increase in analgesic use by ≥ 1 step according to the WHO 3-step system for the management of cancer pain [29], combined and separate analysis.
c. Measured with the functional scales of the EORTC QLQ-C30 and EORTC QLQ-BR23 as well as with the global health status of the EORTC QLQ-C30.
d. Severe AEs are operationalized as CTCAE grade ≥ 3.
e. Discontinuation of at least one of both drugs.
f. PT collection of the company, operationalized using the PTs neutropenia, febrile neutropenia and neutrophil count decreased.
g. The following events are considered (MedDRA coding): anaemia (PT, severe AEs), eye disorders (SOC, AEs), gastrointestinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), renal and urinary disorders (SOC, AEs).
h. No usable data (see Section 2.4.2.1).
i. Incomplete observation for potentially informative reasons.
j. 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).
k. Outcome not recorded.
l. In the MONARCH plus study, only the subcomponent "worst pain in the last 24 hours" of the mBPI-SF was recorded for the outcome of pain.

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

**MONARCH 2**

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

The certainty of results for the outcome of discontinuation due to AEs is limited despite a low risk of bias. Premature treatment discontinuation for reasons other than AEs is a competing

event for the outcome of discontinuation due to AEs to be recorded. This means that, after discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It cannot be estimated how many AEs this concerns.

In all other outcomes with usable data, the risk of bias of the results is rated as high due to incomplete observations for potentially informative reasons.

**MONARCH plus**

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

The certainty of results for the outcome of discontinuation due to AEs is limited despite low risk of bias (for reasons, see MONARCH 2). In all other outcomes with usable data, the risk of bias of the results is rated as high due to incomplete observations for potentially informative reasons.

#### 2.4.2.3 Results

Table 15 summarizes the results of the comparison of abemaciclib in combination with fulvestrant versus fulvestrant in postmenopausal patients with HR-positive and HER2-negative locally advanced or metastatic breast cancer as initial endocrine-based therapy (research question A1). Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves on the event time analyses of the outcomes in the included studies are presented in Appendix B.1 of the full dossier assessment. No Kaplan-Meier curves for the specific AEs identified in the review of study results are available for the MONARCH plus study. Results on common AEs can be found in Appendix B.2 of the full dossier assessment.

Table 15: Results (mortality, morbidity, and side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine-based therapy) (multipage table)

| Outcome category<br>Outcome<br>Study | Abemaciclib + fulvestrant | | Placebo + fulvestrant | | Abemaciclib + fulvestrant vs. placebo + fulvestrant |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value[a] |
| **Mortality** | | | | | |
| Overall survival | | | | | |
| MONARCH 2[b] | 246 | 44.0 [37.8; 51.7]<br>123 (50.0) | 128 | 37.3 [33.0; 48.9]<br>68 (53.1) | 0.82 [0.61; 1.10]; 0.186 |
| MONARCH plus[b] | 81 | NA<br>20 (24.7) | 40 | NA [19.9; NC]<br>14 (35.0) | 0.56 [0.28; 1.11]; 0.091 |
| Total[c] | | | | | 0.77 [0.59; 1.01]; 0.061 |
| **Morbidity** | | | | | |
| Pain (composite outcome), time to first deterioration[d] | | | | | |
| MONARCH 2[b] | 245 | 11.1 [6.0; 14.8]<br>124 (50.6) | 128 | 9.3 [5.8; 18.4]<br>64 (50.0) | 0.95 [0.70; 1.28]; 0.722 |
| MONARCH plus[b] | | | Outcome not recorded | | |
| Worst pain in the last 24 hours (deterioration by ≥ 2 points on the mBPI-SF symptom scale) | | | | | |
| MONARCH 2[b] | 245 | 16.6 [8.1; 34.9]<br>104 (42.4) | 128 | 16.7 [8.7; 24.7]<br>54 (42.2) | 0.94 [0.67; 1.31]; 0.695 |
| MONARCH plus[b] | 81 | NA [13.6; NC]<br>26 (32.1) | 40 | NA [10.3; NC]<br>10 (25.0) | 1.22 [0.59; 2.53]; 0.600 |
| Total[c] | | | | | 0.98 [0.73; 1.33]; 0.899 |
| Increase in analgesic use by ≥ 1 step | | | | | |
| MONARCH 2[b] | 245 | NA<br>46 (18.8) | 128 | NA<br>22 (17.2) | 0.94 [0.56; 1.56]; 0.804 |
| MONARCH plus[b] | | | Outcome not recorded | | |
| Symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23) | | | No usable data[e] | | |
| Health status (EQ-5D VAS) | | | No usable data[e] | | |
| **Health-related quality of life** | | | | | |
| EORTC QLQ-C30 and EORTC QLQ-BR23 | | | No usable data[e] | | |

Table 15: Results (mortality, morbidity, and side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine-based therapy) (multipage table)

| Outcome category<br>Outcome<br>Study | Abemaciclib + fulvestrant | | Placebo + fulvestrant | | Abemaciclib + fulvestrant vs. placebo + fulvestrant |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value[a] |
| **Side effects** | | | | | |
| AEs (supplementary information) | | | | | |
| MONARCH 2[b] | 245 | 0.1 [0.1; 0.1]<br>242 (98.8) | 128 | 0.6 [0.5; 1.0]<br>117 (91.4) | – |
| MONARCH plus[b] | 81 | 0.1 [0.1; 0.2]<br>81 (100) | 40 | 1.0 [0.4; 2.1]<br>34 (85.0) | – |
| SAEs | | | | | |
| MONARCH 2[b] | 245 | NA [36.8; NC]<br>72 (29.4) | 128 | 52.0 [42.5; NC]<br>18 (14.1) | 1.96 [1.17; 3.30]; 0.009 |
| MONARCH plus[b] | 81 | NA [26.7; NC]<br>18 (22.2) | 40 | NA<br>3 (7.5) | 2.60 [0.76; 8.84]; 0.113 |
| Total[c] | | | | | 2.05 [1.27; 3.30]; 0.003 |
| Severe AEs[f] | | | | | |
| MONARCH 2[b] | 245 | 3.7 [2.7; 5.6]<br>166 (67.8) | 128 | 42.5 [20.8; NC]<br>38 (29.7) | 3.39 [2.37; 4.85]; < 0.001 |
| MONARCH plus[b] | 81 | 8.4 [3.7; 13.1]<br>52 (64.2) | 40 | NA [10.7; NC]<br>8 (20.0) | 3.99 [1.90; 8.41]; < 0.001 |
| Total[c] | | | | | 3.50 [2.53; 4.83]; < 0.001 |
| Discontinuation due to AEs[g] | | | | | |
| MONARCH 2[b] | 245 | NA<br>52 (21.2) | 128 | NA<br>7 (5.5) | 3.50 [1.59; 7.72]; < 0.001 |
| MONARCH plus[b] | 81 | NA [26.8; NC]<br>10 (12.3) | 40 | NA<br>1 (2.5) | 3.60 [0.46; 28.20]; 0.192 |
| Total[c] | | | | | 3.51 [1.68; 7.35]; < 0.001 |
| Neutropenia[h] (severe AEs)[f] | | | | | |
| MONARCH 2[b] | 245 | NA<br>63 (25.7) | 128 | NA<br>2 (1.6) | 18.27 [4.47; 74.70]; < 0.001 |
| MONARCH plus[b] | 81 | NA [14.7; NC]<br>28 (34.6) | 40 | NA<br>2 (5.0) | 7.14 [1.70; 29.99]; 0.002 |
| Total[c] | | | | | 11.52 [4.22; 31.49]; < 0.001 |

Table 15: Results (mortality, morbidity, and side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine-based therapy) (multipage table)

| Outcome category<br>Outcome<br>Study | Abemaciclib + fulvestrant | | Placebo + fulvestrant | | Abemaciclib + fulvestrant vs. placebo + fulvestrant |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value[a] |
| Diarrhoea (PT, severe AEs)[f] | | | | | |
| MONARCH 2[b] | 245 | NA<br>35 (14.3) | 128 | NA<br>1 (0.8) | 18.30 [2.51; 133.70]; < 0.001 |
| MONARCH plus[b] | 81 | NA<br>1 (1.2[i]) | 40 | NA<br>0 (0) | NC[j]; 0.482 |
| Total[c] | | | | | NC |
| Anaemia (PT, severe AEs)[f] | | | | | |
| MONARCH 2[b] | 245 | NA<br>19 (7.8) | 128 | NA<br>2 (1.6) | 4.15 [0.96; 17.89]; 0.038 |
| MONARCH plus[b] | 81 | NA [26.7; NC]<br>14 (17.3) | 40 | NA<br>1 (2.5) | 5.73 [0.75; 43.71]; 0.057 |
| Total[c] | | | | | 4.63 [1.41; 15.17]; 0.011 |
| Eye disorders (SOC, AEs) | | | | | |
| MONARCH 2[b] | 245 | NA<br>48 (19.6) | 128 | NA<br>9 (7.0) | 2.65 [1.30; 5.40]; 0.005 |
| MONARCH plus[b] | 81 | ND<br>7 (8.6[i]) | 40 | ND<br>1 (2.5[i]) | 2.97 [0.37; 24.17]; 0.309[k] |
| Total[c] | | | | | 2.68 [1.36; 5.26]; 0.004 |
| Gastrointestinal disorders (SOC, AEs) | | | | | |
| MONARCH 2[b] | 245 | 0.2 [0.1; 0.2]<br>232 (94.7) | 128 | 3.7 [2.3; 8.0]<br>81 (63.3) | 3.87 [2.97; 5.04]; < 0.001 |
| MONARCH plus[b] | 81 | 0.2 [0.1; 0.3]<br>70 (86.4) | 40 | NA [4.8; NC]<br>14 (35.0) | 5.29 [2.95; 9.50]; < 0.001 |
| Total[c] | | | | | 4.08 [3.21; 5.19]; < 0.001 |
| Skin and subcutaneous tissue disorders (SOC, AEs) | | | | | |
| MONARCH 2[b] | 245 | 8.5 [6.3; 19.0]<br>117 (47.8) | 128 | NA [33.3; NC]<br>29 (22.7) | 2.38 [1.58; 3.57]; < 0.001 |
| MONARCH plus[b] | 81 | NA<br>18 (22.2) | 40 | NA<br>3 (7.5) | 2.59 [0.76; 8.82]; 0.114 |
| Total[c] | | | | | 2.40 [1.63; 3.53]; < 0.001 |

