IQWiG Reports – Commission No. A20-32

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 2.7 of the dossier assessment *Abemaciclib (Mammakarzinom; Kombination mit Fulvestrant) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung)* (Version 1.0; Status: 10 June 2020). 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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Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

Due to the corona pandemic, no external experts were involved.

IQWiG employees involved in the dossier assessment

- Susanne Haag
- Ulrich Grouven
- Charlotte Hecker
- Stefan Kobza
- Petra Kohlepp
- Ulrike Lampert
- Katrin Nink
- Ulrike Seay

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Table of contents

List of tables[2]

Page

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
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
EQ-5D-5L	European Quality of Life-5 Dimensions 5 Levels
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
mBPI-SF	modified Brief Pain Inventory-Short Form
MID	minimally important difference
PFS	progression-free survival
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug abemaciclib. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 17 March 2020.

The decision was limited because the data on overall survival available from the MONARCH 2 study for the first assessment were only preliminary and there was only a small number of events for this outcome. For the new benefit assessment after expiry of the decision, the final study results from the ongoing MONARCH 2 study for all outcomes used to prove an added benefit were to be presented in the dossier.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

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 line of treatment and the patients' menopausal status, the G-BA distinguished between 4 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 3 research questions A1, B1 and B2 presented in Table 2 (designation according to the first assessment).

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

Research question	Subindication	ACT[a]
Women with HR-positive, HER2-negative locally advanced or metastatic breast cancer[b]		
A1	Postmenopausal women, initial endocrine therapy	Anastrozole or letrozole or **fulvestrant** or, if applicable, tamoxifen if aromatase inhibitors are unsuitable
B1	Postmenopausal women who received prior endocrine therapy	Further endocrine therapy depending on prior therapy with: ▪ tamoxifen or ▪ anastrozole or ▪ **fulvestrant** (only for patients with recurrence or progression following antioestrogen therapy[c]) or ▪ letrozole; only for patients with recurrence or progression following antioestrogen therapy, or ▪ exemestane; only for patients with progression following antioestrogen therapy, or ▪ everolimus in combination with exemestane; only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor
B2	Pre- and perimenopausal women who received prior endocrine therapy	Endocrine therapy specified by the physician under consideration of the respective approval[c, d]

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could 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. Furthermore, it is assumed that ovarian function is suppressed by oophorectomy or with a GnRH analogue in pre- and perimenopausal patients.
c. In postmenopausal women, the approval of fulvestrant provides for use of the drug only after prior antioestrogen therapy [1]. Fulvestrant is not approved for the use in pre- and perimenopausal women (B2), but according to guidelines, besides further drugs such as tamoxifen, fulvestrant is an established treatment option together with suppression of ovarian function. In this special therapeutic and health care situation the G-BA sees a medical reason that justifies assessing fulvestrant or fulvestrant alone as a sufficiently suitable comparator without taking into account further endocrine therapies indicated in accordance with the guidelines in the present treatment situation and also using the data from the MONARCH 2 study for the benefit assessment for subpopulations B1 and B2 [2].
d. Tamoxifen, letrozole, exemestane, megestrol acetate and medroxyprogesterone acetate are approved in the present therapeutic indication.

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

The company cited fulvestrant as ACT for all 3 research questions of the present assessment (A1, B1 and B2). Thus, the company followed the specification of the G-BA only for research questions A1 and B1. For pre- and perimenopausal patients (research question B2), the company deviated from the comparator therapy specified by the G-BA. However, in this special therapeutic and health care situation the G-BA sees a sufficient medical reason that, despite remaining uncertainties, justifies assessing fulvestrant or fulvestrant alone as a sufficiently

suitable comparator. Hence, study results with comparative data versus fulvestrant were also used for subpopulation B2 for the assessment.

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

Results (research questions A1, B1 and B2)

Study pool and study characteristics

For assessing research questions A1, B1 and B2, a subpopulation of the MONARCH 2 study was included in each case.

Deviating from the company, a subpopulation of the MONARCH plus study was additionally considered relevant in each case for the assessment of research questions A1 and B1. Results of the MONARCH plus study based on the subpopulations A1 and B1 were not available.

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 (including 44 endocrine-naive patients) and randomized in a 2:1 ratio to the 2 treatment arms. From among these patients, 374 patients are relevant for the assessment of research question A1 (postmenopausal women with initial endocrine therapy), 210 patients for the assessment of research question B1 (postmenopausal women who received prior endocrine therapy) and 46 patients for the assessment of research question B2 (pre- and perimenopausal women who 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 is a double-blind RCT in which abemaciclib in combination with fulvestrant is directly compared with fulvestrant (+ placebo). The study included 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 for the benefit assessment, and randomized in a 2:1 ratio to the 2 treatment arms. The study comprises patients who are either relevant for the research question A1 or for research question B1. It is unclear how the included patients are distributed between both subpopulations. Separate analyses are not available.

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, the results of the first data cut-off from 29 March 2019 are available. The end and thus also the final analysis of the study are planned for November 2020.

Risk of bias and certainty of results (research question A1, research question B1 and research question B2)

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

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

The results are described primarily for the MONARCH 2 study. Following the description of the results of the MONARCH 2 study, the available results of the total population of the MONARCH plus study are considered in terms of whether they support or question the results of the MONARCH 2 study.

All-cause mortality

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This resulted in no hint of an added benefit of abemaciclib in combination with fulvestrant in comparison with fulvestrant. An added benefit is therefore not proven.

Morbidity

Symptoms, recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) (symptom scales)

No statistically significant difference between the treatment groups was shown for each of the outcomes "fatigue", "pain", "dyspnoea", "insomnia" and "appetite loss". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for the outcome "nausea and vomiting". This resulted in a hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for the outcome "constipation". The extent of the effect in this non-serious/non-severe outcome was no more than marginal, however. This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

A statistically significant difference to the disadvantage of abemaciclib + fulvestrant was shown for the outcome "diarrhoea". This resulted in a hint of lesser benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

Symptoms, recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module 23 (EORTC QLQ-BR23) (symptom scales)

No statistically significant difference between the treatment groups was shown for the outcome "side effects of systemic treatment". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome; an added benefit is therefore not proven.

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for the outcome "breast symptoms". The extent of the effect in this non-serious/non-severe outcome was no more than marginal, however. This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for the outcome "arm symptoms". There was an effect modification by the characteristic "age", however. This resulted in a hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant in patients < 65 years of age for the outcome "arm symptoms". For patients ≥ 65 years of age, there was no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

There were no usable analyses for the outcome "upset by hair loss". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

Pain (modified Brief Pain Inventory-Short Form [mBPI-SF]) and health status (European Quality of Life-5 Dimensions 5 Levels [EQ-5D-5L] visual analogue scale [VAS])

There were no usable analyses for the outcome "pain" (mBPI-SF) and for health status (EQ-5D-5L VAS). This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; 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)

No statistically significant difference between the treatment groups was shown for any of the following outcomes: global health status, physical functioning, role functioning, emotional functioning, and cognitive functioning. This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for the outcome "social functioning". This resulted in a hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

Health-related quality of life, recorded using the EORTC QLQ-BR23 (functional scales)

There was no statistically significant difference between the treatment groups for any of the outcomes "body image", "sexual functioning" and "future perspective". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

There were no usable analyses for the outcome "sexual enjoyment". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

Side effects

A statistically significant difference to the disadvantage of abemaciclib + fulvestrant was shown for each of the outcomes "serious AEs (SAEs)", "severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)" as well as "discontinuation due to AEs". This resulted in a hint of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for each of these outcomes.

There were no usable analyses for the specific AEs (neutropenia [CTCAE grade ≥ 3] and diarrhoea [CTCAE grade ≥ 3]).

MONARCH plus study: assessment of the available results in comparison with the MONARCH 2 study

The few available data from the total population of the MONARCH plus study did not call into question the analyses of the MONARCH 2 study. Rather, the results on SAEs supported the greater harm from abemaciclib + fulvestrant in comparison with fulvestrant observed in the MONARCH 2 study.

Results for research question B1: postmenopausal women who received prior endocrine therapy

The results are described primarily for the MONARCH 2 study. Following the description of the results of the MONARCH 2 study, the available results of the total population of the MONARCH plus study are considered in terms of whether they support or question the results of the MONARCH 2 study.

All-cause mortality

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for the outcome "overall survival". Due to the low risk of bias, this resulted in an indication of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

Morbidity

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

No statistically significant difference between the treatment groups was shown for any of the outcomes "fatigue", "dyspnoea", "appetite loss", "constipation" and "diarrhoea". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for each of the outcomes "nausea and vomiting" and "pain". This resulted in a hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for each of these outcomes.

No statistically significant difference between the treatment groups was shown for the outcome "insomnia". There was an effect modification by the characteristic "age", however. This resulted in a hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant in patients ≥ 65 years of age for the outcome "insomnia". For patients < 65 years of age, there was 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-BR23 (symptom scales)

No statistically significant difference between the treatment groups was shown for any of the outcomes "side effects of systemic treatment", "breast symptoms" and "arm symptoms". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

There were no usable analyses for the outcome "upset by hair loss". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

Pain (mBPI-SF) and health status (EQ-5D-5L VAS)

There were no usable analyses for the outcome "pain" (mBPI-SF) and for health status (EQ-5D-5L VAS). This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; 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)

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for each of the outcomes "global health status", "physical functioning" and "emotional functioning". This resulted in a hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for each of these outcomes.

No statistically significant difference between the treatment groups was shown for any of the outcomes "role functioning", "cognitive functioning" and "social functioning". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

Health-related quality of life, recorded using the EORTC QLQ-BR23 (functional scales)

There was no statistically significant difference between the treatment groups for any of the outcomes "body image", "sexual functioning" and "future perspective". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

There were no usable analyses for the outcome "sexual enjoyment". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

Side effects

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". Hence, there was 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.

A statistically significant difference to the disadvantage of abemaciclib + fulvestrant was shown for each of the outcomes "severe AEs (CTCAE grade ≥ 3)" as well as "discontinuation due to AEs". This resulted in a hint of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for each of these outcomes.

There were no usable analyses for the specific AEs (neutropenia [CTCAE grade ≥ 3] and diarrhoea [CTCAE grade ≥ 3]).

MONARCH plus study: assessment of the available results in comparison with the MONARCH 2 study

The few available data from the total population did not call into question the analyses of the MONARCH 2 study. Rather, the results supported the presented positive effect in overall survival and the negative effect in SAEs.

Results (research question B2): pre- and perimenopausal women who received prior endocrine therapy

The results are based on the MONARCH 2 study (subpopulation B2).

Mortality

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This resulted in no hint of an added benefit of abemaciclib in combination with fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

Morbidity

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

No statistically significant difference between the treatment arms was shown for any of the following symptom scales: fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, diarrhoea, breast symptoms, and arm symptoms. A statistically significant difference in favour of abemaciclib + fulvestrant was shown for each of the outcomes "constipation" and "side effects of systemic therapy". However, the effect in each case was no more than marginal. This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven for these outcomes.

Pain (mBPI-SF) and health status (EQ-5D-5L VAS)

There were no usable analyses for the outcome "pain" (mBPI-SF) and for health status (EQ-5D-5L VAS). This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; 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) or the EORTC QLQ-BR23 (functional scales)

No statistically significant difference between the treatment arms was shown for global health status or any of the following functional scales: physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, body image, sexual functioning, and future perspective. This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven for these outcomes.

Side effects

There was no statistically significant difference between the treatment groups for the outcomes "SAEs" and "discontinuation due to AEs". Hence, there was no hint of greater or lesser harm of abemaciclib + fulvestrant in comparison with fulvestrant for either of these outcomes; greater or lesser harm is therefore not proven.

A statistically significant difference to the disadvantage of abemaciclib + fulvestrant was shown for the outcome "severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

There were no usable analyses for the specific AEs (neutropenia [CTCAE grade ≥ 3] and diarrhoea [CTCAE grade ≥ 3]).

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 the 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 therapy)

In the overall consideration, there are both positive and negative effects of abemaciclib + fulvestrant in comparison with fulvestrant on the basis of the results of the MONARCH 2 study. Hints of an added benefit were shown in 2 non-serious/non-severe symptoms, one of which with minor extent, and one (in the subgroup of patients < 65 years) with considerable extent. In addition, there was a hint of an added benefit in one scale of health-related quality of life with considerable extent (social functioning). This was accompanied by hints of negative effects in all superordinate AE outcomes as well as in the non-serious/non-severe symptom "diarrhoea".

In the subpopulation A1 available here, the side effects were shown in particular in severe AEs (CTCAE grade ≥ 3) with major extent, and in SAEs with considerable extent. There were no usable analyses on specific AEs.

Overall, the negative effects with partly major extent (severe AEs) outweighed the positive effects in the MONARCH 2 study.

[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 [3,4].

The results of the total population of the MONARCH plus study, which the company did not include in its assessment, were additionally taken into account in the assessment of the added benefit. The available data supported the presented negative effects in SAEs.

In summary, there is therefore a hint of lesser benefit of abemaciclib in combination with fulvestrant versus fulvestrant alone for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer with initial endocrine therapy (research question A1).

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

In the overall consideration, there are both positive and negative effects of abemaciclib in combination with fulvestrant in comparison with fulvestrant on the basis of the results of the MONARCH 2 study. The positive effect for the outcome "overall survival", for which there was an indication of a minor added benefit, was decisive for the overall conclusion. In addition, the MONARCH 2 study showed several positive effects of minor or considerable extent from the category of non-severe/non-serious side effects and health-related quality of life, each with the probability "hint". This was accompanied by negative effects from the outcome category of side effects. This resulted in a hint of considerably greater harm and a hint of major greater harm in severe/serious side effects.

Overall, the negative effects did not question the positive effects, and particularly not the advantage in overall survival.

The results of the total population of the MONARCH plus study, which the company did not include in its assessment, were additionally taken into account in the assessment of the added benefit. The available data on the basis of the total population supported the presented positive effect in overall survival and the negative effect in SAEs.

In summary, there is an indication of a minor added benefit of abemaciclib in combination with fulvestrant versus fulvestrant alone for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer who already received endocrine therapy for the locally advanced or metastatic stage (research question B1).

Research question B2: pre- and perimenopausal women who received prior endocrine therapy

In the overall consideration, there is only a negative effect of abemaciclib in combination with fulvestrant in comparison with fulvestrant on the basis of the results of the MONARCH 2 study (subpopulation B2). This is a hint of greater harm with major extent in severe/serious side effects (CTCAE grade ≥ 3). There were no usable analyses on specific AEs.

In summary, there is therefore a hint of lesser benefit of abemaciclib in combination with fulvestrant versus fulvestrant alone for pre- and perimenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer who received prior endocrine therapy (research question B2).

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	Subindication	ACT[a]	Probability and extent of added benefit
Women with HR-positive, HER2-negative locally advanced or metastatic breast cancer[b]			
A1	Postmenopausal women, initial endocrine therapy	Anastrozole or letrozole or **fulvestrant** or, if applicable, tamoxifen if aromatase inhibitors are unsuitable	Hint of lesser benefit[c]
B1	Postmenopausal women who received prior endocrine therapy	Further endocrine therapy depending on prior therapy with: ▪ tamoxifen or ▪ anastrozole or ▪ **fulvestrant** (only for patients with recurrence or progression following antioestrogen therapy) or ▪ letrozole; only for patients with recurrence or progression following antioestrogen therapy, or ▪ exemestane; only for patients with progression following antioestrogen therapy, or everolimus in combination with exemestane; only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor	Indication of minor added benefit[c, d]
B2	Pre- and perimenopausal women who received prior endocrine therapy	Endocrine therapy specified by the physician under consideration of the respective approval[e]	Hint of lesser benefit[c, d]

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could 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. Furthermore, it is assumed that ovarian function is suppressed by oophorectomy or with a GnRH analogue in pre- and perimenopausal patients.
c. Only patients with an ECOG PS of 0 or 1 were included in the MONARCH 2 study. 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.
e. Tamoxifen, letrozole, exemestane, megestrol acetate and medroxyprogesterone acetate are approved in the present therapeutic indication.

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

The approach for deriving 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 [5].

Depending on the line of treatment and the patients' menopausal status, the G-BA distinguished between 4 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 3 research questions A1, B1 and B2 [6] presented in Table 4 (designation according to the first assessment [7]).

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

Research question	Subindication	ACT[a]
Women with HR-positive, HER2-negative locally advanced or metastatic breast cancer[b]		
A1	Postmenopausal women, initial endocrine therapy	Anastrozole or letrozole or **fulvestrant** or, if applicable, tamoxifen if aromatase inhibitors are unsuitable
B1	Postmenopausal women who received prior endocrine therapy	Further endocrine therapy depending on prior therapy with: ▪ tamoxifen or ▪ anastrozole or ▪ **fulvestrant** (only for patients with recurrence or progression following antioestrogen therapy[c]) or ▪ letrozole; only for patients with recurrence or progression following antioestrogen therapy, or ▪ exemestane; only for patients with progression following antioestrogen therapy, or ▪ everolimus in combination with exemestane; only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor
B2	Pre- and perimenopausal women who received prior endocrine therapy	Endocrine therapy specified by the physician under consideration of the respective approval[c, d]

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could 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. Furthermore, it is assumed that ovarian function is suppressed by oophorectomy or with a GnRH analogue in pre- and perimenopausal patients.
c. In postmenopausal women, the approval of fulvestrant provides for use of the drug only after prior antioestrogen therapy [1]. Fulvestrant is not approved for the use in pre- and perimenopausal women (B2), but according to guidelines, besides further drugs such as tamoxifen, fulvestrant is an established treatment option together with suppression of ovarian function. In this special therapeutic and health care situation the G-BA sees a medical reason that justifies assessing fulvestrant or fulvestrant alone as a sufficiently suitable comparator without taking into account further endocrine therapies indicated in accordance with the guidelines in the present treatment situation and also using the data from the MONARCH 2 study for the benefit assessment for subpopulations B1 and B2 [2].
d. Tamoxifen, letrozole, exemestane, megestrol acetate and medroxyprogesterone acetate are approved in the present therapeutic indication.