Table 15: Results (mortality, morbidity, and side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine-based therapy) (multipage table)

| Outcome category<br>Outcome<br>Study | Abemaciclib + fulvestrant | | Placebo + fulvestrant | | Abemaciclib + fulvestrant vs. placebo + fulvestrant |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value[a] |
| Renal and urinary disorders (SOC, AEs) | | | | | |
| MONARCH 2[b] | 245 | NA<br>36 (14.7) | 128 | NA<br>5 (3.9) | 3.35 [1.31; 8.58]; 0.007 |
| MONARCH plus[b] | 81 | ND<br>7 (8.6[i]) | 40 | ND<br>1 (2.5[i]) | 2.61 [0.32; 21.24]; 0.371[k] |
| Total[c] | | | | | 3.22 [1.37; 7.58]; 0.008 |

a. HR [95% CI]: Cox proportional hazards model with treatment group as factor; p-value: unstratified log-rank test.
b. Data cut-off: MONARCH 2 study: 20 June 2019, MONARCH plus study: 18 May 2020.
c. Calculated from meta-analysis.
d. Time to first deterioration defined as an increase of 2 points on the mBPI-SF symptom scale "worst pain in the last 24 hours" (scale range: 0 to 11) from baseline or increase in analgesic use by ≥ 1 step (according to the WHO 3-step system for the management of cancer pain [29]), in each case first occurrence. In the analysis, death is not rated as an event and censored.
e. No usable data; see Section 2.4.2.1 for reasons.
f. Severe AEs are operationalized as CTCAE grade ≥ 3.
g. Discontinuation of at least one of both drugs.
h. PT collection of the company, operationalized using the PTs neutropenia, febrile neutropenia and neutrophil count decreased.
i. Institute's calculation.
j. Since no events occurred in one study arm, the HR cannot be estimated.
k. p-value presumably Wald test.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer-Breast Cancer Module 23; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; mBPI-SF: modified Brief Pain Inventory-Short Form; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; WHO: World Health Organization

On the basis of the available data of the studies MONARCH 2 and MONARCH plus, at most proof, e.g. of an added benefit, can be determined for the outcome of overall survival, and, due to the high risk of bias or the limited certainty of results (discontinuation due to AEs), at most indications for all other outcomes. For outcomes with high risk of bias and available results from only one study, no more than hints can be derived.

**Mortality**

***Overall survival***

For the outcome of overall survival, the meta-analysis of the studies does not show any statistically significant differences between treatment groups. This results in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

**Morbidity**

***Pain***

For the outcome of pain (worst pain in the last 24 hours and increase in analgesic use), the studies showed no statistically significant difference between the treatment groups, neither for the composite outcome nor for its individual components. In each case, this results in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

***Symptoms, recorded using the EORTC QLQ-C30 and the EORTC QLQ-BR23 (symptom scales)***

There are no usable data for the outcome of symptoms, recorded with the EORTC QLQ-C30 and EORTC QLQ-BR23 symptom scales (see Section 2.4.2.1). In each case, this results in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

***Health status (EQ-5D VAS)***

There are no usable data for the outcome of health status recorded with the EQ-5D VAS (see Section 2.4.2.1). This results in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

**Health-related quality of life**

***Health-related quality of life, recorded using the EORTC QLQ-C30 (global health status and functional scales) and the EORTC QLQ-BR23 (functional scales)***

There are no usable data for the outcome of health-related quality of life, recorded using the scales of EORTC QLQ-C30 (global health status and functional scales) and EORTC QLQ-BR23 (functional scales) (see Section 2.4.2.1). In each case, this results in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

**Side effects**

***SAEs and severe AEs (CTCAE grade ≥ 3), as well as discontinuation due to AEs***

The meta-analysis shows a statistically significant difference to the disadvantage of abemaciclib + fulvestrant for each of the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3) as well as

discontinuation due to AEs. This results in an indication of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for each of these outcomes.

***Specific AEs***

*Neutropenia (severe AEs)*

The meta-analysis shows a statistically significant difference to the disadvantage of abemaciclib + fulvestrant for the outcome of neutropenia (severe AEs). Due to the size of the effect, which was already evident in both studies at an early point in the course of the studies and almost exclusively in the intervention arms (see Figure 9 and Figure 21 of the full dossier assessment), there is a high certainty of results for this outcome despite high risk of bias. This results in proof of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

*Diarrhoea (severe AEs)*

The MONARCH 2 study showed a statistically significant difference to the disadvantage of abemaciclib for the outcome of diarrhoea (severe AEs). As no events occurred in the control arm of the MONARCH plus study, the effect estimate cannot be calculated and a meta-analysis cannot be conducted in a meaningful way. This results in a hint of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

*Anaemia (severe AEs), eye disorders (AEs), gastrointestinal disorders (AEs), skin and subcutaneous tissue disorders (AEs) as well as renal and urinary disorders (AEs)*

For the specific AEs of anaemia (severe AEs), eye disorders (AEs), gastrointestinal disorders (AEs), skin and subcutaneous tissue disorders (AEs) as well as renal and urinary disorders (AEs), the meta-analysis shows a statistically significant difference to the disadvantage of abemaciclib + fulvestrant. This results in an indication of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for each of these outcomes.

#### 2.4.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are considered in the benefit assessment:

- age (< 65 years/≥ 65 years)
- type of disease (visceral metastases versus non-visceral metastases)
- sensitivity to endocrine therapy (primary versus secondary)

The mentioned characteristics were defined a priori. In the dossier, the company presented subgroup analyses for outcomes of the present benefit assessment with the following exceptions: Subgroup analyses, but no interaction tests, are available for the specific AEs in the company's dossier. These were therefore calculated by the Institute based on the available data.

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 one subgroup.

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

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

### 2.4.3 Probability and extent of added benefit

For research question A1 (postmenopausal women, initial endocrine-based therapy), the probability and extent of added benefit are derived below at the outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

#### 2.4.3.1 Assessment of the added benefit at outcome level

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

**Determination of the outcome category for the outcomes on side effects**

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

***Side effects***

Again, there is no information about the severity grade attributable to the events that resulted in discontinuation due to AEs. Therefore, the outcome of discontinuation due to AEs is assigned to the outcome category of non-serious/non-severe side effects. Due to the missing data, it cannot be ruled out that the category “serious/severe” is applicable, however.

Table 16: Extent of added benefit at outcome level: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine-based therapy) (multipage table)

| **Observation period**<br>**Outcome category**<br>**Outcome**<br>**Subscale**<br>**Effect modifier**<br>**Subgroup** | **Abemaciclib + fulvestrant vs. placebo + fulvestrant**<br>**Median time to event (months)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Total observation period** | | |
| **Mortality** | | |
| Overall survival | 44.0 and NA vs. 37.3 and NA months<br>HR: 0.77 [0.59; 1.01]<br>p = 0.061 | Lesser benefit/added benefit not proven |
| **Shortened observation period** | | |
| **Morbidity** | | |
| Pain | | |
| Pain (composite outcome: worst pain in the last 24 hours **or** increase in analgesic use by ≥ 1 step) | 11.1 vs. 9.3 months<br>HR: 0.95 [0.70; 1.28]<br>p = 0.722 | Lesser benefit/added benefit not proven |
| Worst pain in the last 24 hours | 16.6 and NA vs. 16.7 and NA months<br>HR: 0.98 [0.73; 1.33]<br>p = 0.899 | |
| Increase in analgesic use by ≥ 1 step | NA vs. NA months<br>HR: 0.94 [0.56; 1.56]<br>p = 0.804 | |
| Symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23) | No usable data | Lesser benefit/added benefit not proven |
| Health status (EQ-5D VAS) | No usable data | Lesser benefit/added benefit not proven |
| **Health-related quality of life** | | |
| EORTC QLQ-C30 and EORTC QLQ-BR23 | No usable data | Lesser benefit/added benefit not proven |
| **Side effects** | | |
| SAEs | NA and NA vs. 52.0 and NA months<br>HR: 2.05 [1.27; 3.30]<br>HR: 0.49 [0.30; 0.79][c]<br>p = 0.003<br>Probability: “indication” | Outcome category: serious/severe side effects<br>$0.75 \leq CI_u < 0.90$<br>Greater harm, extent: “considerable” |
| Severe AEs | 3.7 and 8.4 vs. 42.5 and NA months<br>HR: 3.50 [2.53; 4.83]<br>HR: 0.29 [0.21; 0.40][c]<br>p < 0.001<br>Probability: “indication” | Outcome category: severe/serious side effects<br>$CI_u < 0.75$, risk ≥ 5%<br>Greater harm, extent: “major” |

Table 16: Extent of added benefit at outcome level: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine-based therapy) (multipage table)

| **Observation period**<br>**Outcome category**<br>**Outcome**<br>**Subscale**<br>**Effect modifier**<br>**Subgroup** | **Abemaciclib + fulvestrant vs. placebo + fulvestrant**<br>**Median time to event (months)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability[a]** | **Derivation of extent[b]** |
|---|---|---|
| Discontinuation due to AEs[d] | NA and NA vs. NA and NA months<br>HR: 3.51 [1.68; 7.35]<br>HR: 0.28 [0.14; 0.60][c]<br>p < 0.001<br>Probability: "indication" | Outcome category: non-severe/non-serious side effects<br>$CI_u$ < 0.80<br>Greater harm, extent: "considerable" |
| Neutropenia (severe AEs) | NA and NA vs. NA and NA months<br>HR: 11.52 [4.22; 31.49]<br>HR: 0.09 [0.03; 0.24][c]<br>p < 0.001<br>Probability: "proof" | Outcome category: severe/serious side effects<br>$CI_u$ < 0.75, risk ≥ 5%<br>Greater harm, extent: "major" |
| Diarrhoea (severe AEs) | MONARCH 2<br>NA vs. NA months<br>HR: 18.30 [2.51; 133.70]<br>HR: 0.05 [0.01; 0.40][c]<br>p < 0.001<br>MONARCH plus<br>NA vs. NA months<br>HR: NC[e]<br>p = 0.482<br>Probability: "hint" | Outcome category: severe/serious side effects<br>$CI_u$ < 0.75, risk ≥ 5%<br>Greater harm, extent: "major" |
| Anaemia (severe AEs) | NA and NA vs. NA and NA months<br>HR: 4.63 [1.41; 15.17]<br>HR: 0.22 [0.07; 0.71][c]<br>p = 0.011<br>Probability: "indication" | Outcome category: serious/severe side effects<br>$CI_u$ < 0.75, risk ≥ 5%<br>Greater harm, extent: "major" |
| Eye disorders (AEs) | NA and ND vs. NA and ND months<br>HR: 2.68 [1.36; 5.26]<br>HR: 0.37 [0.19; 0.74][c]<br>p = 0.004<br>Probability: "indication" | Outcome category: non-severe/non-serious side effects<br>$CI_u$ < 0.80<br>Greater harm, extent: "considerable" |
| Gastrointestinal disorders (AEs) | 0.2 and 0.2 vs. 3.7 and NA months<br>HR: 4.08 [3.21; 5.19]<br>HR: 0.25 [0.19; 0.31][c]<br>p < 0.001<br>Probability: "indication" | Outcome category: non-severe/non-serious side effects<br>$CI_u$ < 0.80<br>Greater harm, extent: "considerable" |

Table 16: Extent of added benefit at outcome level: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine-based therapy) (multipage table)

| **Observation period**<br>**Outcome category**<br>**Outcome**<br>**Subscale**<br>**Effect modifier**<br>**Subgroup** | **Abemaciclib + fulvestrant vs. placebo + fulvestrant**<br>**Median time to event (months)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| Skin and subcutaneous tissue disorders (AEs) | 8.5 and NA vs. NA and NA months<br>HR: 2.40 [1.63; 3.53]<br>HR: 0.42 [0.28; 0.61][c]<br>p < 0.001<br>Probability: "indication" | Outcome category: non-severe/non-serious side effects<br>$CI_u$ < 0.80<br>Greater harm, extent: "considerable" |
| Renal and urinary disorders (AEs) | NA and NC vs. NA and NC months<br>HR: 3.22 [1.37; 7.58]<br>HR: 0.31 [0.13; 0.73][c]<br>p = 0.008<br>Probability: "indication" | Outcome category: non-severe/non-serious side effects<br>$CI_u$ < 0.80<br>Greater harm, extent: "considerable" |

a. Probability provided if statistically significant differences are present.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval ($CI_u$).
c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
d. Discontinuation of at least one of both drugs.
e. Since no events occurred in one study arm, the HR could not be estimated. However, if added benefit/lesser benefit or greater/lesser harm was derived from the other studies, the event rates of the studies without effect estimation were considered to see if they supported the overall result.

AE: adverse event; CI: confidence interval; $CI_u$: upper limit of confidence interval; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module 23; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

#### 2.4.3.2 Overall conclusion on added benefit

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

Table 17: Positive and negative effects from the assessment of abemaciclib + fulvestrant in comparison with placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine-based therapy)

| **Positive effects** | **Negative effects** |
|---|---|
| **Total observation period** | |
| – | – |
| **Shortened observation period** | |
| – | Serious/severe side effects<br>▪ SAEs: indication of greater harm – extent "considerable"<br>▪ Severe AEs: indication of greater harm – extent: "major", including:<br>▫ Neutropenia (severe AEs): proof of greater harm – extent: "major"<br>▫ Diarrhoea (severe AEs): hint of greater harm – extent "major"<br>▫ Anaemia (severe AEs): indication of greater harm – extent: "major" |
| – | Non-serious/non-severe side effects<br>▪ Discontinuation due to AEs: indication of greater harm – extent: "considerable"<br>▪ Eye disorders (AEs): indication of greater harm – extent "considerable"<br>▪ Gastrointestinal disorders (AEs): indication of greater harm – extent: "considerable"<br>▪ Skin and subcutaneous tissue disorders (AEs): indication of greater harm – extent: "considerable"<br>▪ Renal and urinary disorders (AEs): indication of greater harm – extent: "considerable" |
| The data on morbidity (except pain) and health-related quality of life are not usable | |
| AE: adverse event; SAE: serious adverse event | |

In the overall consideration, there are only negative effects of abemaciclib + fulvestrant in comparison with fulvestrant on the basis of the results of the studies MONARCH 2 and MONARCH plus. These refer exclusively to the shortened period until the end of treatment. The analyses presented on morbidity (except pain) and health-related quality of life are not usable.

In the present data situation, there is particular uncertainty as to whether adequate analyses of the outcomes on morbidity and health-related quality of life would influence the overall weighing in favour of abemaciclib in combination with fulvestrant.

Taking into account this uncertainty and the narrowly not statistically significant result of overall survival, there is no hint of an added benefit of abemaciclib in combination with fulvestrant compared with fulvestrant alone for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer with initial endocrine-based therapy (research question A1); an added benefit is therefore not proven.

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

## 2.5 Research question B1: postmenopausal women who received prior endocrine therapy

Details on the information retrieval and on the study pool relevant to research question B1 can be found in Section 2.3.

### 2.5.1 Study characteristics

**MONARCH 2**

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

***Subpopulation relevant to the assessment of research question B1***

Among the patients included in the MONARCH 2 study, only the subpopulation of postmenopausal women who have already received endocrine therapy for the locally advanced or metastatic stage are relevant to the assessment of research question B1 (see Section 2.2). Out of the total of 713 patients, this applies to 210 (29.5%), of which 144 patients were treated with abemaciclib in combination with fulvestrant and 66 patients were treated with fulvestrant (+ placebo). Analogous to the previous benefit assessment, the company presented analyses of this subpopulation in its dossier. These are used for the benefit assessment.

***Abemaciclib starting dose and suitability of fulvestrant as an appropriate comparator therapy***

As already described in detail in A20-32, although there are deviations with regard to the starting dose of abemaciclib provided for in the initial study protocol (200 mg instead of 150 mg) and the pretreatment when using fulvestrant, which was partly not in compliance with the approval, analogous to the previous procedures, this has no consequences for the present benefit assessment (for details see Section 2.4.1 in dossier assessment A20-32 [4] and, e.g., the G-BA justification on benefit assessment procedure A18-73 [6].

**MONARCH plus**

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

***Subpopulation relevant to research question B1***

Among the patients included in the MONARCH plus study, only the subpopulation of postmenopausal women who have already received endocrine therapy for the locally advanced or metastatic stage are relevant to the assessment of research question B1 (see Section 2.2). In the current dossier, the company presented for the first time analyses for the subpopulations relevant to the assessment. Out of the total of 157 patients, 36 (22.9%) patients are relevant to research question B1, of which 23 patients were treated with abemaciclib in combination with fulvestrant and 13 patients were treated with fulvestrant (+ placebo).

**Patient characteristics**

Table 18 shows the characteristics of the patients (research question B1) in the studies included.

Table 18: Characteristics of the study populations – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy) (multipage table)

| Study Characteristic Category | MONARCH 2 | | MONARCH plus | |
|---|---|---|---|---|
| | Abemaciclib + fulvestrant Na = 144 | Placebo + fulvestrant Na = 66 | Abemaciclib + fulvestrant Na = 23 | Placebo + fulvestrant Na = 13 |
| Sex [F/M],% | 100/0 | 100/0 | 100/0 | 100/0 |
| Age [years], mean (SD) | 63 (10) | 66 (10) | 61 (10) | 57 (12) |
| Age group, n (%) | | | | |
| < 65 years | 79 (55) | 28 (42) | 16 (70) | 9 (69) |
| ≥ 65 years | 65 (45) | 38 (58) | 7 (30) | 4 (31) |
| Family origin n (%) | | | | |
| Caucasian | 81 (56) | 47 (71) | 2 (9) | 0 (0) |
| Asian | 43 (30) | 13 (20) | 21 (91) | 13 (100) |
| Other | 20 (14)[b, c] | 6 (9)[b, c] | – | – |
| Region, n (%) | | | | |
| Europe | 76 (53) | 37 (56) | – | – |
| North America | 25 (17) | 16 (24) | – | – |
| South America | – | – | 2 (9) | 0 (0) |
| Asia | 43 (30) | 13 (20) | 21 (91) | 13 (100) |
| Starting dose, n (%) | | | | |
| 150 mg abemaciclib per dose | 104 (72) | 49 (74) | 23 (100) | 13 (100) |
| 200 mg abemaciclib per dose | 40 (28) | 17 (26) | – | – |
| ECOG PS, n (%)[d] | | | | |
| 0 | 83 (58) | 36 (55) | 8 (35) | 7 (54) |
| 1 | 58 (40) | 30 (45) | 15 (65) | 6 (46) |
| Type of disease, n (%) | | | | |
| Visceral metastases | 78 (54) | 39 (59) | 17 (74) | 10 (77) |
| Non-visceral metastases | 66 (46)[e] | 27 (41)[e] | 6 (26) | 3 (23) |
| Sensitivity to endocrine therapy, n (%) | | | | |
| Primary resistance | 27 (19) | 10 (15) | 6 (26) | 2 (15) |
| Secondary resistance | 117 (81) | 56 (85) | 17 (74) | 11 (85) |
| No prior therapy | – | – | – | – |
| Previous anti-oestrogen therapy, n (%) | | | | |
| Yes | 69 (48) | 38 (58) | 12 (52) | 7 (54) |
| No | 75 (52) | 28 (42) | 11 (48) | 6 (46) |
| Disease duration (time between first diagnosis and randomization) [months], mean (SD) | 91.3 (80.8) | 103.3 (89.8) | 93.7 (78.0) | 78.8 (65.3) |
| Treatment discontinuation, n (%) | ND[f] | ND[f] | ND[g] | ND[g] |
| Study discontinuation, n (%) | ND | ND | ND | ND |