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

The company cited fulvestrant as ACT for all 3 research questions of the present assessment (A1, B1 and B2). Thus, the company followed the specification of the G-BA only for research questions A1 and B1. Fulvestrant is approved for women who received prior endocrine therapy only after previous antioestrogen therapy, however [1]. In accordance with the note by the G-BA [2], studies in which patients had been pretreated with aromatase inhibitors were also used for the comparison with fulvestrant for research question B1 (see 2.5.1).

For pre- and perimenopausal patients (research question B2), the company deviated from the comparator therapy specified by the G-BA. As already described in dossier assessment A18-73 and in the corresponding addendum A19-10, fulvestrant as monotherapy is approved exclusively for postmenopausal patients and not for pre- and perimenopausal patients with locally advanced or metastatic breast cancer [1]. Furthermore, it is true for research question B2 that even if fulvestrant were a treatment option of physician's choice, the implementation of the ACT (treatment of physician's choice) is still unclear for the MONARCH 2 study used by the company. The investigators did not have the choice from several treatment options that are options in the present therapeutic indication. It is therefore unclear in what respect fulvestrant would have been the appropriate endocrine therapy of physician's choice for all pre- and perimenopausal patients who had received prior endocrine therapy.

However, in this special therapeutic and health care situation the G-BA sees a sufficient medical reason that, despite remaining uncertainties, justifies assessing fulvestrant or fulvestrant alone as a sufficiently suitable comparator [2]. According to guidelines, besides further drugs such as tamoxifen, fulvestrant is an established treatment option together with suppression of ovarian function also for pre- and perimenopausal patients. According to the G-BA, this view was also supported in corresponding statements by medical experts in the present procedure [2]. Hence, study results with comparative data versus fulvestrant were also used for subpopulation B2 for the assessment.

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

2.3 Information retrieval and study pool

2.3.1 Information retrieval

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: 22 January 2020)
- bibliographical literature search on abemaciclib (last search on 22 January 2020)
- search in trial registries for studies on abemaciclib (last search on 23 January 2020)

To check the completeness of the study pool:

- search in trial registries for studies on abemaciclib (last search on 7 April 2020)

Besides the MONARCH 2 study, the check of the completeness of the company's study pool produced one additional study relevant for the benefit assessment – the MONARCH plus study (cohort B) – in the therapeutic indication.

Relevance of the MONARCH plus study for the present assessment

The MONARCH plus study included postmenopausal patients with locally recurrent or metastatic HR-positive, HER2-negative breast cancer who either had or had not received prior endocrine therapy. In cohort B of the study, abemaciclib + fulvestrant is compared with fulvestrant. Thus, the study comprises patients who are to be considered for the assessment of research questions A1 and B1. A total of 157 patients were included in the study (cohort B) and randomized in a 2:1 ratio to the 2 treatment arms. There is no information on how the patients included in the study are distributed between the 2 research questions A1 and B1. In comparison, the subpopulations A1 and B1 of the MONARCH 2 study considered by the company comprise 584 patients. Hence, a total of 741 patients are relevant for research questions A1 and B1, so that the MONARCH plus study has a proportion of about 21% of the patients. The MONARCH plus study was therefore considered sufficiently large that an influence of the study on the result of the benefit assessment based on the MONARCH 2 was assumed.

The company also identified the MONARCH plus study conducted by the company, but did not consider the study in its benefit assessment. It justified this by stating that it was an ongoing study for which final results were not yet available. Furthermore, the company assumed that the data of this study with almost exclusively Asian patients would not provide any additional relevant evidence for the present benefit assessment.

The company's reasoning was inadequate. While it is true that this is an ongoing study in the therapeutic indication (study start: December 2016; planned study end: November 2020), this is not a reason for exclusion, as results are already available. A first data cut-off (conducted on 29 March 2019) MONARCH plus study was already analysed and published. These results should have been considered in the dossier.

The reasoning of the company that the majority of patients were Asian without additional relevant evidence for the present benefit assessment was also not followed. It is true that mainly Asian patients were included in the study (142 von 157; ≙ 90.4%). However, the patients' origin is not a reason for exclusion per se, and studies with predominantly Asian patients are regularly included in benefit assessments. (e.g. [8]). It must be investigated on a project-specific basis using concrete data whether the origin is an effect modifier (and therefore the studies cannot be meaningfully pooled in a meta-analysis, for example). The exclusion of the study based on the predominantly Asian origin of the patients was therefore inadequate.

Overall, the study pool presented by the company for the benefit assessment is incomplete. The MONARCH plus study was considered in the benefit assessment and the influence of the study on the assessment was estimated (see Sections 2.4.2.3 [research question A1] and 2.5.2.3 [research question B1]). The results of the study (total population) are presented as supplementary information in Appendix D of the full dossier assessment.

2.3.2 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	No[e]	Yes [9-11]	Yes [7,12-17]
I3Y-CR-JPBQ (MONARCH plus[d, f])	No	Yes	No	No[e]	Yes [18,19]	No

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 with this abbreviated form.
e. Due to the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.
f. Study additionally identified in the framework of the check of the information retrieval (see Section 2.3.1). The study is considered relevant for the benefit assessment (research questions A1 and B1).

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

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	Data presented by the company	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 therapy	▪ Subpopulation of the MONARCH 2 study	▪ Subpopulation of the MONARCH 2 study ▪ Subpopulation of the MONARCH plus study[a]	Assessment in Section 2.4
B1	Postmenopausal women who received prior endocrine therapy	▪ Subpopulation of the MONARCH 2 study	▪ Subpopulation of the MONARCH 2 study[b] ▪ Subpopulation of the MONARCH plus study[a]	Assessment in Section 2.5
B2	Pre- and perimenopausal women who received prior endocrine therapy	▪ Subpopulation of the MONARCH 2 study	▪ Subpopulation of the MONARCH 2 study[b]	Assessment in Section 2.6

a. The company did not consider the MONARCH plus study in its assessment. The approach of the company is inadequate (see Section 2.3.1 for reasons) and the study (or in each case a subpopulation) is considered relevant for the assessment of the research questions A1 and B1 (postmenopausal women). Results of the MONARCH plus study based on the subpopulations A1 and B1 were not available. The available results of the total population are presented as supplementary information in Appendix D of the full dossier assessment.
b. In the special therapeutic and health care situation, the G-BA assesses fulvestrant as a sufficiently suitable comparator (see Section 2.2 and [2]).

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

Due to the G-BA's specification of the ACT, subpopulations from the MONARCH 2 study for research questions A1, B1 and B2 were considered relevant for the benefit assessment and included. This concurs with the company's approach. The MONARCH 2 study is known from the first assessment of abemaciclib in combination with fulvestrant [6,12]. This RCT included women, regardless of their menopausal status, who either had or had not received prior endocrine therapy.

Deviating from the company, the MONARCH plus study was additionally identified as relevant for the benefit assessment in the check of the information retrieval (see Section 2.3.1). This RCT included exclusively postmenopausal women who either had or had not received prior endocrine therapy. Thus, the study includes patients who are relevant for answering the research questions A1 and B1. However, there are no analyses for this study for the respective subpopulations of research questions A1 and B1.

2.4 Research question A1: postmenopausal women, initial endocrine therapy

Details on the information retrieval and on the study pool relevant for 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] placebo + fulvestrant (N = 223)[c] Relevant subpopulations thereof: ▪ Postmenopausal, initial endocrine therapy (A1) ▫ abemaciclib + fulvestrant (n = 246) ▫ placebo + fulvestrant (n = 128) ▪ Postmenopausal, after progression under endocrine therapy (B1) ▫ abemaciclib + fulvestrant (n = 144[d]) ▫ placebo + fulvestrant (n = 66) ▪ Pre- and perimenopausal women who received prior endocrine therapy (B2) ▫ abemaciclib + fulvestrant (n = 26) ▫ placebo + fulvestrant (n = 20)	▪ Screening: up to 28 days ▪ Treatment: until disease progression, participation in another study or treatment discontinuation following decision by physician, patient or sponsor ▪ Observation[e]: 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 8/2014–ongoing first interim analysis (planned after 265 PFS events) second interim analysis on 14 Feb 2017 (planned after 378 PFS events) third interim analysis on 20 Jun 2019 (planned after 331 deaths)[f]	▪ Primary: PFS ▪ 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 recurrent or metastatic breast cancer[b] and ECOG PS ≤ 1	Abemaciclib + fulvestrant (N = 104)[g] Placebo + fulvestrant (N = 53)[g] Relevant subpopulations thereof: ▪ Postmenopausal, initial endocrine therapy (A1) ▫ abemaciclib + fulvestrant (n = ND) ▫ placebo + fulvestrant (n = ND) ▪ Postmenopausal, after progression under endocrine therapy (B1) ▫ abemaciclib + fulvestrant (n = ND) ▫ placebo + fulvestrant (n = ND)	▪ Screening: up to 28 days ▪ Treatment: until disease progression, participation in another study or treatment discontinuation following decision by physician, patient or sponsor ▪ Observation[e]: 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 12/2016–ongoing ▪ final analysis for the primary outcome "PFS": 29 Mar 2019 ▪ final analysis: planned for Nov 2020	▪ Primary: PFS ▪ 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 only include information on relevant available outcomes for this benefit assessment.
b. Patients with initial endocrine 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 subpopulation A1. Based on the G-BA decision on the first benefit assessment of abemaciclib, the company takes these patients into account in the present dossier when analysing the subpopulations [2,20].
d. The patient number in the intervention arm deviates marginally from the first assessment (n = 147). A justification for this cannot be inferred from the available documents.
e. Outcome-specific information is provided in Table 9.
f. The study is ongoing (expected study end is January 2024 [9]). If the result on the outcome "overall survival" was not yet significant at the third interim analysis, a final analysis was to be performed after 441 deaths. Although the result (in relation to the ITT population) was significant, a further analysis of overall survival after 441 deaths (as originally planned) will take place [14].
g. The MONARCH plus study investigates 2 different cohorts: cohort A (abemaciclib + anastrozole or letrozole vs. placebo + anastrozole or letrozole) and cohort B (abemaciclib + fulvestrant vs. placebo + fulvestrant). Only cohort B, the cohort relevant for the present benefit assessment, is listed here.

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; ND: no data; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

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 + 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 + fulvestrant 500 mg IM on days 1 and 15 of the first cycle, then on day 1 of each following cycle
	Dose adjustments: ▪ Abemaciclib/placebo: ▫ 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] ▪ Fulvestrant: ▫ reduction to 250 mg for patients with moderate hepatic impairment (defined as Child-Pugh Class B) ▫ in case of toxicity delay of administration (or of the cycle) of up to 14 days[c] or treatment discontinuation with continuation of abemaciclib/placebo possible	
	Permitted pretreatment: ▪ neoadjuvant or adjuvant chemotherapy ▪ prior anticancer therapies (including specifically aromatase inhibitors, antioestrogens, 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) **Non-permitted pretreatment:** ▪ prior chemotherapy (except for adjuvant/neoadjuvant) or treatment with fulvestrant, everolimus, or a CDK4 or CDK6 inhibitor ▪ autologous or allogeneic stem cell transplantation **Permitted concomitant treatment:** ▪ any supportive care to maximize quality of life ▪ dexamethasone (if possible ≤ 7 days) ▪ supportive measures and instructions on the treatment of diarrhoea ▪ GnRH analogues (for included patients who are postmenopausal due to ovarian suppression) ▪ bisphosphonates or approved RANK ligands (e.g. denosumab) for patients with bone metastases if treatment started at least 7 days prior to randomization **Non-permitted concomitant treatment** ▪ other anticancer therapies (including aromatase inhibitors, antioestrogens [besides fulvestrant], chemotherapy, radiotherapy[d], and immunotherapy) ▪ megestrol acetate (as an appetite stimulant) ▪ inducers and strong inhibitors of CYP3A	
MONARCH plus[e]	Abemaciclib 150 mg orally, twice daily (every 12 hours), cycle duration: 28 days + 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 + fulvestrant 500 mg IM on days 1 and 15 of the first cycle, then on day 1 of each following cycle

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. b. The decision was based on the severity grade and type of toxicity (haematological, non-haematological, diarrhoea, ALT increased) according to the study protocol. c. In exceptional situations, a delay > 14 days was possible upon request to the sponsor. d. Surgery with subsequent radiotherapy was allowed if study treatment had rendered the locally advanced breast cancer operable. e. The company did not consider the MONARCH plus study in its assessment. A comprehensive presentation of further information (e.g. regarding dose adjustments, permitted and non-permitted prior and concomitant treatments) was not provided. ALT: alanine aminotransferase; CDK: cyclin-dependent kinase; CTCAE: Common Terminology Criteria for Adverse Events; CYP: cytochrome P450; GnRH: gonadotropin-releasing hormone; RANK: receptor activator of nuclear factor kappa-B; RCT: randomized controlled trial; vs.: versus		

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. In the beginning of the study, patients were included for initial endocrine therapy or after prior endocrine therapy. In an amendment to the study protocol dated 30 March 2015, the inclusion criteria of the study were changed so that patients who had not received endocrine therapy at any prior time (endocrine-naive patients) were excluded from further recruitment. The company had not included the endocrine-naive patients already enrolled up to this point in time (n = 44) in its analysis in the intention to treat (ITT) population and in the first assessment, but considered them in the current assessment (see below). 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 (including 44 endocrine-naive patients) 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) [1,5]. 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, this had no consequences for the present benefit assessment (see text below).

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 for 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 endocrine therapy are relevant for the assessment of research question A1 (see Section 2.2). The company presented analyses of this subpopulation in its dossier. These were used for the benefit assessment. In accordance with the G-BA decision, and contrary to the first assessment, the company also considered endocrine-naive patients in the present dossier (see above). Out of the total of 713 patients, 374 (52.5%) are relevant for the present research question, of which 246 patients were treated with abemaciclib in combination with fulvestrant and 128 patients were treated with fulvestrant (+ placebo).

Abemaciclib starting dose (200 mg versus 150 mg)

The initial study protocol of the MONARCH 2 study mandated a starting dose of 200 mg abemaciclib every 12 hours. Dose reductions to 150 mg, 100 mg and 50 mg were allowed. The abemaciclib dosage of 200 mg does not concur with the approved dosage of 150 mg, however [5]. With the protocol change dated 12 January 2015, the starting dose was reduced to 150 mg every 12 hours. All patients who were receiving 200 mg abemaciclib at this time point reduced their dose to 150 mg. At the time of the protocol change, 76 (31%) patients in subpopulation A1 had already been included in the abemaciclib arm and 41 (32%) in the comparator arm.

To investigate the influence of the 200 mg starting dose on the study results, the company presented subgroup analyses according to starting dose (200 mg versus 150 mg) for the subpopulations investigated. None of the subgroup analyses showed a relevant effect modification (see Module 4 B, p. 215 ff.), so that it can be assumed that the starting dose had no important effect on the study results of the respective subpopulation. Corresponding investigations at the level of the subpopulations were not available in the first assessment.

The company also stated that treatment with 200 mg abemaciclib was only carried out over a relatively short period of time compared with the total duration of therapy (median: 34 days versus 383 days; based on the entire study population) and that therefore the median dose intensity also hardly differed between patients with different starting doses (278.9 mg/day versus 272.3 mg/day). Following the company's reasoning, the G-BA therefore also assumed in the first assessment that the high starting dose did not significantly influence the study results [2]. Although the analyses of treatment duration and dose intensity are still only available for

the total population and not for the relevant subpopulations, the starting dose, which was initially too high, continues to lose importance in view of the now overall longer study duration.

Overall, it is therefore assumed that the high abemaciclib starting dose did not have important influences on the study results. There are no consequences for the benefit assessment.

Suitability of fulvestrant as comparator therapy

The G-BA specified fulvestrant as one of the options of the ACT for research question A1.

However, fulvestrant is only approved in postmenopausal patients who are either endocrine-naive or with relapse on or after adjuvant antioestrogen therapy, or disease progression on antioestrogen therapy [1]. Hence, endocrine pretreatment – e.g. with an aromatase inhibitor – does not concur with the approved therapeutic indication. Based on the new data cut-off, the proportion of women who received prior antioestrogen therapy in subpopulation A1 is 44% in the abemaciclib arm and 41% in the comparator arm (see Table 10). Besides, the 36 endocrine-naive patients received approval-compliant treatment with fulvestrant (≙ about 10% in both study arms). However, the G-BA specified fulvestrant without restriction as ACT in this treatment situation. The total subpopulation A1 was therefore relevant for the derivation of the added benefit.

Subgroup analyses by previous antioestrogen therapy (yes versus no) also showed that there was no effect modification according to the characteristic “prior therapy”.