Table 18: Characteristics of the study populations – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy) (multipage table)

| Study Characteristic Category | MONARCH 2 | | MONARCH plus | |
|---|---|---|---|---|
| | Abemaciclib + fulvestrant Na = 144 | Placebo + fulvestrant Na = 66 | Abemaciclib + fulvestrant Na = 23 | Placebo + fulvestrant Na = 13 |

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. Including Native American, Native Alaskan, Black/African American, multiple, and patients with missing information on family history.
c. Institute's calculation.
d. Study MONARCH 2: one patient with ECOG PS 2 in the intervention arm. No information on ECOG status is available for 2 patients.
e. Institute's calculation: totalled from the categories of bone metastases and other.
f. Data on the most common reasons for discontinuation are only available for the ITT population (446 vs. 223 patients), in which 364 (intervention arm) vs. 215 (control arm) patients discontinued therapy: Here, the most common reason for discontinuing therapy was disease progression in 269 (74%) vs. 187 (87%) patients who discontinued therapy.
g. Data on the most common reasons for discontinuation are only available for the ITT population (104 vs. 53 patients), in which 50 (intervention arm) vs. 40 (control arm) patients discontinued therapy: The most common reason for discontinuing therapy was disease progression in 40 (80%) vs. 33 (83%) patients who discontinued therapy.

ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; M: male; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The characteristics of the postmenopausal patients with initial endocrine-based therapy (research question A1) are largely comparable between the respective study arms of the MONARCH 2 study and of the MONARCH plus study.

The mean age of the patients in the MONARCH 2 study on study entry was about 64 years. 61% of the patients were of Caucasian family origin. A little more than half of the patients had an ECOG PS of 0, and about 56% of the patients had visceral metastases.

The mean age of the patients in the MONARCH plus study on study entry was about 60 years. The study was conducted predominantly in Asia and in Asian patients. About 58% of the patients had an ECOG PS of 1, and 3 quarters of the patients had visceral metastases.

Analogous to the population of research question A1, there are differences between the studies, which particularly concern age and family origin.

However, the differences do not fundamentally call into question the feasibility of a meta-analysis, as the studies are considered sufficiently comparable for the research question investigated. For the benefit assessment, before using or calculating meta-analyses, heterogeneity tests are used to check whether the 2 studies are sufficiently homogeneous for statistical pooling [1].

**Median treatment duration**

Table 19 shows the median treatment duration of the patients and the median observation period for individual outcomes in the studies MONARCH 2 and MONARCH plus.

Table 19: Information on the course of the study – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy) (multipage table)

| **Study**<br>**Duration of the study phase**<br>**Outcome category** | **Abemaciclib + fulvestrant** | **Placebo + fulvestrant** |
|---|---|---|
| **Study MONARCH 2 (data cut-off: 20 June 2019)** | N = 143 | N = 66 |
| Duration of treatment with abemaciclib/placebo [months] | | |
| Median [Q1; Q3] | 11.6 [3.2; 24.4] | 5.7 [2.8; 14.7] |
| Observation period [months] | | |
| Overall survival[a] | | |
| Median [95% CI] | 47.8 [46.4; 48.5] | 49.5 [46.5; 50.9] |
| Morbidity (EORTC QLQ-C30, EORTC QLQ-BR23) | | |
| Median [min; max] | 13.7 [< 0.1; 54.4] | 5.6 [1.0; 47.2] |
| Morbidity pain (mBPI-SF) | ND | ND |
| Morbidity (EQ-5D VAS) | | |
| Median [min; max] | 13.7 [< 0.1; 54.4] | 5.6 [1.0; 47.2] |
| Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23) | | |
| Median [min; max] | 13.7 [< 0.1; 54.4] | 5.6 [1.0; 47.2] |
| Side effects | | |
| Median [min; max] | 14.4 [1.0; 54.7] | 6.7 [1.5; 47.9] |
| **Study MONARCH plus (data cut-off: 18 May 2020)** | N = 23 | N = 13 |
| Duration of treatment with abemaciclib/placebo [months] | | |
| Median [Q1; Q3] | 11.1 [6.5; 23.5] | 5.5 [1.8; 7.7] |
| Observation period [months] | | |
| Overall survival[a] | | |
| Median [95% CI] | 26.2 [23.0; 27.8] | 25.1 [5.9; 27.4] |
| Morbidity (EORTC QLQ-C30) | | |
| Median [min; max] | 12.6 [1.0; 25.9] | 3.8 [< 0.1; 25.4] |
| Morbidity pain (mBPI-SF) | ND | ND |
| Health-related quality of life (EORTC QLQ-C30) | | |
| Median [min; max] | 12.6 [1.0; 25.9] | 3.8 [< 0.1; 25.4] |
| Side effects | | |
| Median [min; max] | 12.1 [2.4; 28.7] | 6.3 [1.5; 27.3] |

Table 19: Information on the course of the study – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy) (multipage table)

| Study | Abemaciclib + fulvestrant | Placebo + fulvestrant |
|---|---|---|
| **Duration of the study phase** | | |
| **Outcome category** | | |
| a. The company did not provide any information on the methods used to determine observation periods in the subpopulation. However, it can be assumed that the observation period is calculated using the Kaplan-Meier method as indicated in the statistical analysis plan for the total population. | | |
| AE: adverse event; CI: confidence interval; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module 23; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; max: maximum; mBPI-SF: modified Brief Pain Inventory-Short Form; min: minimum; N: number of analysed patients; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; VAS: visual analogue scale | | |

With the present benefit assessment, the company presented for the first time information on the median treatment durations and observation periods for the relevant subpopulations of the studies MONARCH 2 and MONARCH plus. In both studies, the treatment durations are longer in the intervention arms than in the control arms. Treatment in the intervention arms (approximately 11 months) was twice as long as in the control arms (approximately 5.5 months). The observation period for the outcome of overall survival was similar in the arms of the studies, but at about 48 months markedly longer overall in the MONARCH 2 study than in the MONARCH plus study at about 25 months. For the other outcomes, whose observation period was linked to treatment end (see Table 9), there were both markedly shorter observation periods and marked differences in observation periods between the study arms of the 2 studies, as shown for research question A1. This data situation influences the interpretability of the outcomes with shorter observation period (see Section 2.4.2.1).

**Subsequent therapies**

After treatment discontinuation, patients in both studies could start subsequent therapy. The data on the subsequent therapies used in the studies are available for the first time for the respective subpopulations and are presented in Appendix C.3 of the full dossier assessment (Table 50 and Table 51).

In the MONARCH 2 study, a large proportion of patients with progression had received at least one subsequent systemic therapy by the final data cut-off. However, the proportion of patients with subsequent systemic therapy in the intervention arm was lower than that in the control arm (79.5% versus 92.3%), also in relation to the individual substance classes (chemotherapy, endocrine therapy, targeted therapy, other systemic therapies). In both study arms, chemotherapy was the most common subsequent therapy.

In the MONARCH plus study, 55.6% of patients with progression in the intervention arm had received at least one subsequent systemic therapy (mainly chemotherapy) at the available data cut-off, whereas this was the case for only 33.3% of patients with progression in the control

arm. Overall, an interpretation of the data on subsequent therapies is difficult due to the small number of patients relevant to research question B1.

**Risk of bias across outcomes (study level)**

Table 12 (Section 2.4.1) shows the risk of bias across outcomes (risk of bias at study level).

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

**Transferability of the study results to the German health care context**

The company's assessment of the transferability of the studies MONARCH 2 and MONARCH plus to the German health care context is described in 2.4.1 (see text section on transferability).

### 2.5.2 Results on added benefit

#### 2.5.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms, measured using the symptom scales of the questionnaires EORTC QLQ-C30 and EORTC QLQ-BR23
  - pain (measured with the mBPI-SF as well as the increase in analgesic use by ≥ 1 step)
  - health status, measured with the EQ-5D VAS
- Health-related quality of life
  - measured with the functional scales of the EORTC QLQ-C30 and of the EORTC QLQ-BR23
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuations due to AEs
  - neutropenia, PT collection of the company (severe AEs [CTCAE grade ≥ 3])
  - diarrhoea, PT (severe AEs [CTCAE grade ≥ 3])
  - further specific AEs, if any

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

Table 20 shows the outcomes for which data were available in the studies included.

Table 20: Matrix of outcomes – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy)

| Study | Outcomes | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Overall survival | Symptoms (EORTC QLQ-C30)[a] | Symptoms (EORTC QLQ-BR23)[a] | Pain[b] | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30)[c] | Health-related quality of life (EORTC QLQ-BR23)[c] | SAEs | Severe AEs[d] | Discontinuation due to AEs[e] | Neutropenia[f] (severe AEs)[d] | Diarrhoea PT (severe AEs)[d] | Further specific AEs[g] |
| MONARCH 2 | Yes | No[h] | No[h] | Yes | No[h] | No[h] | No[h] | Yes | Yes | Yes | Yes | Yes | Yes |
| MONARCH plus | Yes | No[h] | No[i] | Yes[j] | No[i] | No[h] | No[i] | Yes | Yes | Yes | Yes | Yes | Yes |

a. Measured with the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-BR23.
b. Measured with the mBPI-SF symptom scale "worst pain in the last 24 hours" and the increase in analgesic use by ≥ 1 step according to the WHO 3-step system for the management of cancer pain [29], combined and separate analysis.
c. Measured with the functional scales of the EORTC QLQ-C30 and EORTC QLQ-BR23 as well as with the global health status of the EORTC QLQ-C30.
d. Severe AEs are operationalized as CTCAE grade ≥ 3.
e. Discontinuation of at least one of both drugs.
f. PT collection of the company, operationalized using the PTs neutropenia, febrile neutropenia and neutrophil count decreased.
g. The following events are considered (MedDRA coding): gastrointestinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs).
h. No usable data (for explanation see running text below and Section 2.4.2.1).
i. Outcome not recorded.
j. In the MONARCH plus study, only the subcomponent "worst pain in the last 24 hours" of the mBPI-SF was recorded for the outcome of pain.

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

**Usability of the analyses presented by the company on patient-reported outcomes on symptoms and health-related quality of life (EORTC scales and EQ-5D VAS)**

As explained in Section 2.4.2.1, the analyses presented by the company on the so-called "definitive deterioration" of the patient-reported outcomes on symptoms and health-related quality of life (EORTC scales as well as EQ-5D VAS) cannot be meaningfully interpreted in

the present data situation, but are presented as supplementary information in Appendix C.4 of the full dossier assessment (referred to in the benefit assessment as "confirmed deterioration under treatment").

Thus, for the patient-reported outcomes, suitable analyses (time to first deterioration) are only available for the outcome of pain (recorded using mBPI-SF and analgesic use) (see Section 2.4.2.1), but also only for a shortened observation period.

#### 2.5.2.2 Risk of bias

Table 21 describes the risk of bias for the results of the relevant outcomes in the included studies MONARCH 2 and MONARCH plus in research question B1 (postmenopausal women who have received prior endocrine therapy).

Table 21: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy)

| Study | | Outcomes | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study level | Overall survival | Symptoms (EORTC QLQ-C30)[a] | Symptoms (EORTC QLQ-BR23)[a] | Pain[b] | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30)[c] | Health-related quality of life (EORTC QLQ-BR23)[c] | SAEs | Severe AEs[d] | Discontinuation due to AEs[e] | Neutropenia[f] (severe AEs)[d] | Diarrhoea PT (severe AEs)[d] | Further specific AEs[g] |
| MONARCH 2 | L | L | –[h] | –[h] | H[i] | –[h] | –[h] | –[h] | H[i] | H[i] | L[j] | H[i] | H[i] | H[i] |
| MONARCH plus | L | L | –[h] | –[k] | H[i, l] | –[k] | –[h] | –[k] | H[i] | H[i] | L[j] | H[i] | H[i] | H[i] |

a. Measured with the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-BR23.
b. Measured with the mBPI-SF symptom scale "worst pain in the last 24 hours" and the increase in analgesic use by ≥ 1 step according to the WHO 3-step system for the management of cancer pain [29], combined and separate analysis.
c. Measured with the functional scales of the EORTC QLQ-C30 and EORTC QLQ-BR23 as well as with the global health status of the EORTC QLQ-C30.
d. Severe AEs are operationalized as CTCAE grade ≥ 3.
e. Discontinuation of at least one of both drugs.
f. PT collection of the company, operationalized using the PTs neutropenia, febrile neutropenia and neutrophil count decreased.
g. The following events are considered (MedDRA coding): gastrointestinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs).
h. No usable data available (for explanation see Sections 2.5.2.1 and 2.4.2.1).
i. Incomplete observations for potentially informative reasons.
j. 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).
k. Outcome not recorded.
l. In the MONARCH plus study, only the subcomponent "worst pain in the last 24 hours" of the mBPI-SF was recorded for the outcome of pain.

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

**MONARCH 2**

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

The certainty of results for the outcome of discontinuation due to AEs is limited despite a low risk of bias. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome of discontinuation due to AEs to be recorded. This means that, after

discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It cannot be estimated how many AEs this concerns.

In all other outcomes with usable data, the risk of bias of the results is rated as high due to incomplete observations for potentially informative reasons.

**MONARCH plus**

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

The certainty of results for the outcome of discontinuation due to AEs is limited despite low risk of bias (for reasons, see MONARCH 2). In all other outcomes with usable data, the risk of bias of the results is rated as high due to incomplete observations for potentially informative reasons.

#### 2.5.2.3 Results

Table 22 summarizes the results of the comparison of abemaciclib in combination with fulvestrant versus fulvestrant in postmenopausal patients with HR-positive and HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy (research question B1).

The Kaplan-Meier curves on the event time analyses of the outcomes in the included studies are presented in Appendix C.1 of the full dossier assessment. No Kaplan-Meier curves for the specific AEs identified in the review of study results are available for the MONARCH plus study. Likewise, the Kaplan-Meier curves for the subgroups identified as relevant to the conclusion are missing (see Section 2.5.2.4). Results on common AEs can be found in Appendix C.2 of the full dossier assessment.

Table 22: Results (mortality, morbidity, and side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy) (multipage table)

| Outcome category<br>Outcome<br>Study | Abemaciclib + fulvestrant | | Placebo + fulvestrant | | Abemaciclib + fulvestrant vs. placebo + fulvestrant |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value[a] |
| **Mortality** | | | | | |
| Overall survival | | | | | |
| MONARCH 2[b] | 144 | 48.8 [35.2; NC]<br>66 (45.8) | 66 | 34.8 [28.8; 41.3]<br>44 (66.7) | 0.67 [0.46; 0.98]; 0.037 |
| MONARCH plus[b] | 23 | NA [21.5; NC]<br>6 (26.1) | 13 | NA [5.7; NC]<br>5 (38.5) | 0.45 [0.14; 1.49]; 0.179 |
| Total[c] | | | | | 0.64 [0.45; 0.93]; 0.017 |
| **Morbidity** | | | | | |
| Pain (composite outcome), time to first deterioration[d] | | | | | |
| MONARCH 2[b] | 143 | 13.9 [9.3; 22.2]<br>70 (49.0) | 66 | 6.0 [2.6; 20.3]<br>32 (48.5) | 0.74 [0.49; 1.14]; 0.171 |
| MONARCH plus[b] | | | Outcome not recorded | | |
| Worst pain in the last 24 hours (deterioration by ≥ 2 points on the mBPI-SF symptom scale) | | | | | |
| MONARCH 2[b] | 143 | 18.5 [11.1; 38.7]<br>61 (42.7) | 66 | 16.8 [3.8; 35.0]<br>29 (43.9) | 0.70 [0.45; 1.10]; 0.121 |
| MONARCH plus[b] | 23 | NA [3.2; NC]<br>8 (34.8) | 13 | NA [1.0; NC]<br>3 (23.1) | 1.45 [0.38; 5.50]; 0.573 |
| Total[c] | | | | | 0.76 [0.49; 1.16]; 0.196 |
| Increase in analgesic use by ≥ 1 step | | | | | |
| MONARCH 2[b] | 143 | NA<br>23 (16.1) | 66 | NA<br>7 (10.6) | 1.10 [0.47; 2.60]; 0.827 |
| MONARCH plus[b] | | | Outcome not recorded | | |
| Symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23) | | | | No usable data[e] | |
| Health status (EQ-5D VAS) | | | | No usable data[e] | |
| **Health-related quality of life** | | | | | |
| EORTC QLQ-C30 and EORTC QLQ-BR23 | | | | No usable data[e] | |

Table 22: Results (mortality, morbidity, and side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy) (multipage table)

| Outcome category<br>Outcome<br>Study | Abemaciclib + fulvestrant | | Placebo + fulvestrant | | Abemaciclib + fulvestrant vs. placebo + fulvestrant |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event n (%) | N | Median time to event in months [95% CI]<br>Patients with event n (%) | HR [95% CI]; p-value[a] |
| **Side effects** | | | | | |
| AEs (supplementary information) | | | | | |
| MONARCH 2[b] | 143 | 0.1 [< 0.1; 0.1]<br>140 (97.9) | 66 | 0.5 [0.3; 1.0]<br>59 (89.4) | – |
| MONARCH plus[b] | 23 | 0.2 [0.1; 0.4]<br>23 (100) | 13 | 0.9 [0.5; NC]<br>9 (69.2) | – |
| SAEs | | | | | |
| MONARCH 2[b] | 143 | 47.1 [34.0; NC]<br>40 (28.0) | 66 | 29.9 [15.1; NC]<br>14 (21.2) | 0.96 [0.52; 1.78]; 0.896 |
| MONARCH plus[b] | 23 | NA [22.9; NC]<br>6 (26.1) | 13 | NA<br>1 (7.7) | 2.21 [0.26; 18.84]; 0.459 |
| Total[c] | | | | | 1.02 [0.56; 1.86]; 0.941 |
| Severe AEs[f] | | | | | |
| MONARCH 2[b] | 143 | 4.6 [1.9; 9.0]<br>99 (69.2) | 66 | 28.0 [9.9; NC]<br>21 (31.8) | 2.61 [1.63; 4.19]; < 0.001 |
| MONARCH plus[b] | 23 | 5.6 [1.8; 13.3]<br>16 (69.6) | 13 | NA [2.7; NC]<br>1 (7.7) | 9.57 [1.27; 72.27]; 0.007 |
| Total[c] | | | | | 2.79 [1.76; 4.43]; < 0.001 |
| Discontinuation due to AEs[g] | | | | | |
| MONARCH 2[b] | 143 | NA [38.1; NC]<br>34 (23.8) | 66 | NA<br>2 (3.0) | 6.49 [1.55; 27.12]; 0.003 |
| MONARCH plus[b] | 23 | NA [18.5; NC]<br>2 (8.7) | 13 | NA<br>1 (7.7) | 0.56 [0.05; 6.73]; 0.643 |
| Total[c] | | | | | 3.53 [1.02; 12.19]; 0.046 |
| Neutropenia[h] (severe AEs)[f] | | | | | |
| MONARCH 2[b] | 143 | NA [26.6; NC]<br>43 (30.1) | 66 | NA<br>1 (1.5) | 20.30 [2.79; 147.50]; < 0.001 |
| MONARCH plus[b] | 23 | NA [3.6; NC]<br>7 (30.4) | 13 | NA<br>0 (0) | NC[i]; 0.055 |
| Total | | | | | NC |