Data cut-offs

The MONARCH 2 study is an ongoing study. So far, 3 data cut-offs 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 study is ongoing (planned end of study in January 2024) and another analysis is planned after 441 deaths [14].

In accordance with the G-BA’s justification of the limitation of the decision, the results of the third data cut-off (20 June 2019) are subject of the present benefit assessment.

Study MONARCH plus

The MONARCH plus study is a double-blind RCT in which abemaciclib in combination with fulvestrant is directly compared with fulvestrant (+ placebo).

The study included 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 for 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 comparator arm. Randomization was stratified by type of disease (visceral metastases versus non-visceral) 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 [1,5]. Regarding the administration of fulvestrant, it can be assumed that, also in the MONARCH plus study, not all patients received approval-compliant treatment (see section on the suitability of fulvestrant in the MONARCH 2 study). However, the G-BA specified fulvestrant without restriction as ACT in this treatment situation. The total subpopulation A1 was therefore relevant for the derivation of the added benefit.

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 for 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 endocrine therapy are relevant for the assessment of research question A1. There is no information on the number of patients concerned. The company did not include the MONARCH plus study in the assessment and did not provide analyses on the relevant subpopulation in Module 4 B of the dossier.

Data cut-offs

The MONARCH plus study is an ongoing study. So far, the results of the first data cut-off from 29 March 2019 are available. This is the planned final analysis for the primary outcome “PFS”. The end and thus also the final analysis of the study are planned for November 2020.

Planned duration of follow-up observation

Table 10 shows the planned duration of follow-up observation in the studies MONARCH 2 and MONARCH plus for the individual outcomes.

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

Study **Outcome category** **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	
Functioning (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	
Functioning (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. Subsequent long-term follow-up observation only for SAEs related to the study protocol or the study medication.

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; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; mBPI-SF: modified Brief Pain Inventory-Short Form; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

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 “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). To be able to draw a reliable conclusion on the total study

period or the time until death of the patients, it would be necessary, however, to record these outcomes over the total period of time, as was the case for overall survival.

Patient characteristics

Table 10 shows the characteristics of the patients (subpopulation 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 therapy) (multipage table)

Study Characteristics Category	**Abemaciclib + fulvestrant N[a] = 246**	**Placebo + fulvestrant N[a] = 128**
MONARCH 2		
Sex [F/M], %	100/0	100/0
Age [years], mean (SD)	62 (10)	64 (9)
Age group, n (%)		
< 65 years	147 (60)	72 (56)
≥ 65 years	99 (40)	56 (44)
Family origin n (%)		
Caucasian	155 (63)	80 (63)
Asian	58 (24)	32 (25)
Other[b, c]	33 (13)	16 (13)
Region, n (%)		
Europe	ND	ND
North America	ND	ND
Asia	ND	ND
Starting dose, n (%)		
150 mg abemaciclib per dose	170 (69)	87 (68)
200 mg abemaciclib per dose	76 (31)	41 (32)
ECOG PS, n (%)		
0	136 (55)	74 (58)
1	110 (45)	54 (42)
Type of disease, n (%)		
Visceral metastases	131 (53)	80 (63)
Bone only metastases	71 (29)	29 (23)
Other	44 (18)	19 (15)
Sensitivity to endocrine therapy, n (%)		
Primary resistance	57 (23)	35 (27)
Secondary resistance	169 (69)	79 (62)
No prior therapy	20 (8)	14 (11)
Previous antioestrogen therapy, n (%)		
Yes	109 (44[c])	52 (41[c])
No	136 (55[c])	76 (59[c])
Disease duration (time between first diagnosis and randomization) [months], mean (SD)	ND	ND
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND
MONARCH plus[d]	ND	ND

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

Study Characteristics Category	Abemaciclib + fulvestrant N[a] = 246	Placebo + fulvestrant N[a] = 128
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 Americans, indigenous population of Alaska, Black/African American, multiple affiliations and missing patients. c. Institute's calculation. d. The company did not consider the MONARCH plus study in its assessment. There are no data on the characteristics of the subpopulation relevant for research question A1. 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; vs.: versus		

The characteristics of the postmenopausal patients with initial endocrine therapy (subpopulation A1) are comparable between the study arms of the MONARCH 2 study. The mean age of the patients 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.

No characteristics for the relevant subpopulation of research question A1 are available for the patients of the MONARCH plus study.

Mean/median treatment duration

There is no information on the mean/median treatment duration of the patients and on the mean/median observation period for individual outcomes for the relevant subpopulation A1 (and B1 and B2) of the MONARCH 2 study. With regard to the data cut-off of the MONARCH 2 study to be assessed (20 June 2019), Module 4 B only showed that the median treatment duration in the total population differed between the 2 study arms (13 cycles in the intervention arm versus 9 cycles in the comparator arm; 1 cycle has a duration of 28 days). As was the case in the first assessment of abemaciclib in combination with fulvestrant (data cut-off: 14 February 2017), it is also shown in the further course of the MONARCH 2 study that the median treatment duration was significantly longer in the intervention arm than in the comparator arm.

The observation period of the outcomes on morbidity, health-related quality and side effects depends on the end of treatment (see Table 9). It can be inferred from this that the observation periods of these outcomes were notably longer in the intervention arm than in the comparator arm.

For the MONARCH plus study, there were no data on the patients' mean/median treatment duration and the mean/median observation periods for individual outcomes for the total population or for the relevant subpopulations (A1 and B1).

Subsequent therapies

For the studies MONARCH 2 and MONARCH plus, there is no information for the relevant subpopulations on the subsequent therapies administered in the study.

Module 4 B only provided information for the total population of the MONARCH 2 study, which is presented as supplementary information in Appendix A.1; Table 36, of the full dossier assessment. However, as the research questions of the benefit assessment refer to different subpopulations (and thus different lines of treatment), it is not possible to derive conclusions on the subsequent therapies in the individual research questions based on the data in the total population of the MONARCH 2 study.

Risk of bias across outcomes (study level)

Table 11 shows the risk of bias across outcomes (risk of bias at study level).

Table 11: Risk of bias across outcomes (study level) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant

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[a]	Yes	Yes	Yes	Yes	Yes	Yes	Low

a. The company did not consider the MONARCH plus study in its assessment.
RCT: randomized controlled trial; vs.: versus

The risk of bias across outcomes was rated as low for the MONARCH 2 study. This concurs with the company's assessment.

The risk of bias across outcomes was also rated as low for the MONARCH plus study. Since the company did not consider the study in its assessment, it also did not assess the risk of bias.

Transferability of the study results to the German health care context

The company described in Module 4 B, Section 4.3.1.2.1, 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 were comparable to those of breast cancer patients in the

locally advanced or metastatic stage in the German health care context [21-24]. According to the company, the study treatment also concurred with German treatment standards [21,25-31]. The company did not provide any further information on the transferability of the study results to the German health care context.

Since the company did not consider the MONARCH plus study in its benefit assessment, it also did not explicitly address the transferability of the study results to the German health care context. However, the company noted in Module 4 B, Section 4.3.1.1.1, that it did not consider the study also because it could be assumed that the study with almost exclusively Asian patients would not provide any additional relevant evidence for the present benefit assessment. This approach was inadequate (see Section 2.3).

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 mBPI-SF and based on the use of analgesics
  - health status measured with the VAS of the EQ-5D-5L questionnaire
- 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) (CTCAE grade ≥ 3)
  - diarrhoea PT (CTCAE grade ≥ 3)
  - if applicable, further specific AEs

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

Table 12 shows for which outcomes data for subpopulation A1 (postmenopausal women with initial endocrine therapy) are available in the included studies MONARCH 2 and MONARCH plus.

Table 12: Matrix of outcomes – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine therapy)

Study	Outcomes											
	Overall survival	Symptoms (EORTC QLQ-C30)[a]	Symptoms (EORTC QLQ-BR23)[a]	Pain (mBPI-SF)	Health status (EQ-5D-5L VAS)	Health-related quality of life (EORTC QLQ-C30)[b]	Health-related quality of life (EORTC QLQ-BR23)[b]	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs[c]	Neutropenia PT (CTCAE grade ≥ 3)	Diarrhoea PT (CTCAE grade ≥ 3)
MONARCH 2	Yes	Yes	Yes	No[d]	No[e]	Yes	Yes	Yes	Yes	Yes	No[f]	No[f]
MONARCH plus	No[g]	No[g]	No[h]	No[g]	No[h]	No[g]	No[h]	No[g]	No[g]	No[g]	No[g]	No[g]

a. Measured with the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-BR23.
b. 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.
c. Discontinuation of at least one of both drugs.
d. No usable data; the company did not present a separate analysis for both response criteria of the outcome. The results are presented as supplementary information in Appendix B.1 (Table 37) of the full dossier assessment.
e. No usable data; the company did not provide any MMRM analyses. The results based on the operationalization provided by the company (definitive deterioration by ≥ 7 or ≥ 10 points) are presented as supplementary information in Appendix B.1 (Table 37) of the full dossier assessment.
f. No usable data; the company did not present any event time analyses.
g. No usable data. The company did not consider the MONARCH plus study in its assessment (see Section 2.3). No separate results are therefore available for the relevant subpopulation A1. The available results of the total population are presented as supplementary information in Appendix D of the full dossier assessment.
h. Outcome not recorded.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; 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; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; mBPI-SF: modified Brief Pain Inventory-Short Form; MMRM: mixed-effects model repeated measures; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

MONARCH 2

No usable data are available for the following patient-relevant outcomes:

- Pain (recorded with the mBPI-SF and based on the use of analgesics): For the operationalization of the outcome "pain", the company presented an event time analysis for the time from randomization to deterioration. It rated as deterioration either an increase by ≥ 2 points from baseline (on the symptom scale "worst pain over the last 24 hours") or an increase in the use of analgesics by more than one step (according to the World Health Organization's 3-step system for the treatment of cancer pain [32]). The event time analyses presented by the company were not usable for the benefit assessment because, as was the case in the first assessment, there were no separate analyses on the 2 response criteria. The results of this outcome, where no significant difference between the treatment arms was shown, can therefore not be assessed adequately. The analyses presented by the company are presented as supplementary information in Appendix B.1 (Table 37) of the full dossier assessment, however.
- Health status (recorded with the EQ-5D-5L VAS): In the dossier, the company presented responder analyses on the time to definitive deterioration by ≥ 7 or ≥ 10 points. The recording of the health status by means of a VAS is regarded as patient-relevant. The company referred to the work of Pickard 2007 [33] to prove the validity of the minimally important difference (MID) of 7 or 10 points. This work is unsuitable for showing the validity of an MID for the EQ-5D-5L VAS, however [34]. The MIDs used by the company were therefore not used. The analyses presented by the company are presented as supplementary information in Appendix B.1 (Table 37) of the full dossier assessment, however.
- Specific AEs (neutropenia CTCAE grade ≥ 3 and diarrhoea CTCAE grade ≥ 3): Although the first assessment of abemaciclib already described that event time analyses are necessary for a meaningful interpretation of the results, the company again only provided information on patients with event for the frequent AEs (including the specific AEs "neutropenia CTCAE grade ≥ 3" and "diarrhoea CTCAE grade ≥ 3" selected for the benefit assessment due to their special significance). Selecting and assessing specific AEs was therefore not possible on the basis of the data presented by the company.

MONARCH plus

The company did not include the MONARCH plus study in its assessment, and, correspondingly, presented no results on patient-relevant outcomes based on this study (see Section 2.3). The results based on the total population available so far were taken into account in the interpretation of the results of the MONARCH 2 study (see Section 2.4.2.3) and are presented as supplementary information in Appendix D of the full dossier assessment.

2.4.2.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes in the included studies MONARCH 2 and MONARCH plus in subpopulation A1 (postmenopausal women with initial endocrine therapy).

Table 13: 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 therapy)

Study	Study level	Outcomes											
		Overall survival	Symptoms (EORTC QLQ-C30)[a]	Symptoms (EORTC QLQ-BR23)[a]	Pain (mBPI-SF)	Health status (EQ-5D-5L VAS)	Health-related quality of life (EORTC QLQ-C30)[b]	Health-related quality of life (EORTC QLQ-BR23)[b]	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs[c]	Neutropenia PT (CTCAE grade ≥ 3)	Diarrhoea PT (CTCAE grade ≥ 3)
MONARCH 2	L	L	H[d]	H[d]	-[e]	-[f]	H[d]	H[d]	H[d]	H[d]	L[g]	-[h]	-[h]
MONARCH plus	L	No usable data[i]											

a. Measured with the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-BR23.
b. 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.
c. Discontinuation of at least one of both drugs.
d. Large proportion of potentially informative censoring in the total population (see text below the table); data for the subpopulations (A1, B1 and B2) are not available.
e. No usable data; the company did not present a separate analysis for both response criteria of the outcome. The results are provided as supplementary information in Appendix B.1 (Table 37) of the full dossier assessment.
f. No usable data; the company did not provide any MMRM analyses. The results based on the operationalization provided by the company (definitive deterioration by 7 or 10 points) are presented as supplementary information in Appendix B.1 (Table 37) of the full dossier assessment.
g. Despite the low risk of bias, the certainty of results for the outcome "discontinuation due to AEs" is assumed to be limited (see text below the table).
h. No usable data; the company did not present any event time analyses.
i: There are no data available for subpopulation A1. The available results of the total population are presented as supplementary information in Appendix D of the full dossier assessment.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; 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; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; H: high; L: low; mBPI-SF: modified Brief Pain Inventory-Short Form; MMRM: mixed-effects model repeated measures; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

MONARCH 2

The risk of bias of the results on the outcome "overall survival" was rated as low. This concurs with the company's assessment.

The certainty of results for the outcome "discontinuation due to AEs" was restricted despite a low risk of bias. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome "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, the risk of bias of the results was rated as high due to incomplete observations for potentially informative reasons. This deviates from the assessment of the company, which rated the risk of bias of the results in these outcomes as low.

MONARCH plus

The company did not include the MONARCH plus study in its assessment, and, correspondingly, presented no results based on this study. The outcome-specific risk of bias of the results was therefore not assessed.

2.4.2.3 Results

Table 14 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 therapy (research question A1).

The Kaplan-Meier curves on the event time analyses of the MONARCH 2 study are presented in Appendix B.2 of the full dossier assessment. The results on common AEs of the MONARCH 2 study can be found in Appendix B.3 of the full dossier assessment. Corresponding information on the MONARCH plus study is not available; available results on the total population of the MONARCH plus study can be found as supplementary information in Appendix D of the full dossier assessment.

Table 14: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine therapy) (multipage table)

Study Outcome category Outcome Subscale	Abemaciclib + fulvestrant N	Abemaciclib + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Placebo + fulvestrant N	Placebo + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Abemaciclib + fulvestrant vs. placebo + fulvestrant HR [95% CI]; p-value[a]
MONARCH 2, data cut-off 20 June 2019					
Mortality					
Overall survival	246	43.96 [37.78; 51.65] 123 (50.0)	128	37.25 [33.04; 48.89] 68 (53.1)	0.82 [0.61; 1.10]; 0.186
Morbidity					
Symptoms					
EORTC QLQ-C30 symptom scales, time to definitive deterioration[b]					
Fatigue	245	41.33 [32.48; 52.08] 90 (36.7)	128	22.59 [11.51; 39.19] 53 (41.4)	0.73 [0.51; 1.03]; 0.068
Nausea and vomiting	245	NA [47.67; NC] 50 (20.4)	128	30.71 [22.68; 46.09] 35 (27.3)	0.54 [0.35; 0.84]; 0.006
Pain	245	51.85 [42.90; NC] 64 (26.1)	128	33.34 [17.79; NC] 38 (29.7)	0.69 [0.46; 1.04]; 0.075
Dyspnoea	245	47.21 [42.84; 51.35] 65 (26.5)	128	NA [40.37; NC] 23 (18.0)	1.16 [0.72; 1.88]; 0.540
Insomnia	245	51.85 [46.88; NC] 47 (19.2)	128	NA [30.08; NC] 25 (19.5)	0.71 [0.43; 1.16]; 0.169
Appetite loss	245	NA [47.05; NC] 55 (22.4)	128	48.46 [27.68; NC] 26 (20.3)	0.93 [0.58; 1.49]; 0.768
Constipation	245	NA [47.67; NC] 33 (13.5)	128	49.74 [35.97; NC] 24 (18.8)	0.53 [0.31; 0.90]; 0.017
Diarrhoea	245	49.91 [44.48; NC] 65 (26.5)	128	NA [48.46; NC] 15 (11.7)	2.13 [1.21; 3.75]; 0.007
EORTC QLQ-BR23 symptom scales, time to definitive deterioration[b]					
Side effects of systemic treatment	245	42.77 [39.42; NC] 76 (31.0)	128	38.96 [23.01; NC] 30 (23.4)	1.17 [0.76, 1.79]; 0.488
Breast symptoms	245	NA [53.03; NC] 28 (11.4)	128	NA [32.22; NC] 20 (15.6)	0.50 [0.28; 0.90]; 0.020
Arm symptoms	245	51.52 [41.03; NC] 65 (26.5)	128	25.12 [13.18; 40.37] 51 (39.8)	0.48 [0.33; 0.70]; < 0.001
Upset by hair loss	No usable data[c]				
Pain (mBPI-SF)	No usable data[d]				
Health status (EQ-5D-5L VAS)	No usable data[e]				