Table 22: Results (mortality, morbidity, and side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy) (multipage table)

| Outcome category<br>Outcome<br>Study | Abemaciclib + fulvestrant | | Placebo + fulvestrant | | Abemaciclib + fulvestrant vs. placebo + fulvestrant |
|---|---|---|---|---|---|
| | N | Median time to event in months [95% CI]<br>Patients with event<br>n (%) | N | Median time to event in months [95% CI]<br>Patients with event<br>n (%) | HR [95% CI]; p-value[a] |
| Diarrhoea (PT, severe AEs)[f] | | | | | |
| MONARCH 2[b] | 143 | NA<br>25 (17.5) | 66 | NA<br>0 (0) | NC[i]; < 0.001 |
| MONARCH plus[b] | 23 | NA<br>1 (4.3) | 13 | NA<br>0 (0) | NC[i]; 0.452 |
| Total | | | | | NC |
| Gastrointestinal disorders (SOC, AEs) | | | | | |
| MONARCH 2[b] | 143 | 0.1 [0.1; 0.2]<br>134 (93.7) | 66 | 3.6 [1.6; 5.6]<br>43 (65.2) | 4.00 [2.78; 5.76]; < 0.001 |
| MONARCH plus[b] | 23 | 0.3 [0.1; 0.7]<br>18 (78.3) | 13 | 12.7 [1.9; NC]<br>4 (30.8) | 4.68 [1.57; 13.99]; 0.003 |
| Total[c] | | | | | 4.07 [2.88; 5.74]; < 0.001 |
| Skin and subcutaneous tissue disorders (SOC, AEs) | | | | | |
| MONARCH 2[b] | 143 | 9.7 [6.1; 18.3]<br>72 (50.3) | 66 | NA [11.7; NC]<br>15 (22.7) | 2.38 [1.36; 4.17]; 0.002 |
| MONARCH plus[b] | 23 | NA [10.8; NC]<br>5 (21.7) | 13 | NA<br>1 (7.7) | 2.49 [0.29; 21.65]; 0.394 |
| Total[c] | | | | | 2.39 [1.39; 4.11]; 0.002 |

a. HR [95% CI]: Cox proportional hazards model with treatment group as factor; p-value: unstratified log-rank test.
b. Data cut-off: MONARCH 2 study: 20 June 2019, MONARCH plus study: 18 May 2020.
c. Calculated from meta-analysis.
d. Time to first deterioration defined as an increase of 2 points on the mBPI-SF symptom scale "worst pain in the last 24 hours" (scale range: 0 to 11) from baseline or increase in analgesic use by ≥ 1 step (according to the WHO 3-step system for the management of cancer pain [29]), in each case first occurrence. In the analysis, death is not rated as an event and censored.
e. No usable data available (for explanation see Sections 2.5.2.1 and 2.4.2.1).
f. Severe AEs are operationalized as CTCAE grade ≥ 3.
g. Discontinuation of at least one of both drugs.
h. PT collection of the company, operationalized using the PTs neutropenia, febrile neutropenia and neutrophil count decreased.
i. Since no events occurred in one study arm, the HR cannot be estimated.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; mBPI-SF: modified Brief Pain Inventory-Short Form; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term, RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; WHO: World Health Organization

On the basis of the available data of the studies MONARCH 2 and MONARCH plus, at most proof, e.g. of an added benefit, can be determined for the outcome of overall survival, and, due to the high risk of bias or the limited certainty of results (discontinuation due to AEs), at most indications for all other outcomes. For outcomes with high risk of bias and available results from only one study, no more than hints can be derived.

**Mortality**

***Overall survival***

The meta-analysis shows a statistically significant difference in favour of abemaciclib + fulvestrant for the outcome of overall survival. There is an effect modification by the characteristic of type of disease, however (see Section 2.5.2.4). This results in proof of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for the outcome of overall survival in patients with visceral metastases. For patients with non-visceral metastases, there is no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

**Morbidity**

***Pain***

For the outcome of pain (worst pain in the last 24 hours and increase in analgesic use), the studies showed no statistically significant difference between the treatment groups, neither for the composite outcome nor for its individual components. However, there is an effect modification by the characteristic of age for the component of pain (worst pain in the last 24 hours), which was recorded in both studies (see Section 2.5.2.4). This results in an indication of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this component for patients ≥ 65 years of age. For patients < 65 years of age, there is no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this component; an added benefit is therefore not proven. In each case, this results in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for the composite outcome as well as for the individual component of increase in analgesic use; an added benefit is therefore not proven.

***Symptoms, recorded using the EORTC QLQ-C30 and the EORTC QLQ-BR23 (symptom scales)***

There are no usable data for the outcome of symptoms, recorded with the EORTC QLQ-C30 and EORTC QLQ-BR23 symptom scales (see Sections 2.5.2.1 and 2.4.2.1). This results in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

***Health status (EQ-5D VAS)***

There are no usable data for the outcome of health status recorded with the EQ-5D VAS (see Sections 2.5.2.1 and 2.4.2.1). This results in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

**Health-related quality of life**

***Health-related quality of life, recorded using the EORTC QLQ-C30 (global health status and functional scales) and the EORTC QLQ-BR23 (functional scales)***

There are no usable data for the outcome of health-related quality of life, recorded using the scales of EORTC QLQ-C30 (global health status and functional scales) and EORTC QLQ-BR23 (functional scales) (see Sections 2.5.2.1 and 2.4.2.1). This results in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

**Side effects**

***SAEs***

For the outcome of SAEs, the meta-analysis does not show any statistically significant differences between treatment groups. This results in no hint of greater or lesser harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome; greater or lesser harm is therefore not proven.

***Severe AEs***

The meta-analysis shows a statistically significant difference to the disadvantage of abemaciclib + fulvestrant for the outcome of severe AEs (CTCAE grade ≥ 3). This results in an indication of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

***Discontinuation due to AEs***

The meta-analysis shows a statistically significant difference to the disadvantage of abemaciclib + fulvestrant for the outcome of discontinuation due to AEs. The extent of the effect in this non-serious/non-severe outcome was no more than marginal, however. This results in no hint of greater or lesser harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome; greater or lesser harm is therefore not proven.

***Specific AEs***

*Neutropenia (severe AEs)*

The MONARCH 2 study showed a statistically significant difference to the disadvantage of abemaciclib for the outcome of neutropenia (severe AEs). As no events occurred in the control arm of the MONARCH plus study, the effect estimate cannot be calculated and a meta-analysis cannot be conducted in a meaningful way. However, the event rates in the intervention arm (7 events) of the MONARCH plus study support the result of MONARCH 2. This results overall in an indication of greater harm from abemaciclib + fulvestrant in comparison with fulvestrant.

*Diarrhoea (severe AEs)*

The MONARCH 2 study showed a statistically significant difference to the disadvantage of abemaciclib for the outcome of diarrhoea (severe AEs). As no events occurred in the control arm of the MONARCH plus study, the effect estimate cannot be calculated and a meta-analysis cannot be conducted in a meaningful way. This results overall in a hint of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

*Gastrointestinal disorders (AEs)*

The meta-analysis shows a statistically significant difference to the disadvantage of abemaciclib + fulvestrant for the outcome of gastrointestinal disorders (AEs). This results in an indication of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

*Skin and subcutaneous tissue disorders (AEs)*

The meta-analysis shows a statistically significant difference to the disadvantage of abemaciclib + fulvestrant for the outcome of skin and subcutaneous tissue disorders (AEs). There is an effect modification by the characteristic of age, however (see Section 2.5.2.4). As no events occurred in patients ≥ 65 years of age in the control arm of the MONARCH plus study, the effect estimate cannot be calculated and a meta-analysis cannot be conducted in a meaningful way. The MONARCH 2 study showed a statistically significant difference to the disadvantage of abemaciclib + fulvestrant for patients ≥ 65 years. Based on these data, there is a hint of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for the outcome of skin and subcutaneous tissue disorders (AEs) in patients ≥ 65 years. In patients < 65 years, based on the data of the meta-analysis of the 2 studies, there is no statistically significant difference between the treatment groups. This results in no hint of greater or lesser harm of abemaciclib + fulvestrant in comparison with fulvestrant for patients < 65 years; greater or lesser harm for these patients is therefore not proven.

#### 2.5.2.4 Subgroups and other effect modifiers

The following subgroup characteristics are considered in the benefit assessment:

- age (< 65 years/≥ 65 years)
- type of disease (visceral metastases versus non-visceral metastases)
- sensitivity to endocrine therapy (primary versus secondary)

The mentioned characteristics were defined a priori. In the dossier, the company presented subgroup analyses for outcomes of the present benefit assessment with the following exceptions: Subgroup analyses, but no interaction tests, are available for the specific AEs in the company's dossier. These were therefore calculated by the Institute based on the available data.

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 one subgroup.

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

The results are presented in Table 23.

Table 23: Subgroups (mortality, morbidity, side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy) (multipage table)

| Outcome Characteristic<br>Study<br>Subgroup | Abemaciclib + fulvestrant<br>N | Abemaciclib + fulvestrant<br>Median time to event in months [95% CI]<br>Patients with event n (%) | Placebo + fulvestrant<br>N | Placebo + fulvestrant<br>Median time to event in months [95% CI]<br>Patients with event n (%) | Abemaciclib + fulvestrant vs. placebo + fulvestrant<br>HR[a] [95% CI] | <br>p-value[b] |
|---|---|---|---|---|---|---|
| **Mortality** | | | | | | |
| **Overall survival** | | | | | | |
| Type of disease | | | | | | |
| MONARCH 2[c] | | | | | | |
| Non-visceral metastases | 66 | ND<br>33 (50.0[d]) | 27 | ND<br>15 (55.6[d]) | 1.09 [0.59; 2.01] | 0.777 |
| Visceral metastases | 78 | ND<br>33 (42.3[d]) | 39 | ND<br>29 (74.4[d]) | 0.46 [0.28; 0.76] | 0.003 |
| MONARCH plus[c] | | | | | | |
| Non-visceral metastases | 6 | ND<br>1 (16.7[d]) | 3 | ND<br>0 (0) | NC[e] | 0.999 |
| Visceral metastases | 17 | ND<br>5 (29.4[d]) | 10 | ND<br>5 (50.0[d]) | 0.34 [0.10; 1.21] | 0.097 |
| Total | | | | | Interaction: | 0.022[f] |
| Non-visceral metastases | | | | | NC | |
| Visceral metastases | | | | | 0.44 [0.28; 0.71] | 0.001 |
| **Morbidity** | | | | | | |
| **Worst pain in the last 24 hours (deterioration by ≥ 2 points on the mBPI-SF symptom scale)[g]** | | | | | | |
| Age | | | | | | |
| MONARCH 2[c] | | | | | | |
| < 65 years | 79 | ND<br>35 (44.3[d]) | 28 | ND<br>9 (32.1[d]) | 1.15 [0.55; 2.39] | 0.719 |
| ≥ 65 years | 64 | ND<br>26 (40.6[d]) | 38 | ND<br>20 (52.6[d]) | 0.48 [0.27; 0.88] | 0.018 |
| MONARCH plus[c] | | | | | | |
| < 65 years | 16 | ND<br>7 (43.8[d]) | 9 | ND<br>2 (22.2[d]) | 1.58 [0.33; 7.66] | 0.571 |
| ≥ 65 years | 7 | ND<br>1 (14.3[d]) | 4 | ND<br>1 (25.0[d]) | 0.82 [0.05; 13.24] | 0.887 |
| Total | | | | | Interaction: | 0.048[f] |
| < 65 years | | | | | 1.21 [0.62; 2.36] | 0.572 |
| ≥ 65 years | | | | | 0.50 [0.28; 0.89] | 0.019 |

Table 23: Subgroups (mortality, morbidity, side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy) (multipage table)

| Outcome<br>Characteristic<br>Study<br>Subgroup | Abemaciclib + fulvestrant<br>N | Abemaciclib + fulvestrant<br>Median time to event in months [95% CI]<br>Patients with event n (%) | Placebo + fulvestrant<br>N | Placebo + fulvestrant<br>Median time to event in months [95% CI]<br>Patients with event n (%) | Abemaciclib + fulvestrant vs. placebo + fulvestrant<br>HR[a] [95% CI] | <br>p-value[b] |
|---|---|---|---|---|---|---|
| **Side effects** | | | | | | |
| **Skin and subcutaneous tissue disorders (SOC, AEs)** | | | | | | |
| Age | | | | | | |
| MONARCH 2[c] | | | | | | |
| < 65 years | 79 | ND<br>41 (51.9[d]) | 28 | ND<br>10 (35.7[d]) | 1.42 [0.71; 2.90] | 0.321 |
| ≥ 65 years | 64 | ND<br>31 (48.4[d]) | 38 | ND<br>5 (13.2[d]) | 4.68 [1.81; 12.10] | 0.001 |
| MONARCH plus[c] | | | | | | |
| < 65 years | 16 | ND<br>3 (18.8[d]) | 9 | ND<br>1 (11.1[d]) | 1.56 [0.16; 15.21] | 0.703 |
| ≥ 65 years | 7 | ND<br>2 (28.6[d]) | 4 | ND<br>0 (0) | NC[e] | 0.998 |
| Total | | | | | Interaction: | 0.046[d, f] |
| < 65 years | | | | | 1.43 [0.74; 2.79] | 0.289 |
| ≥ 65 years | | | | | NC | |

a. HR and CI from unstratified Cox proportional hazards model.
b. Unstratified log-rank test.
c. Related to the following data cut-offs: MONARCH 2 study: 20 June 2019, MONARCH plus study: 18 May 2020.
d. Institute's calculation.
e. Since no events occurred in the control arm, the HR cannot be estimated.
f. Cochran Q test.
g. Time to first deterioration defined as first increase of ≥ 2 points (on the mBPI-SF symptom scale "worst pain in the last 24 hours", scale range: 0 to 11) from baseline. In the analysis, death is not rated as an event and censored.

CI: confidence interval; HR: hazard ratio; mBPI-SF: modified Brief Pain Inventory-Short Form; N: number of analysed patients; n: number of patients with event; NC: not calculable; ND: no data; RCT: randomized controlled trial

## Mortality

### *Overall survival*

There is an effect modification by the characteristic of type of disease for the outcome of overall survival. For patients with visceral metastases, based on the data of the meta-analysis of the 2 studies, there is a statistically significant difference between the treatment groups in favour

of abemaciclib + fulvestrant. This results in proof of added benefit of abemaciclib + fulvestrant for patients with visceral metastases. As no events occurred in patients with visceral metastases in the control arm of the MONARCH plus study, the effect estimate cannot be calculated and therefore a meta-analysis cannot be conducted in a meaningful way. There was no statistically significant difference between treatment groups in the MONARCH 2 study. In this outcome, this results overall in no hint of greater or lesser harm of abemaciclib + fulvestrant in comparison with fulvestrant for patients with non-visceral metastases; greater or lesser harm for these patients is therefore not proven.

*Subgroup results in comparison with the previous benefit assessments*

The effect modification for the outcome of overall survival by the characteristic of type of disease had already been shown at the second data cut-off (14 February 2017) in the MONARCH 2 study (first benefit assessment of abemaciclib in 2018 [3,18]). However, as a further effect modification for the outcome of overall survival was shown by the characteristic of age (</≥ 65 years), a meaningful interpretation of these subgroup results was not possible without examining for cross-interactions. The effect modifications therefore did not affect the conclusion of the benefit assessment.

In accordance with the G-BA's condition of the limitation, the second benefit assessment (in 2020) assessed the third data cut-off (20 June 2019) of the MONARCH 2 study [4]. In this data cut-off, based on the results of the MONARCH 2 study alone, there was no statistically significant interaction test for the outcome of overall survival in the subgroups of type of disease ($p = 0.095$) or age ($p = 0.563$) (see Module 4 B of the corresponding dossier, p. 223 [15]).

**Morbidity**

***Worst pain in the last 24 hours (deterioration by ≥ 2 points on the mBPI-SF symptom scale)***

There is an effect modification by the characteristic of age for the outcome of worst pain in the last 24 hours. The meta-analysis shows a statistically significant difference between the treatment groups in favour of abemaciclib + fulvestrant for patients ≥ 65 years of age, whereas the meta-analysis shows no statistically significant difference for patients < 65 years of age. This results in an indication of an added benefit of abemaciclib + fulvestrant for patients ≥ 65 years of age. For patients < 65 years, there is no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

**Side effects**

***Skin and subcutaneous tissue disorders (SOC, AEs)***

There is an effect modification by the characteristic of age for the outcome of skin and subcutaneous tissue disorders (System Organ Class [SOC], AEs). For patients < 65 years, based on the data of the meta-analysis of the 2 studies, there is no statistically significant difference between the treatment groups. This results in no hint of greater or lesser harm of abemaciclib + fulvestrant in comparison with fulvestrant for patients < 65 years; greater or lesser harm for these patients is therefore not proven. As no events occurred in patients ≥ 65 years of age in the

control arm of the MONARCH plus study, the effect estimate cannot be calculated and therefore a meta-analysis cannot be conducted in a meaningful way. The MONARCH 2 study showed a statistically significant difference between treatment groups to the disadvantage of abemaciclib + fulvestrant. This results overall in a hint of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome for patients ≥ 65 years.

### 2.5.3 Probability and extent of added benefit

For research question B1 (postmenopausal women who have received prior endocrine therapy), the probability and extent of added benefit are derived below at the outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

#### 2.5.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.4.2 (see Table 25).

**Determination of the outcome category for symptom outcomes**

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

***Pain***

For the outcome of pain, there is no information to justify a classification as serious/severe symptoms/late complications. The outcome of pain (worst pain in the last 24 hours or increase in analgesic use by ≥ 1 step) is assigned to the outcome category of non-serious/non-severe symptoms/late complications.

Table 24: Extent of added benefit at outcome level: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy) (multipage table)

| **Observation period**<br>**Outcome category**<br>**Outcome**<br>**Subscale**<br>**Effect modifier**<br>**Subgroup** | **Abemaciclib + fulvestrant vs. placebo + fulvestrant**<br>**Median time to event (months)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Total observation period** | | |
| **Mortality** | | |
| Overall survival | | |
| Type of disease | | |
| Non-visceral metastases | MONARCH 2<br>ND vs. ND<br>HR: 1.09 [0.59; 2.01]<br>p = 0.777<br>MONARCH plus<br>ND vs. ND<br>HR: NC<br>p = 0.999 | Lesser benefit/added benefit not proven |
| Visceral metastases | ND and ND vs. ND and ND<br>HR: 0.44 [0.28; 0.71]<br>p = 0.001<br>Probability: “proof” | Outcome category: mortality<br>$CI_u < 0.85$<br>Added benefit, extent: “major” |
| **Shortened observation period** | | |
| **Morbidity** | | |
| Pain | | |
| Pain (composite outcome: worst pain in the last 24 hours **or** increase in analgesic use) | 13.9 vs. 6.0 months<br>HR: 0.74 [0.49; 1.14]<br>p = 0.171 | Lesser benefit/added benefit not proven |
| Worst pain in the last 24 hours | | |
| Age | | |
| < 65 years | ND and ND vs. ND and ND<br>HR: 1.21 [0.62; 2.36]<br>p = 0.572 | Lesser benefit/added benefit not proven |
| ≥ 65 years | ND and ND vs. ND and ND<br>HR: 0.50 [0.28; 0.89]<br>p = 0.019<br>Probability: “indication” | Outcome category: non-serious/non-severe symptoms/late complications<br>$0.80 \leq CI_u < 0.90$<br>added benefit, extent: “minor” |
| Increase in analgesic use | NA vs. NA months<br>HR: 1.10 [0.47; 2.60]<br>p = 0.827 | Lesser benefit/added benefit not proven |