Table 14: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine therapy) (multipage table)

Study Outcome category Outcome Subscale	Abemaciclib + fulvestrant N	Abemaciclib + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Placebo + fulvestrant N	Placebo + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Abemaciclib + fulvestrant vs. placebo + fulvestrant HR [95% CI]; p-value[a]
Health-related quality of life					
EORTC QLQ-C30 global health status and functional scales, time to definitive deterioration[f]					
Global health status	245	45.99 [40.31; NC] 71 (29.0)	128	32.48 [22.68; NC] 36 (28.1)	0.84 [0.56; 1.26]; 0.390
Physical functioning	245	47.67 [39.81; NC] 66 (26.9)	128	44.78 [26.76; NC] 34 (26.6)	0.85 [0.56; 1.29]; 0.452
Role functioning	245	47.67 [38.93; 55.59] 71 (29.0)	128	40.37 [22.16; 49.74] 42 (32.8)	0.72 [0.49; 1.07]; 0.100
Emotional functioning	245	55.13 [51.85; 55.59] 48 (19.6)	128	51.91 [51.91; NC] 23 (18.0)	0.88 [0.53, 1.45]; 0.605
Cognitive functioning	245	50.43 [43.30; NC] 65 (26.5)	128	44.78 [25.05; 54.81] 37 (28.9)	0.76 [0.50; 1.14]; 0.177
Social functioning	245	51.85 [44.48; NC] 63 (25.7)	128	33.24 [20.32; 40.60] 42 (32.8)	0.58 [0.39; 0.87]; 0.007
EORTC QLQ-BR23 functional scales, time to definitive deterioration[f]					
Body image	245	NA [43.50; NC] 58 (23.7)	128	44.78 [37.58; NC] 28 (21.9)	0.87 [0.55; 1.37]; 0.542
Sexual functioning	245	NA 33 (13.5)	128	NA 15 (11.7)	1.07 [0.58; 1.98]; 0.827
Sexual enjoyment	No usable data[c]				
Future perspective	245	NA [51.85; NC] 38 (15.5)	128	54.81 [40.60; 54.81] 17 (13.3)	1.0 [0.56, 1.78]; 0.987
Side effects					
AEs (supplementary information)	245	0.13 [0.10; 0.13] 242 (98.8)	128	0.58 [0.49; 0.95] 117 (91.4)	–
SAEs	245	NA [36.82; NC] 72 (29.4)	128	51.98 [42.51; NC] 18 (14.1)	1.96 [1.17; 3.30]; 0.009
Severe AEs (CTCAE grade ≥ 3)	245	3.72 [2.73; 5.56] 166 (67.8)	128	42.51 [20.84; NC] 38 (29.7)	3.39 [2.37; 4.85]; < 0.001
Discontinuation due to AEs[g]	245	NA 52 (21.2)	128	NA 7 (5.5)	3.50 [1.59; 7.72]; < 0.001
Neutropenia (PT, CTCAE grade ≥ 3)[h]	245	ND 62 (25.3)	128	ND 2 (1.6)	ND
Diarrhoea (PT, CTCAE grade ≥ 3)[h]	245	ND 35 (14.3)	128	ND 1 (0.8)	ND

Table 14: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine therapy) (multipage table)

Study Outcome category Outcome Subscale	Abemaciclib + fulvestrant N Median time to event in months [95% CI] Patients with event n (%)	Placebo + fulvestrant N Median time to event in months [95% CI] Patients with event n (%)	Abemaciclib + fulvestrant vs. placebo + fulvestrant HR [95% CI]; p-value[a]
MONARCH plus[i]			
All-cause mortality		No usable data[i]	
Morbidity		No usable data[i]	
Health-related quality of life		No usable data[i]	
Side effects		No usable data[i]	

a. HR and CI: unstratified Cox proportional hazards model; p-value: unstratified log-rank test.
b. Definitive deterioration was defined as an increase by at least 10 points from baseline without subsequent improvement to a score below this level. Deaths were not recorded as event.
c. The analyses presented for the scales "upset by hair loss" (symptoms) and "sexual enjoyment" (quality of life) of the EORTC QLQ-BR23 are not usable due to the only small proportion of patients considered in the analysis. The data presented in Module 4 B show that a large proportion of the patients were censored directly at the start of the study (> 75%) so that no data on the development of these patients regarding upset by hair loss and sexual activity over the course of the study are included in the analysis.
d. No usable data; the company did not present a separate analysis for both response criteria of the outcome. The results are provided as supplementary information in Appendix B.1, Table 37, of the full dossier assessment.
e. No usable data; the company did not provide any MMRM analyses. The results based on the operationalization provided by the company (definitive deterioration by 7 or 10 points) are presented as supplementary information in Appendix B.1, Table 37, of the full dossier assessment.
f. Definitive deterioration was defined as a decrease by at least 10 points from baseline without subsequent improvement to a score above this level. Deaths were not recorded as event.
g. Discontinuation of at least one of both drugs.
h. The results are not usable for the assessment of the added benefit, as the company did not present any event time analyses. The rates are presented as supplementary information, however.
i. The company did not include the MONARCH plus study in its assessment, and, correspondingly, presented no results for subpopulation A1 based on this study. The available results of the total population of the MONARCH plus study are presented as supplementary information in Appendix D of the full dossier assessment.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; 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; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; HR: hazard ratio; mBPI-SF: modified Brief Pain Inventory-Short Form; MMRM: mixed-effects model repeated measures; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The results are described primarily for the MONARCH 2 study. On the basis of the available data of the MONARCH 2 study, at most indications, e.g. of an added benefit, can be determined

for the outcome "overall survival", and, due to the high risk of bias or the limited certainty of results (discontinuation due to AEs), at most hints for all other outcomes (see Section 2.4.2.2).

Following the description of the results of the MONARCH 2 study, the available results of the total population of the MONARCH plus study are considered in terms of whether they support or question the results of the MONARCH 2 study.

MONARCH 2

Mortality

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This resulted in no hint of an added benefit of abemaciclib in combination with fulvestrant in comparison with fulvestrant. An added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

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

Fatigue, pain, dyspnoea, insomnia and appetite loss

No statistically significant difference between the treatment groups was shown for each of the outcomes "fatigue", "pain", "dyspnoea", "insomnia" and "appetite loss". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

This concurs with the company's assessment.

Nausea and vomiting

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for the outcome "nausea and vomiting". This resulted in a hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

This deviates from the assessment of the company insofar as the company derived an indication, and not a hint, of an added benefit for the outcome "nausea and vomiting".

Constipation

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for the outcome "constipation". The extent of the effect in this non-serious/non-severe outcome was no more than marginal, however. This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

This deviates from the assessment of the company, which derived an indication of an added benefit for this outcome.

Diarrhoea

A statistically significant difference to the disadvantage of abemaciclib + fulvestrant was shown for the outcome "diarrhoea". This resulted in a hint of lesser benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

This deviates from the assessment of the company insofar as the company derived an indication, and not a hint, of lesser benefit for the outcome "diarrhoea".

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

Side effects of systemic treatment

No statistically significant difference between the treatment groups was shown for the outcome "side effects of systemic treatment". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

Breast symptoms

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for the outcome "breast symptoms". The extent of the effect in this non-serious/non-severe outcome was no more than marginal, however. This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

This deviates from the assessment of the company, which derived an indication of an added benefit for this outcome.

Arm symptoms

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for the outcome "arm symptoms". There was an effect modification by the characteristic "age", however (see Section 2.4.2.4). This resulted in a hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant in patients < 65 years of age for the outcome "arm symptoms". For patients ≥ 65 years of age, there was no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This deviates from the assessment of the company insofar as the company did not consider the effect modification in the derivation of the added benefit and derived an indication of an added benefit for the outcome "arm symptoms" regardless of age.

Upset by hair loss

There were no usable analyses for the outcome "upset by hair" loss (see Table 14 for reasons). This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company also regarded the added benefit as not proven on the basis of the results it used.

Pain (mBPI-SF)

No usable analyses were available for the outcome "pain" (mBPI-SF) (see Section 2.4.2.1 for reasons). This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company also regarded the added benefit as not proven on the basis of the results it used.

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

No usable analyses were available for the outcome "health status" (EQ-5D-5L VAS) (see Section 2.4.2.1). This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an indication of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant based on the responder analyses presented by the company.

Health-related quality of life

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

Global health status, physical functioning, role functioning, emotional functioning, cognitive functioning

No statistically significant difference between the treatment groups was shown for any of the following outcomes: global health status, physical functioning, role functioning, emotional functioning, and cognitive functioning. This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

This concurs with the company's assessment.

Social functioning

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for the outcome "social functioning". This resulted in a hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

This deviates from the assessment of the company insofar as the company derived an indication, and not a hint, of an added benefit for the outcome "social functioning".

Health-related quality of life, recorded using the EORTC QLQ-BR23 (functional scales)

Body image, sexual functioning and future perspective

There was no statistically significant difference between the treatment groups for any of the outcomes "body image", "sexual functioning" and "future perspective". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

This concurs with the company's assessment.

Sexual enjoyment

There were no usable analyses for the outcome "sexual enjoyment" (see Table 14). This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company also regarded the added benefit as not proven on the basis of the results it used.

Side effects

SAEs and severe AEs (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of abemaciclib + fulvestrant was shown for the outcomes "SAEs" and "severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for each of these outcomes.

This deviates from the assessment of the company insofar as the company derived an indication, and not a hint, of greater harm (or lesser benefit) for each of the outcomes "SAEs" and "severe AEs (CTCAE grade ≥ 3)".

Discontinuation due to AEs

A statistically significant difference to the disadvantage of abemaciclib + fulvestrant was shown for the outcome "discontinuation due to AEs". This resulted in a hint of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

This deviates from the assessment of the company insofar as the company derived an indication, and not a hint, of greater harm (or lesser benefit) for the outcome "discontinuation due to AEs".

Specific AEs

As was the case already in the first assessment [7,12], the company did not present any event time analyses, which would have been necessary for an adequate choice and assessment of the specific AEs.

MONARCH plus study (research question A1): assessment of the available results in comparison with the MONARCH 2 study

No data for the subpopulation of research question A1 are available for the MONARCH plus study. Based on the first data cut-off (conducted on 29 March 2019), the total population (cohort B) of the study so far shows a higher rate of deaths in the comparator arm (9 patients; 17.0%) versus the intervention arm (8 patients; 7.7%), with few events overall, however (see Table 47 in Appendix D of the full dossier assessment). No analyses comparable to the MONARCH 2 study are available on symptoms and health-related quality of life. The available results on SAEs show that more patients had an SAE in the intervention arm than in the comparator arm (16 patients [15.4%] versus 4 patients [7.6%]). Thus, the few available data of the total population did not call into question the analyses of the MONARCH 2 study. Rather, the results on SAEs supported the greater harm from abemaciclib + fulvestrant in comparison with fulvestrant observed in the MONARCH 2 study.

2.4.2.4 Subgroups and other effect modifiers

The following subgroup characteristic was considered in the benefit assessment:

- age (< 65 years; ≥ 65 years)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there must be 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.

Table 15: Subgroups (symptoms; time to event) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine therapy)

Study Outcome	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs. placebo + fulvestrant	
Characteristic Subgroup	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]	p-value[b]
MONARCH 2, data cut-off 20 June 2019						
EORTC QLQ-BR23 (arm symptoms, time to definitive deterioration[c])						
Age						
< 65 years	147	NA [40.14; NC] 32 (21.8)	72	32.48 [11.57; 38.86] 31 (43.1)	0.34 [0.21; 0.56]	< 0.001
≥ 65 years	98	41.72 [22.19; 51.52] 33 (33.7)	56	25.12 [9.40; 48.46] 20 (35.7)	0.77 [0.44; 1.34]	0.350
						0.033[d]

a. HR and CI from unstratified Cox proportional hazards model.
b. Unstratified log-rank test.
c. Definitive deterioration was defined as an increase by at least 10 points from baseline without subsequent improvement to a score below this level. Deaths were not recorded as event.
d. Cox proportional hazards model, variables in the model: treatment, subgroup characteristic, interaction term treatment*subgroup characteristic.

CI: confidence interval; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module 23; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; vs.: versus

Morbidity

EORTC QLQ-BR23 symptom scales

Arm symptoms

There was an effect modification by the characteristic "age" for the outcome "arm symptoms". There was a statistically significant difference between the treatment groups in favour of abemaciclib + fulvestrant for patients < 65 years of age, whereas no statistically significant difference was shown for patients ≥ 65 years of age. This resulted in a hint of an added benefit of abemaciclib + fulvestrant for patients < 65 years of age. For patients ≥ 65 years of age, there was no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This deviates from the assessment of the company, which described this effect modification, but generally did not take the effect modifications into account in the derivation of the added benefit, as they were only "quantitative in nature".

2.4.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [3].

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 of the MONARCH 2 study presented in Section 2.4.2 (see Table 16).

Determination of the outcome category for outcomes on symptoms and side effects

The dossier did not provide information for every outcome considered in the present benefit assessment whether it was serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Morbidity

The dossier did not contain any information on the classification of the severity category for the outcomes "nausea and vomiting", "diarrhoea" (EORTC QLQ-C30 symptom scales) and "arm symptoms" (EORTC QLQ-BR23 symptom scale). Therefore, the outcomes were assigned to the outcome category of non-serious/non-severe symptoms.

Side effects

As was the case in the first assessment, there was no information about the severity grade attributable to the events that resulted in discontinuation due to AEs. Therefore, the outcome "discontinuation due to AEs" was 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 therapy) (multipage table)

Outcome category **Outcome** **Subscale** **Effect modifier** **Subgroup**	**Abemaciclib + fulvestrant vs. placebo + fulvestrant** **Median time to event in months** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: 44.0 vs. 37.3 HR: 0.82 [0.61; 1.10] p = 0.186	Lesser benefit/added benefit not proven
Morbidity		
EORTC QLQ-C30 (symptom scales, time to definitive deterioration)		
Fatigue	Median: 41.3 vs. 22.6 HR: 0.73 [0.51; 1.03] p = 0.068	Lesser benefit/added benefit not proven
Nausea and vomiting	Median: NA vs. 30.7 HR: 0.54 [0.35; 0.84] p = 0.006 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Pain	Median: 51.9 vs. 33.3 HR: 0.69 [0.46; 1.04] p = 0.075	Lesser benefit/added benefit not proven
Dyspnoea	Median: 47.2 vs. NA HR: 1.16 [0.72; 1.88] p = 0.540	Lesser benefit/added benefit not proven
Insomnia	Median: 51.9 vs. NA HR: 0.71 [0.43; 1.16] p = 0.169	Lesser benefit/added benefit not proven
Appetite loss	Median: NA vs. 48.5 HR: 0.93 [0.58; 1.49] p = 0.768	Lesser benefit/added benefit not proven
Constipation	Median: NA vs. 49.7 HR: 0.53 [0.31; 0.90] p = 0.017	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[c]
Diarrhoea	Median: 49.9 vs. NA HR: 2.13 [1.21; 3.75] HR[d]: 0.47 [0.27; 0.83] p = 0.007 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Lesser benefit, extent: "minor"

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

Outcome category **Outcome** **Subscale** **Effect modifier** **Subgroup**	**Abemaciclib + fulvestrant vs. placebo + fulvestrant** **Median time to event in months** **Effect estimation [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
EORTC QLQ-BR23 (symptom scales, time to definitive deterioration)		
Side effects of systemic treatment	Median: 42.8 vs. 39.0 HR: 1.17 [0.76; 1.79] p = 0.488	Lesser benefit/added benefit not proven
Breast symptoms	Median: NA vs. NA HR: 0.50 [0.28; 0.90] p = 0.020	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[c]
Arm symptoms Age < 65 years	Median: NA vs. 32.5 HR: 0.34 [0.21; 0.56] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
≥ 65 years	Median: 41.7 vs. 25.1 HR: 0.77 [0.44; 1.34] p = 0.350	Lesser benefit/added benefit not proven
Upset by hair loss	No usable data	
Pain (mBPI-SF)	No usable data	
Health status (EQ-5D-5L VAS)	No usable data	
Health-related quality of life		
EORTC QLQ-C30 (global health status and functional scales, time to definitive deterioration)		
Global health status	Median: 46.0 vs. 32.5 HR: 0.84 [0.56; 1.26] p = 0.390	Lesser benefit/added benefit not proven
Physical functioning	Median: 47.7 vs. 44.8 HR: 0.85 [0.56; 1.29] p = 0.452	Lesser benefit/added benefit not proven
Role functioning	Median: 47.7 vs. 40.4 HR: 0.72 [0.49; 1.07] p = 0.100	Lesser benefit/added benefit not proven
Emotional functioning	Median: 55.1 vs. 51.9 HR: 0.88 [0.53; 1.45] p = 0.605	Lesser benefit/added benefit not proven