Table 24: Extent of added benefit at outcome level: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy) (multipage table)

| **Observation period**<br>**Outcome category**<br>**Outcome**<br>**Subscale**<br>**Effect modifier**<br>**Subgroup** | **Abemaciclib + fulvestrant vs. placebo + fulvestrant**<br>**Median time to event (months)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| Symptoms (EORTC QLQ C30 and EORTC QLQ-BR23) | No usable data | Lesser benefit/added benefit not proven |
| Health status (EQ-5D VAS) | No usable data | Lesser benefit/added benefit not proven |
| **Health-related quality of life** | | |
| EORTC QLQ-C30 and EORTC QLQ-BR23 | No usable data | Lesser benefit/added benefit not proven |
| **Side effects** | | |
| SAEs | 47.1 and NA vs. 29.9 and NA months<br>HR: 1.02 [0.56; 1.86]<br>p = 0.941 | Greater/lesser harm not proven |
| Severe AEs | 4.6 and 5.6 vs. 28.0 and NA months<br>HR: 2.79 [1.76; 4.43]<br>HR: 0.36 [0.23; 0.57][c]<br>p < 0.001<br>Probability: “indication” | Outcome category: severe/serious side effects<br>$CI_u$ < 0.75, risk ≥ 5%<br>greater harm, extent: “major” |
| Discontinuation due to AEs[d] | NA and NA vs. NA and NA months<br>HR: 3.53 [1.02; 12.19]<br>HR: 0.28 [0.08; 0.98][c]<br>p = 0.046 | Outcome category: non-severe/non-serious side effects<br>0.90 ≤ $CI_u$ < 1.00<br>lesser benefit/added benefit not proven[e] |
| Neutropenia (severe AEs) | MONARCH 2<br>NA vs. NA months<br>HR: 20.30 [2.79; 147.50]<br>HR: 0.05 [0.01; 0.36][c]<br>p < 0.001<br>MONARCH plus<br>NA vs. NA months<br>HR: NC[f]<br>p = 0.055<br>probability: “indication” | Outcome category: severe/serious side effects<br>$CI_u$ < 0.75, risk ≥ 5%<br>greater harm, extent: “major” |

Table 24: Extent of added benefit at outcome level: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy) (multipage table)

| **Observation period**<br>**Outcome category**<br>**Outcome**<br>**Subscale**<br>**Effect modifier**<br>**Subgroup** | **Abemaciclib + fulvestrant vs. placebo + fulvestrant**<br>**Median time to event (months)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability[a]** | **Derivation of extent[b]** |
|---|---|---|
| Diarrhoea (severe AEs) | MONARCH 2<br>NA vs. NA months<br>HR: NC[f]<br>p < 0.001<br>MONARCH plus<br>NA vs. NA months<br>HR: NC[f]<br>p = 0.452<br>probability: "hint" | Outcome category: severe/serious side effects<br>greater harm, extent: "non-quantifiable" |
| Gastrointestinal disorders (AEs) | 0.1 and 0.3 vs. 3.6 and 12.7 months<br>HR: 4.07 [2.88; 5.74]<br>HR: 0.25 [0.17; 0.35][c]<br>p < 0.001<br>probability: "indication" | Outcome category: non-severe/non-serious side effects<br>$CI_u$ < 0.80<br>greater harm, extent: "considerable" |
| Skin and subcutaneous tissue disorders (AEs) | | |
| Age | | |
| < 65 years | ND and ND vs. ND and ND<br>HR: 1.43 [0.74; 2.79]<br>p = 0.289 | Greater/lesser harm not proven |
| ≥ 65 years | MONARCH 2<br>ND and ND vs. ND and ND<br>HR: 4.68 [1.81; 12.10]<br>HR: 0.21 [0.08; 0.55][c]<br>p = 0.001<br>MONARCH plus<br>Median: ND<br>HR: NC[f]<br>p = 0.998<br>probability: "hint" | Outcome category: non-severe/non-serious side effects<br>$CI_u$ < 0.80<br>greater harm, extent: "considerable" |

Table 24: Extent of added benefit at outcome level: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy) (multipage table)

| **Observation period**<br>**Outcome category**<br>**Outcome**<br>**Subscale**<br>**Effect modifier**<br>**Subgroup** | **Abemaciclib + fulvestrant vs. placebo + fulvestrant**<br>**Median time to event (months)**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| a. Probability provided if statistically significant differences are present.<br>b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval ($CI_u$).<br>c. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.<br>d. Discontinuation of at least one of both drugs.<br>e. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.<br>f. Since no events occurred in one study arm, the HR cannot be estimated. However, if added benefit/lesser benefit or greater/lesser harm was derived from the other studies, the event rates of the studies without effect estimation were considered to see if they supported the overall result.<br>AE: adverse event; CI: confidence interval; $CI_u$: upper limit of confidence interval; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module 23; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale | | |

### 2.5.3.2 Overall conclusion on added benefit

Table 25 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 25: Positive and negative effects from the assessment of abemaciclib + fulvestrant in comparison with placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy)

| **Positive effects** | **Negative effects** |
|---|---|
| **Total observation period** | |
| Mortality<br>▪ Overall survival<br>Patients with visceral metastases: proof of an added benefit – extent: "major" | – |
| **Shortened observation period** | |
| ▪ Non-serious/non-severe symptoms/late complications<br>▪ Pain (worst pain in the last 24 hours)<br>Age (≥ 65 years): indication of an added benefit – extent: "minor" | – |
| – | Serious/severe side effects<br>▪ Severe AEs: indication of greater harm – extent: "major"<br>▫ Neutropenia (severe AEs): indication of greater harm – extent: "major"<br>▫ Diarrhoea (severe AEs): hint of greater harm – extent: "non-quantifiable" |
| – | Non-serious/non-severe side effects<br>▪ Gastrointestinal disorders (AEs): indication of greater harm – extent: "considerable"<br>▪ Skin and subcutaneous tissue disorders (AEs)<br>Age (≥ 65 years): hint of greater harm – extent: "considerable" |
| The data on morbidity (except pain) and health-related quality of life are not usable | |
| AE: adverse event | |

In the overall consideration, there are positive and negative effects of abemaciclib + fulvestrant in comparison with fulvestrant on the basis of the results of the studies MONARCH 2 and MONARCH plus. Data over the entire observation period are only available for all-cause mortality. The positive effect in the outcome of pain as well as the negative effects in severe and non-severe side effects refer exclusively to the shortened observation period. The analyses presented on morbidity (except pain) and health-related quality of life are not usable and are also only available for the shortened observation period.

Decisive for patients with visceral metastases is proof of a positive effect with major extent for the outcome of overall survival. The clearly negative effects in severe side effects do not completely call into question the positive effect in overall survival. Overall, there is proof of considerable added benefit of abemaciclib in combination with fulvestrant compared with fulvestrant alone for patients with visceral metastases.

For patients with non-visceral metastases, besides a positive effect in the outcome of pain (limited to older patients), mainly negative effects remain, especially in severe side effects. This results in an indication of lesser benefit of abemaciclib in combination with fulvestrant compared with fulvestrant alone.

The assessment described above deviates from that of the company, which derived proof of considerable added benefit for the total subpopulation of research question B1.

## 2.6 Probability and extent of added benefit – summary

Table 26 shows a summary of probability and extent of the added benefit of abemaciclib in combination with fulvestrant for research questions A1 (postmenopausal women, initial endocrine-based therapy) and B1 (postmenopausal women who have received prior endocrine therapy).

Table 26: Abemaciclib in combination with fulvestrant – probability and extent of added benefit

| Research question | Sub-indication | ACT[a] | Probability and extent of added benefit |
|---|---|---|---|
| **Women with HR-positive, HER2-negative locally advanced or metastatic breast cancer[b]** | | | |
| A1 | Post-meno-pausal women, initial endocrine-based therapy | ▪ anastrozole or<br>▪ letrozole or<br>▪ **fulvestrant** or<br>▪ possibly tamoxifen if aromatase inhibitors are unsuitable or<br>▪ ribociclib in combination with an NSAI (anastrozole, letrozole) or<br>▪ abemaciclib in combination with an NSAI (anastrozole, letrozole) or<br>▪ palbociclib in combination with an NSAI (anastrozole, letrozole) or<br>▪ ribociclib in combination with fulvestrant or<br>▪ palbociclib in combination with fulvestrant | Added benefit not proven |
| B1 | Post-meno-pausal women who have received prior endocrine therapy | ▪ tamoxifen or<br>▪ anastrozole or<br>▪ **fulvestrant** as monotherapy; only for patients with recurrence or progression following anti-oestrogen therapy, or<br>▪ letrozole; only for patients with recurrence or progression following anti-oestrogen therapy, or<br>▪ exemestane; only for patients with progression following anti-oestrogen therapy, or<br>▪ everolimus in combination with exemestane; only for patients without symptomatic visceral metastases who have progressed after an NSAI, or<br>▪ ribociclib in combination with an NSAI (anastrozole, letrozole) or<br>▪ abemaciclib in combination with an NSAI (anastrozole, letrozole) or palbociclib in combination with an NSAI (anastrozole, letrozole) or<br>▪ ribociclib in combination with fulvestrant or<br>▪ palbociclib in combination with fulvestrant | Patients with visceral metastases: proof of considerable added benefit[c, d]<br>Patients with non-visceral metastases: indication of lesser benefit[c, d] |

a. Presented is the respective ACT specified by the GBA. 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. It is assumed for the present therapeutic indication that further endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
c. Only patients with an ECOG PS of 0 or 1 were included in the studies MONARCH 2 and MONARCH plus. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
d. The added benefit or lesser benefit exists only in comparison with fulvestrant, which is assessed as sufficiently suitable comparator by the G-BA (see the G-BA justification on benefit assessment procedure A18-73 [6].

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; NSAI: nonsteroidal aromatase inhibitor

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

**References for English extract**

Please see full dossier assessment for full reference list.

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

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