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

Outcome category **Outcome** **Subscale** **Effect modifier** **Subgroup**	**Abemaciclib + fulvestrant vs. placebo + fulvestrant** **Median time to event in months** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Cognitive functioning	Median: 50.4 vs. 44.8 HR: 0.76 [0.50; 1.14] p = 0.177	Lesser benefit/added benefit not proven
Social functioning	Median: 51.9 vs. 33.2 HR: 0.58 [0.39; 0.87] p = 0.007 probability: "hint"	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: "considerable"
EORTC QLQ-BR23 (functional scales, time to definitive deterioration)		
Body image	Median: NA vs. 44.8 HR: 0.87 [0.55; 1.37] p = 0.542	Lesser benefit/added benefit not proven
Sexual functioning	Median: NA vs. NA HR: 1.07 [0.58; 1.98] p = 0.827	Lesser benefit/added benefit not proven
Sexual enjoyment	No usable data	
Future perspective	Median: NA vs. 54.8 HR: 1.0 [0.56; 1.78] p = 0.987	Lesser benefit/added benefit not proven
Side effects		
SAEs	Median: NA vs. 52.0 HR: 1.96 [1.17; 3.30] HR[d]: 0.51 [0.30; 0.85] p = 0.009 probability: "hint"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: "considerable"
Severe AEs (CTCAE grade ≥ 3)	Median: 3.7 vs. 42.5 HR: 3.39 [2.37; 4.85] HR[d]: 0.29 [0.21; 0.42] p < 0.001 probability: "hint"	Outcome category: severe/serious side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Discontinuation due to AEs[e]	Median: NA vs. NA HR: 3.50 [1.59; 7.72] HR[d]: 0.29 [0.13; 0.63] p < 0.001 probability: "hint"	Outcome category: non-severe/non-serious side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Neutropenia (PT, CTCAE grade ≥ 3)	No usable data	
Diarrhoea (PT, CTCAE grade ≥ 3)	No usable data	

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

Outcome category **Outcome** **Subscale** **Effect modifier** **Subgroup**	**Abemaciclib + fulvestrant vs. placebo + fulvestrant** **Median time to event in months** **Effect estimation [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u). c. The extent of the effect in this non-serious/non-severe outcome was no more than marginal. d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. e. Discontinuation of at least one of both drugs. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; 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; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; HR: hazard ratio; mBPI-SF: modified Brief Pain Inventory-Short Form; NA: not achieved; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus		

2.4.3.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion about 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 therapy)

Positive effects[a]	**Negative effects**[a]
Non-serious/non-severe symptoms/late complications ▪ nausea and vomiting: hint of an added benefit – extent: "minor" ▪ arm symptoms: age (< 65 years): hints of an added benefit – extent: "considerable"	Non-serious/non-severe symptoms/late complications ▪ diarrhoea: hint of lesser benefit – extent: "minor"
Health-related quality of life ▪ social functioning: hint of an added benefit – extent: "considerable"	–
–	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: "considerable" ▪ severe AEs (CTCAE grade ≥ 3): hint of greater harm – extent: "major"
–	Non-serious/non-severe side effects discontinuation due to AEs: hint of greater harm – extent: "considerable"
No (usable) data are available for neutropenia (CTCAE grade ≥ 3), diarrhoea (CTCAE grade ≥ 3) and, if applicable, further specific AEs.	
a. The effects are based exclusively on the results of the MONARCH 2 study. The company did not include the MONARCH plus study in its assessment. Results based on the relevant subpopulation A1 of this study were not available for the benefit assessment. The published data based on the total population support the overall picture of the MONARCH 2 study for subpopulation A1, however (see Section 2.4.2.3 and Appendix D of the full dossier assessment). AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events; SAE: serious adverse event	

In the overall consideration, there are both positive and negative effects of abemaciclib + fulvestrant in comparison with fulvestrant on the basis of the results of the MONARCH 2 study. Hints of an added benefit were shown in 2 non-serious/non-severe symptoms, one of which with minor extent, and one (in the subgroup of patients < 65 years) with considerable extent. In addition, there was a hint of an added benefit in one scale of health-related quality of life with considerable extent (social functioning). This was accompanied by hints of negative effects in all superordinate AE outcomes as well as in the non-serious/non-severe symptom "diarrhoea".

In the subpopulation A1 available here, the side effects were shown in particular in severe AEs (CTCAE grade ≥ 3) with major extent, and in SAEs with considerable extent. There were no usable analyses on specific AEs.

Overall, the negative effects with partly major extent (severe AEs) outweighed the positive effects in the MONARCH 2 study.

The results of the total population of the MONARCH plus study, which the company did not include in its assessment, were additionally taken into account in the assessment of the added benefit. The available data supported the presented negative effects in SAEs.

In summary, there is therefore a hint of lesser benefit of abemaciclib in combination with fulvestrant versus fulvestrant alone for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer with initial endocrine therapy (research question A1).

The assessment described above deviates from that of the company, which derived a considerable added benefit, without determining a concrete probability, for the patients of research question A1 based on the results of the MONARCH 2 study and under consideration of further outcomes.

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

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

2.5.1 Study characteristics

MONARCH 2

The study characteristics, information on data cut-offs and the follow-up observation of the MONARCH 2 study are described in detail in Section 2.4.1.

Subpopulation relevant for 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 for 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). The company presented analyses of this subpopulation in its dossier. These were used for the benefit assessment.

Abemaciclib starting dose

The deviations regarding the wrong starting dose of abemaciclib (200 mg versus 150 mg) existed for subpopulation B1 in the MONARCH 2 study analogous to subpopulation A1 (see Section 2.4.1). Regarding subpopulation B1, this concerned 40 (28%) patients in the abemaciclib arm. No relevant effect modification was shown for the subgroup characteristics investigated by the company (starting dose [200 mg versus 150 mg]) also in subpopulation B1.

Suitability of fulvestrant as comparator therapy

The G-BA cited fulvestrant as a possible ACT option also for postmenopausal women who have received prior endocrine therapy, but, in compliance with the approval of fulvestrant, only for patients with recurrence or progression following antioestrogen therapy [1]. The proportion of women who received prior antioestrogen therapy in subpopulation B1 is 48% in the abemaciclib arm and 58% in the comparator arm (see Table 18).

For research question B1, however, the G-BA sees a medical reason that justifies assessing fulvestrant or fulvestrant alone as a sufficiently suitable comparator without taking into account endocrine therapies indicated in accordance with the guidelines in the present treatment situation [2]. According to the G-BA, the guidelines explicitly recommend fulvestrant as a treatment option for postmenopausal women also after pretreatment with aromatase inhibitors in addition to other active ingredients (e.g. tamoxifen). This significance of fulvestrant in the reality of care was also emphasized in the corresponding written statements of medical societies in the first assessment, according to which fulvestrant is a therapy option regularly applied in the present treatment situation alongside other endocrine therapies [2]. Thus, the results of the total subpopulation B1 for the comparison of abemaciclib + fulvestrant versus the comparator fulvestrant are relevant.

Subgroup analyses by previous antioestrogen therapy (yes versus no) also showed that there was no effect modification according to the characteristic “prior therapy”.

MONARCH plus

The study characteristics, information on data cut-offs and the follow-up observation of the MONARCH plus study are described in detail in Section 2.4.1.

Subpopulation relevant for the assessment of 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 for the assessment of research question B1. The number of patients concerned is unclear. Module 4 B in the company’s dossier did not contain any analyses for the relevant subpopulation.

Patient characteristics

Table 18 shows the characteristics of the patients (subpopulation 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 received prior endocrine therapy) (multipage table)

Study Characteristics Category	Abemaciclib + fulvestrant N[a] = 144	Placebo + fulvestrant N[a] = 66
MONARCH 2		
Sex [F/M], %	100/0	100/0
Age [years], mean (SD)	63 (10)	66 (10)
Age group, n (%)		
< 65 years	79 (55)	28 (42)
≥ 65 years	65 (45)	38 (58)
Family origin n (%)		
Caucasian	81 (56)	47 (71)
Asian	43 (30)	13 (20)
Other[b, c]	20 (14)	6 (9)
Region, n (%)[d]		
Europe	75 (52[e])	37 (56[e])
North America	25 (17[e])	16 (24[e])
Asia	43 (30[e])	13 (20[e])
Starting dose, n (%)		
150 mg abemaciclib per dose	104 (72)	49 (74)
200 mg abemaciclib per dose	40 (28)	17 (26)
ECOG PS, n (%)[e]		
0	83 (58)	36 (55)
1	58 (40)	30 (45)
Type of disease, n (%)		
Visceral metastases	78 (54)	39 (59)
Bone only metastases	39 (27)	15 (23)
Other	27 (19)	12 (18)
Sensitivity to endocrine therapy, n (%)		
Primary resistance	27 (19)	10 (15)
Secondary resistance	117 (81)	56 (85)
No prior therapy	0 (0)	0 (0)
Previous antioestrogen therapy, n (%)		
Yes	69 (48[e])	38 (58[e])
No	74 (51[e])	28 (42[e])
Disease duration (time between first diagnosis and randomization) [months], mean (SD)	ND	ND
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND
MONARCH plus[f]	ND	ND

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

Study Characteristics Category	Abemaciclib + fulvestrant N[a] = 144	Placebo + fulvestrant N[a] = 66

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 Americans, indigenous population of Alaska, Black/African American, multiple affiliations and missing patients.
c. Institute's calculation.
d. The data on region were calculated based on the subgroup analyses (characteristic: geographical region) presented by the company in Module 4 B.
e. One patient in the intervention with ECOG PS 2.
f. The company did not consider the MONARCH plus study in its assessment. There are no data on the characteristics of the subpopulation relevant for research question B1.

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; vs.: versus

The characteristics of the postmenopausal patients who received prior endocrine therapy (subpopulation B1) are comparable between the study arms of the MONARCH 2 study. The mean age of the patients on study entry was about 64 years. About 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.

No characteristics for the relevant subpopulation of research question B1 are available for the patients of the MONARCH plus study.

Mean/median treatment duration and subsequent therapies

The evidence base on mean/median treatment duration and subsequent therapies in the studies MONARCH2 and MONARCH plus for research question B1 corresponds to the one in research question A1 (see Section 2.4.1, treatment duration and subsequent therapies).

Risk of bias across outcomes (study level)

Table 11 (see Section 2.4.1) shows the risk of bias across outcomes (risk of bias at study level).

The risk of bias across outcomes was rated as low for the MONARCH 2 study. This concurs with the company's assessment.

The risk of bias across outcomes was also rated as low for the MONARCH plus study. Since the company did not consider the study in its assessment, it did not assess the risk of bias.

Transferability of the study results to the German health care context

The situation regarding the transferability of the study results to the German health care context in the studies MONARCH 2 and MONARCH plus for research question B1 corresponds to the one in research question A1 (see Section 2.4.1, 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
  - measured with the EORTC QLQ-C30 and the EORTC QLQ-BR23
  - pain measured with the mBPI-SF and based on the use of analgesics
  - health status (EQ-5D-5L VAS)
- Health-related quality of life
  - measured with the EORTC QLQ-C30 and the EORTC QLQ-BR23
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - neutropenia PT (CTCAE grade ≥ 3)
  - diarrhoea PT (CTCAE grade ≥ 3)
  - if applicable, further specific AEs

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

Table 19 shows for which outcomes data for subpopulation B1 (postmenopausal women who received prior endocrine therapy) are available in the included studies MONARCH 2 and MONARCH plus.

Table 19: Matrix of outcomes – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who received prior endocrine therapy)

Study	Outcomes											
	Overall survival	Symptoms (EORTC QLQ-C30)[a]	Symptoms (EORTC QLQ-BR23)[a]	Pain (mBPI-SF)	Health status (EQ-5D-5L VAS)	Health-related quality of life (EORTC QLQ-C30)[b]	Health-related quality of life (EORTC QLQ-BR23)[b]	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs[c]	Neutropenia PT (CTCAE grade ≥ 3)	Diarrhoea PT (CTCAE grade ≥ 3)
MONARCH 2	Yes	Yes	Yes	No[d]	No[e]	Yes	Yes	Yes	Yes	Yes	No[f]	No[f]
MONARCH plus	No[g]	No[g]	No[h]	No[g]	No[h]	No[g]	No[h]	No[g]	No[g]	No[g]	No[g]	No[g]

a. Measured with the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-BR23.
b. 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.
c. Discontinuation of at least one of both drugs.
d. No usable data; the company did not present a separate analysis for both response criteria of the outcome. The results are presented as supplementary information in Appendix C.1 (Table 42) of the full dossier assessment.
e. No usable data; the company did not provide any MMRM analyses. The results based on the operationalization provided by the company (definitive deterioration by ≥ 7 or ≥ 10 points) are presented as supplementary information in Appendix C.1 (Table 42) of the full dossier assessment.
f. No usable data; the company did not present any event time analyses.
g. No usable data. The company did not consider the MONARCH plus study in its assessment (see Section 2.3). No separate results are therefore available for the relevant subpopulation B1. The available results of the total population are presented as supplementary information in Appendix D of the full dossier assessment.
h. Outcome not recorded.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; 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; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; mBPI-SF: modified Brief Pain Inventory-Short Form; MMRM: mixed-effects model repeated measures; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

MONARCH 2

Regarding the MONARCH 2 study, no usable analyses are available for the outcomes "pain", "health status" (EQ-5D-5L VAS) and "specific AEs" (see Section 2.4.2.1 for reasons). The analyses presented by the company for the outcomes "pain" and "health status" (EQ-5D-5L VAS) are presented as supplementary information in Appendix C (Table 42) of the full dossier assessment.

MONARCH plus

The company did not include the MONARCH plus study in its assessment, and, correspondingly, presented no results on patient-relevant outcomes based on this study (see Section 2.3). The results based on the total population available so far were taken into account in the interpretation of the results of the MONARCH 2 study (see Section 2.5.2.3) and are presented as supplementary information in Appendix D of the full dossier assessment.

2.5.2.2 Risk of bias

Table 20 describes the risk of bias for the results of the relevant outcomes in the included studies MONARCH 2 and MONARCH plus in subpopulation B1 (postmenopausal women who received prior endocrine therapy).

Table 20: 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 received prior endocrine therapy)

Study	Study level	Outcomes											
		Overall survival	Symptoms (EORTC QLQ-C30)[a]	Symptoms (EORTC QLQ-BR23)[a]	Pain (mBPI-SF)	Health status (EQ-5D-5L VAS)	Health-related quality of life (EORTC QLQ-C30)[b]	Health-related quality of life (EORTC QLQ-BR23)[b]	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs[c]	Neutropenia PT (CTCAE grade ≥ 3)	Diarrhoea PT (CTCAE grade ≥ 3)
MONARCH 2	L	L	H[d]	H[d]	-[e]	-[f]	H[d]	H[d]	H[d]	H[d]	L[g]	-[h]	-[h]
MONARCH plus	L	No usable data[i]											

a. Measured with the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-BR23.
b. 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.
c. Discontinuation of at least one of both drugs.
d. Large proportion of potentially informative censoring in the total population; data for the subpopulations (A1, B1 and B2) are not available.
e. No usable data; the company did not present a separate analysis for both response criteria of the outcome. The results are provided as supplementary information in Appendix C.1 (Table 42) of the full dossier assessment.
f. No usable data; the company did not provide any MMRM analyses. The results based on the operationalization provided by the company (definitive deterioration by 7 or 10 points) are presented as supplementary information in Appendix C.1 (Table 42) of the full dossier assessment.
g. Despite low risk of bias, a limited certainty of results is assumed for the outcome "discontinuation due to AEs" (see research question A1, Section 2.4.2.2).
h. No usable data; the company did not present any event time analyses.
i: There are no data available for subpopulation B1. The available results of the total population are presented as supplementary information in Appendix D of the full dossier assessment.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; 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; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; H: high; L: low; mBPI-SF: modified Brief Pain Inventory-Short Form; MMRM: mixed-effects model repeated measures; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

MONARCH 2

The risk of bias of the results on the outcome "overall survival" was rated as low. This concurs with the company's assessment.

There were no usable analyses for the outcomes "pain", "health status" and "specific AEs" (see Sections 2.4.2.1 and 2.5.2.1). Therefore, the risk of bias was not assessed for these outcomes.

This deviates from the assessment of the company, which used the results in these outcomes and assessed their risk of bias as low.

Although the risk of bias for the outcome "discontinuation due to AEs" was low, the certainty of results for this outcome was limited (see Section 2.4.2.2 for reasons). For all other outcomes, the risk of bias of the results was rated as high due to potentially informative censoring. This deviates from the assessment of the company, which rated the risk of bias of the results in these outcomes as low.

MONARCH plus

The company did not include the MONARCH plus study in its assessment, and, correspondingly, presented no results based on this study. The outcome-specific risk of bias of the results was therefore not assessed.

2.5.2.3 Results

Table 21 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 received prior endocrine therapy (research question B1).

The Kaplan-Meier curves on the event time analyses of the MONARCH 2 study are presented in Appendix C.2 of the full dossier assessment. The results on common AEs of the MONARCH 2 study can be found in Appendix C.3 of the full dossier assessment. Corresponding information on the MONARCH plus study is not available; available results on the total population of the MONARCH plus study can be found as supplementary information in Appendix D of the full dossier assessment.

Table 21: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who received prior endocrine therapy) (multipage table)

Study Outcome category Outcome Subscale	Abemaciclib + fulvestrant N	Abemaciclib + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Placebo + fulvestrant N	Placebo + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Abemaciclib + fulvestrant vs. placebo + fulvestrant HR [95% CI]; p-value[a]
MONARCH 2, data cut-off 20 June 2019					
Mortality					
Overall survival	144	48.82 [35.18; NC] 66 (45.8)	66	34.78 [28.83; 41.29] 44 (66.7)	0.67 [0.46; 0.98]; 0.037
Morbidity					
Symptoms					
EORTC QLQ-C30 symptom scales, time to definitive deterioration[b]					
Fatigue	143	22.88 [14.60; 29.95] 71 (49.7)	66	7.59 [4.67; 28.47] 37 (56.1)	0.68 [0.45; 1.01]; 0.054
Nausea and vomiting	143	44.94 [41.46; NC] 32 (22.4)	66	28.47 [9.63; NC] 21 (31.8)	0.49 [0.28; 0.86]; 0.011
Pain	143	44.19 [29.95; NC] 41 (28.7)	66	22.95 [12.69; 37.48] 26 (39.4)	0.49 [0.29; 0.80]; 0.004
Dyspnoea	143	44.94 [33.37; 49.02] 44 (30.8)	66	NA [23.97; NC] 16 (24.2)	0.93 [0.52; 1.67]; 0.809
Insomnia	143	41.95 [34.32; NC] 36 (25.2)	66	34.95 [15.72; NC] 18 (27.3)	0.58 [0.33; 1.03]; 0.062
Appetite loss	143	39.65 [28.47; NC] 43 (30.1)	66	34.95 [9.27; NC] 22 (33.3)	0.60 [0.35; 1.01]; 0.051
Constipation	143	NA [38.96; NC] 29 (20.3)	66	NA [15.68; NC] 15 (22.7)	0.54 [0.29; 1.03]; 0.057
Diarrhoea	143	45.40 [38.96; 54.41] 42 (29.4)	66	NA [23.05; NC] 12 (18.2)	1.27 [0.66; 2.44]; 0.479
EORTC QLQ-BR23 symptom scales, time to definitive deterioration[b]					
Side effects of systemic treatment	143	40.70 [25.32; 49.02] 52 (36.4)	66	28.47 [13.87; NC] 16 (24.2)	1.07 [0.61; 1.89]; 0.820
Breast symptoms	143	NA 13 (9.1)	66	NA [23.97; NC] 5 (7.6)	0.71 [0.25; 2.06]; 0.531
Arm symptoms	143	36.85 [28.93; 50.63] 43 (30.1)	66	37.48 [16.57; NC] 16 (24.2)	0.85 [0.48; 1.53]; 0.592
Upset by hair loss	No usable data[c]				
Pain (mBPI-SF)	No usable data[d]				
Health status (EQ-5D-5L VAS)	No usable data[e]				

Table 21: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who received prior endocrine therapy) (multipage table)

Study Outcome category Outcome Subscale	Abemaciclib + fulvestrant N	Abemaciclib + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Placebo + fulvestrant N	Placebo + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Abemaciclib + fulvestrant vs. placebo + fulvestrant HR [95% CI]; p-value[a]
Health-related quality of life					
EORTC QLQ-C30 global health status and functional scales, time to definitive deterioration[f]					
Global health status	143	30.81 [19.27; 38.96] 57 (39.9)	66	14.56 [5.98; 28.47] 28 (42.4)	0.63 [0.40; 1.00]; 0.049
Physical functioning	143	44.91 [27.68; NC] 37 (25.9)	66	28.47 [9.27; NC] 22 (33.3)	0.54 [0.31; 0.92]; 0.021
Role functioning	143	35.97 [27.29; 44.94] 56 (39.2)	66	19.89 [7.99; 33.11] 26 (39.4)	0.72 [0.45; 1.16]; 0.180
Emotional functioning	143	44.22 [29.95; NC] 37 (25.9)	66	23.05 [13.18; 37.48] 22 (33.3)	0.47 [0.27; 0.81]; 0.005
Cognitive functioning	143	33.93 [19.76; 41.46] 52 (36.3)	66	16.57 [9.63; 28.47] 25 (37.9)	0.66 [0.40; 1.06]; 0.085
Social functioning	143	31.23 [22.75; 46.55] 53 (37.1)	66	23.05 [12.69; NC] 23 (34.8)	0.79 [0.48, 1.29]; 0.338
EORTC QLQ-BR23 functional scales, time to definitive deterioration[f]					
Body image	143	NA [24.89; NC] 40 (28.0)	66	34.55 [17.06; NC] 13 (19.7)	1.10 [0.59; 2.07]; 0.763
Sexual functioning	143	NA 17 (11.9)	66	42.41 [42.41; NC] 8 (12.1)	0.62 [0.26; 1.46]; 0.270
Sexual enjoyment	No usable data[c]				
Future perspective	143	41.72 [32.38; NA] 37 (25.9)	66	NA [37.48; NC] 7 (10.6)	1.53 [0.67; 3.46]; 0.309
Side effects					
AEs (supplementary information)	143	0.10 [0.07; 0.13] 140 (97.9)	66	0.54 [0.26; 0.95] 59 (89.4)	–
SAEs	143	47.11 [34.03; NC] 40 (28.0)	66	29.92 [15.06; NC] 14 (21.2)	0.96 [0.52; 1.78]; 0.896
Severe AEs (CTCAE grade ≥ 3)	143	4.64 [1.91; 9.01] 99 (69.2)	66	27.98 [9.93; NC] 21 (31.8)	2.61 [1.63; 4.19]; < 0.001
Discontinuation due to AEs[g]	143	NA [38.07; NC] 34 (23.8)	66	NA 2 (3.0)	6.49 [1.55; 27.12]; 0.003
Neutropenia (PT, CTCAE grade ≥ 3)[h]	143	ND 42 (29.4)	66	ND 1 (1.5)	ND
Diarrhoea (PT, CTCAE grade ≥ 3)[h]	143	ND 25 (17.5)		ND 0 (0)	ND

Table 21: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who received prior endocrine therapy) (multipage table)

Study Outcome category Outcome Subscale	Abemaciclib + fulvestrant N	Abemaciclib + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Placebo + fulvestrant N	Placebo + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Abemaciclib + fulvestrant vs. placebo + fulvestrant HR [95% CI]; p-value[a]
MONARCH plus[i]					
All-cause mortality	No usable data[i]				
Morbidity	No usable data[i]				
Health-related quality of life	No usable data[i]				
Side effects	No usable data[i]				

a. HR and CI: unstratified Cox proportional hazards model; p-value: unstratified log-rank test.
b. Definitive deterioration was defined as an increase by at least 10 points from baseline without subsequent improvement to a score below this level. Deaths were not recorded as event.
c. The analyses presented for the scales "upset by hair loss" (symptoms) and "sexual enjoyment" (quality of life) of the EORTC QLQ-BR23 are not usable due to the only small proportion of patients considered in the analysis. The data presented in Module 4 B show that a large proportion of the patients were censored directly at the start of the study (> 75%) so that no data on the development of these patients regarding upset by hair loss and sexual activity over the course of the study are included in the analysis.
d. No usable data; the company did not present a separate analysis for both response criteria of the outcome. The results are provided as supplementary information in Appendix C.1 (Table 42) of the full dossier assessment.
e. No usable data; the company did not provide any MMRM analyses. The results based on the operationalization provided by the company (definitive deterioration by 7 or 10 points) are presented as supplementary information in Appendix C.1 (Table 42) of the full dossier assessment.
f. Definitive deterioration was defined as a decrease by at least 10 points from baseline without subsequent improvement to a score above this level. Deaths were not recorded as event.
g. Discontinuation of at least one of both drugs.
h. The results are not usable for the assessment of the added benefit, as the company did not present any event time analyses. The rates are presented as supplementary information, however.
i. The company did not include the MONARCH plus study in its assessment, and, correspondingly, presented no results for subpopulation B1 based on this study. The available results of the total population of the MONARCH plus study are presented as supplementary information in Appendix D of the full dossier assessment.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; 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; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; HR: hazard ratio; mBPI-SF: modified Brief Pain Inventory-Short Form; MMRM: mixed-effects model repeated measures; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The results are described primarily for the MONARCH 2 study. On the basis of the available data of the MONARCH 2 study, at most indications, e.g. of an added benefit, can be determined

for the outcome "overall survival", and, due to the high risk of bias or the limited certainty of results (discontinuation due to AEs), at most hints for all other outcomes (see Sections 2.5.2.2 and 2.4.2.2).

Following the description of the results of the MONARCH 2 study, the available results of the total population of the MONARCH plus study are considered in terms of whether they support or question the results of the MONARCH 2 study.

MONARCH 2

Mortality

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for the outcome "overall survival". This resulted in an indication of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

This concurs with the company's assessment.

Morbidity

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

Fatigue, dyspnoea, appetite loss, constipation and diarrhoea

No statistically significant difference between the treatment groups was shown for any of the outcomes "fatigue", "dyspnoea", "appetite loss", "constipation" and "diarrhoea". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

This concurs with the company's assessment.

Nausea and vomiting, and pain

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for each of the outcomes "nausea and vomiting" and "pain". This resulted in a hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for each of these outcomes.

This deviates from the assessment of the company insofar as the company derived an indication, and not a hint, of an added benefit for each of the outcomes "nausea and vomiting" and "pain".

Insomnia

No statistically significant difference between the treatment groups was shown for the outcome "insomnia". There was an effect modification by the characteristic "age", however (see Section 2.5.2.4). This resulted in a hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant in patients ≥ 65 years of age for the outcome "insomnia". For patients < 65 years of age, there was no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This deviates from the assessment of the company, which did not consider the effect modification in the derivation of the added benefit and therefore considered the added benefit as not proven.

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

Side effects of systemic treatment, breast symptoms and arm symptoms

No statistically significant difference between the treatment groups was shown for any of the outcomes "side effects of systemic treatment", "breast symptoms" and "arm symptoms". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

This concurs with the company's assessment.

Upset by hair loss

There were no usable analyses for the outcome "upset by hair" loss (see Table 19 for reasons). This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company also regarded the added benefit as not proven on the basis of the results it used.

Pain (mBPI-SF)

No usable analyses were available for the outcome "pain" (mBPI-SF) (see Section 2.4.2.1 and Table 19 for reasons). This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company also regarded the added benefit as not proven on the basis of the results it used.

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

No usable analyses were available for the outcome "health status" (EQ-5D-5L VAS) (see Section 2.4.2.1 and Table 19 for reasons). This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company also regarded the added benefit as not proven on the basis of the results it used.

Health-related quality of life

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

Global health status, physical functioning, emotional functioning

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for each of the outcomes "global health status", "physical functioning" and "emotional functioning". This resulted in a hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for each of these outcomes.

For the outcomes "physical functioning" and "emotional functioning", this deviates from the assessment of the company insofar as the company derived an indication, and not a hint, of an added benefit for each of both outcomes. For the outcome "global health status", this deviates from the assessment of the company, which considered the added benefit as not proven.

Role functioning, cognitive functioning, social functioning

No statistically significant difference between the treatment groups was shown for any of the outcomes "role functioning", "cognitive functioning" and "social functioning". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life, recorded using the EORTC QLQ-BR23 (functional scales)

Body image, sexual functioning and future perspective

There was no statistically significant difference between the treatment groups for any of the outcomes "body image", "sexual functioning" and "future perspective". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

This concurs with the company's assessment.

Sexual enjoyment

There were no usable analyses for the outcome "sexual enjoyment" (see Table 19 for reasons). This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company also regarded the added benefit as not proven on the basis of the results it used.

Side effects

SAEs

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". Hence, there was 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.

This concurs with the company's assessment.

Severe AEs (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of abemaciclib + fulvestrant was shown for the outcome "severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

This deviates from the assessment of the company insofar as the company derived an indication, and not a hint, of greater harm (or lesser benefit) for the outcome "severe AEs (CTCAE grade ≥ 3)".

Discontinuation due to AEs

A statistically significant difference to the disadvantage of abemaciclib + fulvestrant was shown for the outcome "discontinuation due to AEs". Due to the limited certainty of results, this resulted in a hint of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

This deviates from the assessment of the company insofar as the company derived an indication, and not a hint, of greater harm (or lesser benefit) for the outcome "discontinuation due to AEs".

Specific AEs

As was the case already in the first assessment [7,12], the company did not present any event time analyses, which would have been necessary for an adequate choice and assessment of the specific AEs.

MONARCH plus study (research question B1): assessment of the available results in comparison with the MONARCH 2 study

No data for the subpopulation of research question B1 are available for the MONARCH plus study. Based on the first data cut-off (conducted on 29 March 2019), the total population (cohort B) of the study so far shows a higher rate of deaths in the comparator arm (9 patients; 17.0%) versus the intervention arm (8 patients; 7.7%), with few events overall, however (see Table 47 in Appendix D of the full dossier assessment). No analyses comparable to the MONARCH 2 study are available on symptoms and health-related quality of life. The available results on SAEs show that more patients had an SAE in the intervention arm than in the comparator arm (16 patients [15.4%] versus 4 patients [7.6%]). Thus, the few available data of the total population did not call into question the analyses of the MONARCH 2 study. Rather, the results supported the presented positive effect in overall survival (due to the lower death rate in the

abemaciclib arm versus the comparator arm, with few deaths overall) as well as the negative effect in SAEs.

2.5.2.4 Subgroups and other effect modifiers

The following subgroup characteristic was considered in the benefit assessment:

- age (< 65 years; ≥ 65 years)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there must be 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.

Table 22: Subgroups (symptoms; time to event) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who received prior endocrine therapy)

Study Outcome	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs. placebo + fulvestrant	
Characteristic Subgroup	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]	p-value[b]
MONARCH 2, data cut-off 20 June 2019						
EORTC QLQ-C30 (insomnia, time to definitive deterioration[c])						
Age						
< 65 years	79	41.49 [33.04; NC] 23 (29.1)	28	NA [NC; NC] 1 (3.6)	5.43 [0.73; 40.31]	0.065
≥ 65 years	64	41.95 [27.29; NC] 13 (20.3)	38	15.72 [5.98; 34.95] 17 (44.8)	0.28 [0.13; 0.58]	< 0.001
					Interaction:	0.006[d]

a. HR and CI from unstratified Cox proportional hazards model.
b. Unstratified log-rank test.
c. Definitive deterioration was defined as an increase by at least 10 points from baseline without subsequent improvement to a score below this level. Deaths were not recorded as event.
d. Cox proportional hazards model, variables in the model: treatment, subgroup characteristic, interaction term treatment*subgroup characteristic.

CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; HR: hazard ratio; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; vs.: versus

Morbidity

EORTC QLQ-C30 symptom scales

Insomnia

There was an effect modification by the characteristic "age" for the outcome "insomnia". There was a statistically significant difference between the treatment groups in favour of abemaciclib + fulvestrant for patients ≥ 65 years of age, whereas no statistically significant difference was shown for patients < 65 years of age. This resulted in a hint of an added benefit of abemaciclib + fulvestrant for patients ≥ 65 years of age. For patients < 65 years of age, there was no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This deviates from the assessment of the company, which described this effect modification, but generally did not take the effect modifications into account in the derivation of the added benefit, as they were only "quantitative in nature".

2.5.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [3].

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 of the MONARCH 2 study presented in Section 2.5.2 (see Table 23).

Determination of the outcome category for outcomes on symptoms and side effects

The dossier did not provide information for every outcome considered in the present benefit assessment whether it was serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Morbidity

The dossier did not contain any information on the classification of the severity category for the outcomes "nausea and vomiting", "pain" and "insomnia" (EORTC QLQ-C30 symptom scales). Therefore, the outcomes were assigned to the outcome category of non-serious/non-severe symptoms.

Side effects

As was the case in the first assessment, there was no information about the severity grade attributable to the events that resulted in discontinuation due to AEs. Therefore, the outcome

"discontinuation due to AEs" was assigned to the outcome category of non-serious/non-severe side effects. This concurs with the company's assessment. Due to the missing data, it cannot be ruled out that the category "serious/severe" is applicable, however.

Table 23: Extent of added benefit at outcome level: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who received prior endocrine therapy) (multipage table)

Outcome category **Outcome** **Subscale** **Effect modifier** **Subgroup**	**Abemaciclib + fulvestrant vs. placebo + fulvestrant** **Median time to event in months** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: 48.8 vs. 34.8 HR: 0.67 [0.46; 0.98] p = 0.037 probability: "hint"	Outcome category: mortality $0.95 \leq CI_u < 1.00$ added benefit, extent: "minor"
Morbidity		
EORTC QLQ-C30 (symptom scales, time to definitive deterioration)		
Fatigue	Median: 22.9 vs. 7.6 HR: 0.68 [0.45; 1.01] p = 0.054	Lesser benefit/added benefit not proven
Nausea and vomiting	Median: 44.9 vs. 28.5 HR: 0.49 [0.28; 0.86] p = 0.011 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Pain	Median: 44.2 vs. 23.0 HR: 0.49 [0.29; 0.80] p = 0.004 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ added benefit, extent: "minor"
Dyspnoea	Median: 44.9 vs. NA HR: 0.93 [0.52; 1.67] p = 0.809	Lesser benefit/added benefit not proven
Insomnia Age		
< 65 years	Median: 41.5 vs. NA HR: 5.43 [0.73; 40.31] p = 0.065	Lesser benefit/added benefit not proven
≥ 65 years	Median: 42.0 vs. 15.7 HR: 0.28 [0.13; 0.58] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: "considerable"
Appetite loss	Median: 39.7 vs. 35.0 HR: 0.60 [0.35; 1.01] p = 0.051	Lesser benefit/added benefit not proven

Table 23: Extent of added benefit at outcome level: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who received prior endocrine therapy) (multipage table)

Outcome category **Outcome** **Subscale** **Effect modifier** **Subgroup**	**Abemaciclib + fulvestrant vs. placebo + fulvestrant** **Median time to event in months** **Effect estimation [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
Constipation	Median: NA vs. NA HR: 0.54 [0.29; 1.03] p = 0.057	Lesser benefit/added benefit not proven
Diarrhoea	Median: 45.4 vs. NA HR: 1.27 [0.66; 2.44] p = 0.479	Lesser benefit/added benefit not proven
EORTC QLQ-BR23 (symptom scales, time to definitive deterioration)		
Side effects of systemic treatment	Median: 40.7 vs. 28.5 HR: 1.07 [0.61; 1.89] p = 0.820	Lesser benefit/added benefit not proven
Breast symptoms	Median: NA vs. NA HR: 0.71 [0.25; 2.06] p = 0.531	Lesser benefit/added benefit not proven
Arm symptoms	Median: 36.9 vs. 37.5 HR: 0.85 [0.48; 1.53] p = 0.592	Lesser benefit/added benefit not proven
Upset by hair loss	No usable data	
Pain (mBPI-SF)	No usable data	
Health status (EQ-5D-5L VAS)	No usable data	
Health-related quality of life		
EORTC QLQ-C30 (global health status and functional scales, time to definitive deterioration)		
Global health status	Median: 30.8 vs. 14.6 HR: 0.63 [0.40; 1.00] p = 0.049 probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$[c] added benefit, extent: “minor”
Physical functioning	Median: 44.9 vs. 28.5 HR: 0.54 [0.31; 0.92] p = 0.021 probability: “hint”	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ added benefit, extent: “minor”
Role functioning	Median: 36.0 vs. 19.9 HR: 0.72 [0.45; 1.16] p = 0.180	Lesser benefit/added benefit not proven
Emotional functioning	Median: 44.2 vs. 23.1 HR: 0.47 [0.27; 0.81] p = 0.005 probability: “hint”	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ added benefit, extent: “considerable”

Table 23: Extent of added benefit at outcome level: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who received prior endocrine therapy) (multipage table)

Outcome category **Outcome** **Subscale** **Effect modifier** **Subgroup**	**Abemaciclib + fulvestrant vs. placebo + fulvestrant** **Median time to event in months** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Cognitive functioning	Median: 33.9 vs. 16.6 HR: 0.66 [0.40; 1.06] p = 0.085	Lesser benefit/added benefit not proven
Social functioning	Median: 31.2 vs. 23.1 HR: 0.79 [0.48; 1.29] p = 0.338	Lesser benefit/added benefit not proven
EORTC QLQ-BR23 (functional scales, time to definitive deterioration)		
Body image	Median: NA vs. 34.6 HR: 1.10 [0.59; 2.07] p = 0.763	Lesser benefit/added benefit not proven
Sexual functioning	Median: NA vs. 42.4 HR: 0.62 [0.26; 1.46] p = 0.270	Lesser benefit/added benefit not proven
Sexual enjoyment	No usable data	
Future perspective	Median: 41.7 vs. NA HR: 1.53 [0.67; 3.46] p = 0.309	Lesser benefit/added benefit not proven
Side effects		
SAEs	Median: 47.1 vs. 29.9 HR: 0.96 [0.52; 1.78] p = 0.896	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	Median: 4.6 vs. 28.0 HR: 2.61 [1.63; 4.19] HR[d]: 0.38 [0.24; 0.61] p < 0.001 probability: “hint”	Outcome category: severe/serious side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: “major”
Discontinuation due to AEs[e]	Median: NA vs. NA HR: 6.49 [1.55; 27.12] HR[d]: 0.15 [0.04; 0.65] p = 0.003 probability: “hint”	Outcome category: non-severe/non-serious side effects CI_u < 0.80 greater harm, extent: “considerable”
Neutropenia (PT, CTCAE grade ≥ 3)	No usable data	
Diarrhoea (PT, CTCAE grade ≥ 3)	No usable data	

Table 23: Extent of added benefit at outcome level: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who received prior endocrine therapy) (multipage table)

Outcome category **Outcome** **Subscale** **Effect modifier** **Subgroup**	**Abemaciclib + fulvestrant vs. placebo + fulvestrant** **Median time to event in months** **Effect estimation [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
a. Probability provided if there is a statistically significant and relevant effect. b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u). c. Although the upper limit of the confidence interval cited by the company in Module 4 B is 1.00, the presence of an effect is assumed due to the statistically significant p-value. d. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit. e. Discontinuation of at least one of both drugs. AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; 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; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; HR: hazard ratio; mBPI-SF: modified Brief Pain Inventory-Short Form; NA: not achieved; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus		

2.5.3.2 Overall conclusion on added benefit

Table 24 summarizes the results considered in the overall conclusion about the extent of added benefit.

Table 24: Positive and negative effects from the assessment of abemaciclib + fulvestrant in comparison with placebo + fulvestrant (research question B1: postmenopausal women who received prior endocrine therapy)

Positive effects[a]	**Negative effects**[a]
Mortality ▪ overall survival: hint of an added benefit – extent "minor"	–
Non-serious/non-severe symptoms/late complications ▪ nausea and vomiting: hint of an added benefit – extent: "minor" ▪ pain: hint of an added benefit – extent "minor" ▪ insomnia age ≥ 65 years: hint of an added benefit – extent: "considerable"	–
Health-related quality of life ▪ global health status: hint of an added benefit – extent: "minor" ▪ physical functioning: hint of an added benefit – extent: "minor" ▪ emotional functioning: hint of an added benefit – extent: "considerable"	–
–	Serious/severe side effects ▪ severe AEs (CTCAE grade ≥ 3): hint of greater harm – extent: "major"
–	Non-serious/non-severe side effects ▪ discontinuation due to AEs: hint of greater harm – extent: "considerable"
No (usable) data are available for neutropenia (CTCAE grade ≥ 3), diarrhoea (CTCAE grade ≥ 3) and, if applicable, further specific AEs.	
a. The effects are based exclusively on the results of the MONARCH 2 study. The company did not include the MONARCH plus study in its assessment. Results based on the relevant subpopulation B1 of this study were not available for the benefit assessment. The published data based on the total population support the overall picture of the MONARCH 2 study, however (see Section 2.5.2.3 and Appendix D of the full dossier assessment). AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events	

In the overall consideration, there are both positive and negative effects of abemaciclib in combination with fulvestrant in comparison with fulvestrant on the basis of the results of the MONARCH 2 study. The positive effect for the outcome "overall survival", for which there was an indication of a minor added benefit, was decisive for the overall conclusion (research question B1). In addition, the MONARCH 2 study showed several positive effects of minor or considerable extent from the category of non-severe/non-serious side effects and health-related quality of life, each with the probability "hint". This was accompanied by negative effects from the outcome category of side effects. This resulted in a hint of considerably greater harm and a hint of major greater harm in severe/serious side effects.

Overall, the negative effects did not question the positive effects, and particularly not the advantage in overall survival.

The results of the total population of the MONARCH plus study, which the company did not include in its assessment, were additionally taken into account in the assessment of the added

benefit. The available data on the basis of the total population supported the presented positive effect in overall survival and the negative effect in SAEs.

In summary, there is an indication of a minor added benefit of abemaciclib in combination with fulvestrant versus fulvestrant alone for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer who already received endocrine therapy for the locally advanced or metastatic stage (research question B1).

The assessment described above deviates from that of the company, which derived a considerable added benefit, without determining a concrete probability, for the patients of research question B1 based on the results of the MONARCH 2 study and under consideration of further outcomes.

2.6 Research question B2: pre- and perimenopausal women who received prior endocrine therapy

Details on the information retrieval and on the study pool relevant for this research question B2 can be found in Section 2.3.

2.6.1 Study characteristics

MONARCH 2

The study characteristics, information on data cut-offs and the follow-up observation of the MONARCH 2 study are described in detail in Section 2.4.1.

Subpopulation relevant for the assessment of research question B2

Among the patients included in the MONARCH 2 study, only the subpopulation of pre- and perimenopausal women who received prior endocrine therapy are relevant for the assessment of research question B2 (see Section 2.2).

Out of the total of 713 patients, this applies to 46 (6.5%), of which 26 patients were treated with abemaciclib in combination with fulvestrant and 20 patients were treated with fulvestrant (+ placebo). The company presented analyses of this subpopulation in its dossier. These were used for the benefit assessment.

Abemaciclib starting dose

The deviations regarding the wrong starting dose of abemaciclib (200 mg versus 150 mg) existed for subpopulation B2 in the MONARCH 2 study analogous to subpopulation A1 (see Section 2.4.1). Regarding subpopulation B2, this concerned 7 (27%) patients in the abemaciclib arm. Analogous to the approach in research questions A1 and B1, it is assumed that the high abemaciclib starting dose did not have important influences on the study results, however.

Suitability of fulvestrant as comparator therapy

The G-BA named endocrine therapy specified by the physician under consideration of the respective approval as ACT for pre- and perimenopausal patients who received prior endocrine therapy (see Section 2.2). Tamoxifen, letrozole, exemestane, megestrol acetate and medroxyprogesterone acetate are approved in the present therapeutic indication. It is assumed that ovarian function is suppressed by oophorectomy or with a GnRH analogue.

Choosing fulvestrant as ACT, the company deviated from the ACT specified by the G-BA. However, in this special therapeutic and health care situation the G-BA sees a sufficient medical reason that, despite remaining uncertainties, justifies assessing fulvestrant as a sufficiently suitable comparator [2]. According to guidelines, besides further drugs such as tamoxifen, fulvestrant is an established treatment option together with suppression of ovarian function also for pre- and perimenopausal patients. According to the G-BA, this view was also supported in corresponding statements by medical experts in the present procedure.

Thus, the results of the total subpopulation B2 for the comparison of abemaciclib + fulvestrant versus the comparator fulvestrant are relevant.

Patient characteristics

Table 25 shows the characteristics of the patients (subpopulation B2) in the studies included.

Table 25: Characteristics of the study population – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B2: pre- and perimenopausal women who received prior endocrine therapy) (multipage table)

Study **Characteristics** **Category**	**Abemaciclib + fulvestrant** **N[a] = 26**	**Placebo + fulvestrant** **N[a] = 20**
MONARCH 2		
Sex [F/M], %	100/0	100/0
Age [years], mean (SD)	46 (6)	49 (9)
Age group, n (%)		
< 65 years	26 (100)	20 (95)
≥ 65 years	0 (0)	1 (5)
Family origin n (%)		
Caucasian	4 (15)	9 (45)
Asian	21 (81)	10 (50)
Other[b, c]	1 (4)	1 (5)
Region, n (%)		
Europe	ND	ND
North America	ND	ND
Asia	ND	ND

Table 25: Characteristics of the study population – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B2: pre- and perimenopausal women who received prior endocrine therapy) (multipage table)

Study Characteristics Category	**Abemaciclib + fulvestrant N[a] = 26**	**Placebo + fulvestrant N[a] = 20**
Starting dose, n (%)		
150 mg abemaciclib per dose	19 (73)	15 (75)
200 mg abemaciclib per dose	7 (27)	5 (25)
ECOG PS, n (%)		
0	20 (77)	18 (90)
1	6 (23)	2 (10)
Type of disease, n (%)		
Visceral metastases	17 (65)	10 (50)
Bone only metastases	5 (19)	5 (25)
Other	4 (15)	5 (25)
Sensitivity to endocrine therapy, n (%)		
Primary resistance	12 (46)	8 (40)
Secondary resistance	14 (54)	12 (60)
No prior therapy	0 (0)	0 (0)
Previous antioestrogen therapy, n (%)		
Yes	ND	ND
No	ND	ND
Disease duration (time between first diagnosis and randomization) [months], mean (SD)	ND	ND
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	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 Americans and indigenous population of Alaska.
c. Institute's calculation.

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; vs.: versus

The population of pre- and perimenopausal women who received prior endocrine therapy (subpopulation B2) showed differences between the treatment groups in some patient characteristics (e.g. family origin). This was probably due to the small subpopulation. It is assumed that these differences had no relevant influence on the study results.

The mean age of the patients on study entry was about 47 years, and most of them were Asian (81% in the abemaciclib arm and 50% in the comparator arm). A large proportion of the patients had an ECOG PS of 0, and about 60% of the patients had visceral metastases.

Mean/median treatment duration and subsequent therapies

The evidence base on mean/median treatment duration and subsequent therapies in the studies MONARCH 2 and MONARCH plus for research question B2 corresponds to the one in research question A1 (see Section 2.4.1, treatment duration and subsequent therapies).

Risk of bias across outcomes (study level)

Table 11 (see Section 2.4.1) shows the risk of bias across outcomes (risk of bias at study level).

The risk of bias across outcomes was rated as low for the MONARCH 2 study. This concurs with the company's assessment.

Transferability of the study results to the German health care context

The situation regarding the transferability of the study results to the German health care context in the MONARCH 2 study for research question B2 corresponds to the one in research question A1 (see Section 2.4.1, transferability).

2.6.2 Results on added benefit

2.6.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - measured with the EORTC QLQ-C30 and the EORTC QLQ-BR23
  - pain measured with the mBPI-SF and based on the use of analgesics
  - health status (EQ-5D-5L VAS)
- Health-related quality of life
  - measured with the EORTC QLQ-C30 and the EORTC QLQ-BR23
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - neutropenia PT (CTCAE grade ≥ 3)
  - diarrhoea PT (CTCAE grade ≥ 3)
  - if applicable, further specific AEs

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

Table 26 shows for which outcomes data for subpopulation B2 (pre- and perimenopausal women who received prior endocrine therapy) are available in the included MONARCH 2 study.

Table 26: Matrix of outcomes – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B2: pre- and perimenopausal women who received prior endocrine therapy)

Study	Outcomes											
	Overall survival	Symptoms (EORTC QLQ-C30)[a]	Symptoms (EORTC QLQ-BR23)[a]	Pain (mBPI-SF)	Health status (EQ-5D-5L VAS)	Health-related quality of life (EORTC QLQ-C30)[b]	Health-related quality of life (EORTC QLQ-BR23)[b]	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs[c]	Neutropenia PT (CTCAE grade ≥ 3)	Diarrhoea PT (CTCAE grade ≥ 3)
MONARCH 2	Yes	Yes	Yes	No[d]	No[e]	Yes	Yes	Yes	Yes	Yes	No[f]	No[f]

a. Measured with the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-BR23.
b. 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.
c. Discontinuation of at least one of both drugs.
d. No usable data; the company did not present a separate analysis for both response criteria of the outcome. The results are presented as supplementary information in Table 49 of the full dossier assessment.
e. No usable data; the company did not provide any MMRM analyses. The results based on the operationalization provided by the company (definitive deterioration by ≥ 7 or ≥ 10 points) are presented as supplementary information in Table 49 of the full dossier assessment.
f. No usable data; the company did not present any event time analyses.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; 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; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; mBPI-SF: modified Brief Pain Inventory-Short Form; MMRM: mixed-effects model repeated measures; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Regarding the MONARCH 2 study, no usable analyses are available for the outcomes “pain”, “health status” (EQ-5D-5L VAS) and “specific AEs” (see Section 2.4.2.1 for reasons). The analyses presented by the company for the outcomes “pain” and “health status” (EQ-5D-5L VAS) are presented as supplementary information in Appendix E (Table 49) of the full dossier assessment.

2.6.2.2 Risk of bias

Table 27 describes the risk of bias for the results of the relevant outcomes in the included MONARCH 2 study in subpopulation B2 (pre- and perimenopausal women who received prior endocrine therapy).

Table 27: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B2: pre- and perimenopausal women who received prior endocrine therapy)

Study		Outcomes											
	Study level	Overall survival	Symptoms (EORTC QLQ-C30)[a]	Symptoms (EORTC QLQ-BR23)[a]	Pain (mBPI-SF)	Health status (EQ-5D-5L VAS)	Health-related quality of life (EORTC QLQ-C30)[b]	Health-related quality of life (EORTC QLQ-BR23)[b]	SAEs	Severe AEs (CTCAE grade ≥ 3)	Discontinuation due to AEs[c]	Neutropenia PT (CTCAE grade ≥ 3)	Diarrhoea PT (CTCAE grade ≥ 3)
MONARCH 2	L	L	H[d]	H[d]	-[e]	-[f]	H[d]	H[d]	H[d]	H[d]	L[g]	-[h]	-[h]

a. Measured with the symptom scales of the EORTC QLQ-C30 and EORTC QLQ-BR23.
b. 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.
c. Discontinuation of at least one of both drugs.
d. Large proportion of potentially informative censoring in the total population; data for the subpopulations (A1, B1 and B2) are not available.
e. No usable data; the company did not present a separate analysis for both response criteria of the outcome. The results are provided as supplementary information in Table 49 of the full dossier assessment.
f. No usable data; the company did not provide any MMRM analyses. The results based on the operationalization provided by the company (definitive deterioration by 7 or 10 points) are presented as supplementary information in Table 49 of the full dossier assessment.
g. Despite low risk of bias, a limited certainty of results is assumed for the outcome "discontinuation due to AEs" (see research question A1, Section 2.4.2.2).
h. No usable data; the company did not present any event time analyses.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; 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; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; H: high; L: low; mBPI-SF: modified Brief Pain Inventory-Short Form; MMRM: mixed-effects model repeated measures; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The risk of bias of the results on the outcome "overall survival" was rated as low. This concurs with the company's assessment.

There were no usable analyses for the outcomes “pain”, “health status” and “specific AEs” (see Sections 2.4.2.1 and 2.6.2.1). Therefore, the risk of bias was not assessed for these outcomes. This deviates from the assessment of the company, which used the results in these outcomes and assessed their risk of bias as low.

Although the risk of bias for the outcome “discontinuation due to AEs” was low, the certainty of results for this outcome was limited (see Section 2.4.2.2 for reasons). For all other outcomes, the risk of bias of the results was rated as high due to potentially informative censoring. This deviates from the assessment of the company, which rated the risk of bias of the results in these outcomes as low.

2.6.2.3 Results

Table 28 summarizes the results of the comparison of abemaciclib in combination with fulvestrant versus fulvestrant in pre- and perimenopausal women with HR-positive and HER2-negative locally advanced or metastatic breast cancer who received prior endocrine therapy (research question B2).

The Kaplan-Meier curves on the event time analyses of the MONARCH 2 study are presented in Appendix E.2 of the full dossier assessment. The results on common AEs of the MONARCH 2 study can be found in Appendix E.3 of the full dossier assessment.

Table 28: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B2: pre- and perimenopausal women who received prior endocrine therapy) (multipage table)

Study Outcome category Outcome	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs. placebo + fulvestrant
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
MONARCH 2, data cut-off 20 June 2019					
Mortality					
Overall survival	26	NA [38.96; NC] 8 (30.8)	20	45.83 [27.16; NC] 9 (45.0)	0.55 [0.21, 1.45]; 0.217
Morbidity					
Symptoms					
EORTC QLQ-C30 symptom scales, time to definitive deterioration[b]					
Fatigue	26	NA [18.94; NC] 9 (34.6)	20	17.16 [7.43; NC] 8 (40.0)	0.45 [0.17; 1.24]; 0.115
Nausea and vomiting	26	53.23 [19.92; 53.23] 8 (30.8)	20	NA [10.59; NC] 2 (10.0)	1.63 [0.33; 8.19]; 0.546
Pain	26	47.70 [38.96; NC] 9 (34.6)	20	35.93 [10.59; NC] 5 (25.0)	0.71 [0.22; 2.32]; 0.565
Dyspnoea	26	NA [19.92; NC] 8 (30.8)	20	NA [9.27; NC] 4 (20.0)	0.93 [0.27; 3.19]; 0.899
Insomnia	26	51.35 [47.70; NC] 7 (26.9)	20	19.69 [3.75; NC] 8 (40.0)	0.34 [0.11; 1.05]; 0.050
Appetite loss	26	51.75 [38.96; 53.23] 8 (30.8)	20	32.12 [11.51; NC] 5 (25.0)	0.46 [0.14; 1.58]; 0.210
Constipation	26	NA 3 (11.5)	20	39.85 [9.21; 39.85] 5 (25.0)	0.21 [0.05; 0.93]; 0.026
Diarrhoea	26	39.12 [5.56; 47.70] 14 (53.8)	20	NA [11.51; NC] 2 (10.0)	3.36 [0.73; 15.49]; 0.100
EORTC QLQ-BR23 symptom scales, time to definitive deterioration[b]					
Side effects of systemic treatment	26	NA [42.21; NC] 6 (23.1)	20	30.51 [9.34; NC] 7 (35.0)	0.31 [0.09; 1.03]; 0.045
Breast symptoms	26	NA [47.24; NC] 4 (15.4)	20	NA [10.59; NC] 2 (10.0)	0.77 [0.12; 4.86]; 0.779
Arm symptoms	26	52.08 [31.04; 52.08] 7 (26.9)	20	NA [9.53; NC] 5 (25.0)	0.42 [0.11; 1.56]; 0.185
Upset by hair loss	No usable data[c]				
Pain (mBPI-SF)	No usable data[d]				
Health status (EQ-5D-5L VAS)	No usable data[e]				

Table 28: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B2: pre- and perimenopausal women who received prior endocrine therapy) (multipage table)

Study Outcome category Outcome	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs. placebo + fulvestrant
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
Health-related quality of life					
EORTC QLQ-C30 global health status and functional scales, time to definitive deterioration[f]					
Global health status	26	NA [35.54; NC] 5 (19.2)	20	22.65 [9.21; NC] 6 (30.0)	0.33 [0.09; 1.22]; 0.083
Physical functioning	26	NA 4 (15.4)	20	33.17 [10.59; NC] 5 (25.0)	0.37 [0.10; 1.45]; 0.140
Role functioning	26	47.70 [37.58; NC] 9 (34.6)	20	38.70 [10.59; 42.87] 8 (40.0)	0.37 [0.12; 1.12]; 0.067
Emotional functioning	26	NA [44.25; NC] 3 (11.5)	20	NA [10.59; NC] 3 (15.0)	0.29 [0.05; 1.63]; 0.142
Cognitive functioning	26	47.70 [18.94; NC] 9 (34.6)	20	19.36 [5.82; NC] 8 (40.0)	0.43 [0.16; 1.21]; 0.101
Social functioning	26	NA [51.42; NC] 5 (19.2)	20	24.89 [9.34; NC] 5 (25.0)	0.34 [0.09; 1.29]; 0.098
EORTC QLQ-BR23 functional scales, time to definitive deterioration[f]					
Body image	26	NA [23.54; NC] 6 (23.1)	20	NA 3 (15.0)	0.98 [0.24; 4.04]; 0.979
Sexual functioning	26	NA [11.93; NC] 7 (26.9)	20	45.63 [12.89; 45.63] 4 (20.0)	0.93 [0.27; 3.23]; 0.907
Sexual enjoyment				No usable data[c]	
Future perspective	26	NA 3 (11.5)	20	36.89 [13.15; NC] 3 (6.7)	0.32 [0.05; 2.06]; 0.208
Side effects					
AEs (supplementary information)	26	0.13 [0.07; 0.23] 25 (96.2)	20	0.44 [0.16; 1.58] 19 (95.0)	–
SAEs	26	NA [37.45; NC] 7 (26.9)	20	NA 1 (5.0)	4.33 [0.52; 36.10]; 0.140
Severe AEs (CTCAE grade ≥ 3)	26	3.02 [0.95; 6.77] 19 (73.1)	20	27.35 [9.24; NA] 4 (20.0)	5.75 [1.94, 17.06]; < 0.001
Discontinuation due to AEs[g]	26	NA [48.72; NC] 3 (11.5)	20	NA 0 (0)	–[h]; 0.213
Neutropenia (PT, CTCAE grade ≥ 3)[i]	26	ND 14 (53.8)	20	ND 0 (0)	ND
Diarrhoea (PT, CTCAE grade ≥ 3)[i]	26	ND 2 (7.7)	20	ND 0 (0)	ND

Table 28: Results (mortality, morbidity, health-related quality of life and side effects) – RCT, direct comparison: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B2: pre- and perimenopausal women who received prior endocrine therapy) (multipage table)

Study Outcome category Outcome	Abemaciclib + fulvestrant		Placebo + fulvestrant		Abemaciclib + fulvestrant vs. placebo + fulvestrant
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
a. HR and CI: unstratified Cox proportional hazards model; p-value: unstratified log-rank test. b. Definitive deterioration was defined as an increase by at least 10 points from baseline without subsequent improvement to a score below this level. Deaths were not recorded as event. c. The analyses presented for the scales "upset by hair loss" (symptoms) and "sexual enjoyment" (quality of life) of the EORTC QLQ-BR23 are not usable due to the only small proportion of patients considered in the analysis. The data presented in Module 4 B show that a large proportion of the patients were censored directly at the start of the study (> 75%) so that no data on the development of these patients regarding upset by hair loss and sexual activity over the course of the study are included in the analysis. d. No usable data; the company did not present a separate analysis for both response criteria of the outcome. The results are provided as supplementary information in Table 49 of the full dossier assessment. e. No usable data; the company did not provide any MMRM analyses. The results based on the operationalization provided by the company (definitive deterioration by 7 or 10 points) are presented as supplementary information in Table 49 of the full dossier assessment. f. Definitive deterioration was defined as a decrease by at least 10 points from baseline without subsequent improvement to a score above this level. Deaths were not recorded as event. g. Discontinuation of at least one of both drugs. h. No meaningful estimation of HR possible (no event in the control arm). i. The results are not usable for the assessment of the added benefit, as the company did not present any event time analyses. The rates are presented as supplementary information, however. AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; 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; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; HR: hazard ratio; mBPI-SF: modified Brief Pain Inventory-Short Form; MMRM: mixed-effects model repeated measures; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus					

On the basis of the available data of the MONARCH 2 study, at most indications, e.g. of an added benefit, can be determined for the outcome "overall survival", and, due to the high risk of bias or the limited certainty of results (discontinuation due to AEs), at most hints for all other outcomes (see Sections 2.6.2.2 and 2.4.2.2).

MONARCH 2

Mortality

There was no statistically significant difference between the treatment arms for the outcome "overall survival". This resulted in no hint of an added benefit of abemaciclib in combination with fulvestrant in comparison with fulvestrant. An added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

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

Fatigue, nausea and vomiting, pain, dyspnoea, insomnia, appetite loss, and diarrhoea

No statistically significant difference between the treatment groups was shown for any of the outcomes "fatigue", "nausea and vomiting", "pain", "dyspnoea", "insomnia", "appetite loss" and "diarrhoea". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

This concurs with the company's assessment.

Constipation

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for the outcome "constipation". The extent of the effect in this non-serious/non-severe outcome was no more than marginal, however. This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

This deviates from the assessment of the company, which derived an indication of an added benefit for this outcome.

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

Side effects of systemic treatment

A statistically significant difference in favour of abemaciclib + fulvestrant was shown for the outcome "side effects of systemic treatment". The extent of the effect in this non-serious/non-severe outcome was no more than marginal, however. This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

This concurs with the company's assessment.

Breast symptoms and arm symptoms

There was no statistically significant difference between the treatment groups for the outcomes "breast symptoms" and "arm symptoms". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

This concurs with the company's assessment.

Upset by hair loss

There were no usable analyses for the outcome "upset by hair" loss (see Table 28 for reasons). This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company also regarded the added benefit as not proven on the basis of the results it used.

Pain (mBPI-SF)

No usable analyses were available for the outcome "pain" (mBPI-SF) (see Section 2.4.2.1 for reasons). This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company also regarded the added benefit as not proven on the basis of the results it used.

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

No usable analyses were available for the outcome "health status" (EQ-5D-5L VAS) (see Section 2.4.2.1). This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company also regarded the added benefit as not proven on the basis of the results it used.

Health-related quality of life

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

No statistically significant difference between the treatment groups was shown in each case for global health status as well as for the functional scales of physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning. This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health-related quality of life, recorded using the EORTC QLQ-BR23 (functional scales)

Body image, sexual functioning and future perspective

There was no statistically significant difference between the treatment groups for any of the outcomes "body image", "sexual functioning" and "future perspective". This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

This concurs with the company's assessment.

Sexual enjoyment

There were no usable analyses for the outcome "sexual enjoyment" (see Table 28 for reasons). This resulted in no hint of an added benefit of abemaciclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company also regarded the added benefit as not proven on the basis of the results it used.

Side effects

SAEs

No statistically significant difference between the treatment groups was shown for the outcome "SAEs". Hence, there was 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.

This concurs with the company's assessment.

Severe AEs (CTCAE grade ≥ 3)

A statistically significant difference to the disadvantage of abemaciclib + fulvestrant was shown for the outcome "severe AEs (CTCAE grade ≥ 3)". This resulted in a hint of greater harm of abemaciclib + fulvestrant in comparison with fulvestrant for this outcome.

This deviates from the assessment of the company insofar as the company derived an indication, and not a hint, of greater harm (or lesser benefit) for the outcome "severe AEs (CTCAE grade ≥ 3)".

Discontinuation due to AEs

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". Hence, there was 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.

This concurs with the company's assessment.

Specific AEs

As was the case already in the first assessment [7,12], the company did not present any event time analyses, which would have been necessary for an adequate choice and assessment of the specific AEs.

2.6.2.4 Subgroups and other effect modifiers

The following subgroup characteristic was considered in the benefit assessment:

- age (< 65 years; ≥ 65 years)

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. Moreover, for binary data, there must be 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.

In accordance with the methods described above, no relevant effect modification was identified for the present research question. This concurs with the company's assessment.

2.6.3 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are presented below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [3].

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.

2.6.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results of the MONARCH 2 study presented in Section 2.6.2 (see Table 29).

Determination of the outcome category for outcomes on symptoms and side effects

The dossier did not provide information for every outcome considered in the present benefit assessment whether it was serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Morbidity

The dossier did not contain any information on the classification of the severity category for the outcomes "constipation" (EORTC QLQ-C30 symptom scale) and "side effects of systemic treatment" (EORTC QLQ-BR23 symptom scale). Therefore, the outcomes were assigned to the outcome category of non-serious/non-severe symptoms.

Table 29: Extent of added benefit at outcome level: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B2: pre- and perimenopausal women who received prior endocrine therapy) (multipage table)

Outcome category **Outcome** **Subscale** **Effect modifier** **Subgroup**	**Abemaciclib + fulvestrant vs. placebo + fulvestrant** **Median time to event in months** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	Median: NA vs. 45.8 HR: 0.55 [0.21; 1.45] p = 0.217	Lesser benefit/added benefit not proven
Morbidity		
EORTC QLQ-C30 (symptom scales, time to definitive deterioration)		
Fatigue	Median: NA vs. 17.2 HR: 0.45 [0.17; 1.24] p = 0.115	Lesser benefit/added benefit not proven
Nausea and vomiting	Median: 53.2 vs. NA HR: 1.63 [0.33; 8.19] p = 0.546	Lesser benefit/added benefit not proven
Pain	Median: 47.7 vs. 35.9 HR: 0.71 [0.22; 2.32] p = 0.565	Lesser benefit/added benefit not proven
Dyspnoea	Median: NA vs. NA HR: 0.93 [0.27; 3.19] p = 0.899	Lesser benefit/added benefit not proven
Insomnia	Median: 51.4 vs. 19.7 HR: 0.34 [0.11; 1.05] p = 0.050	Lesser benefit/added benefit not proven
Appetite loss	Median: 51.8 vs. 32.1 HR: 0.46 [0.14; 1.58] p = 0.210	Lesser benefit/added benefit not proven
Constipation	Median: NA vs. 39.9 HR: 0.21 [0.05; 0.93] p = 0.026	Outcome category: non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ lesser benefit/added benefit not proven[c]
Diarrhoea	Median: 39.1 vs. NA HR: 3.36 [0.73; 15.49] p = 0.100	Lesser benefit/added benefit not proven

Table 29: Extent of added benefit at outcome level: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B2: pre- and perimenopausal women who received prior endocrine therapy) (multipage table)

Outcome category **Outcome** **Subscale** **Effect modifier** **Subgroup**	**Abemaciclib + fulvestrant vs. placebo + fulvestrant** **Median time to event in months** **Effect estimation [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
EORTC QLQ-BR23 (symptom scales, time to definitive deterioration)		
Side effects of systemic treatment	Median: NA vs. 30.5 HR: 0.31 [0.09; 1.03] p = 0.045	Outcome category: non-serious/non-severe symptoms/late complications $CI_u > 0.90$[d] lesser benefit/added benefit not proven[c]
Breast symptoms	Median: NA vs. NA HR: 0.77 [0.12; 4.86] p = 0.779	Lesser benefit/added benefit not proven
Arm symptoms	Median: 52.1 vs. NA HR: 0.42 [0.11; 1.56] p = 0.185	Lesser benefit/added benefit not proven
Upset by hair loss	No usable data	
Pain (mBPI-SF)	No usable data	
Health status (EQ-5D-5L VAS)	No usable data	
Health-related quality of life		
EORTC QLQ-C30 (global health status and functional scales, time to definitive deterioration)		
Global health status	Median: NA vs. 22.7 HR: 0.33 [0.09; 1.22] p = 0.083	Lesser benefit/added benefit not proven
Physical functioning	Median: NA vs. 33.2 HR: 0.37 [0.10; 1.45] p = 0.140	Lesser benefit/added benefit not proven
Role functioning	Median: 47.7 vs. 38.7 HR: 0.37 [0.12; 1.12] p = 0.067	Lesser benefit/added benefit not proven
Emotional functioning	Median: NA vs. NA HR: 0.29 [0.05; 1.63] p = 0.142	Lesser benefit/added benefit not proven
Cognitive functioning	Median: 47.7 vs. 19.4 HR: 0.43 [0.16; 1.21] p = 0.101	Lesser benefit/added benefit not proven
Social functioning	Median: NA vs. 24.9 HR: 0.34 [0.09; 1.29] p = 0.098	Lesser benefit/added benefit not proven

Table 29: Extent of added benefit at outcome level: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B2: pre- and perimenopausal women who received prior endocrine therapy) (multipage table)

Outcome category **Outcome** **Subscale** **Effect modifier** **Subgroup**	**Abemaciclib + fulvestrant vs. placebo + fulvestrant** **Median time to event in months** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
EORTC QLQ-BR23 (functional scales, time to definitive deterioration)		
Body image	Median: NA vs. NA HR: 0.98 [0.24; 4.04] p = 0.979	Lesser benefit/added benefit not proven
Sexual functioning	Median: NA vs. 45.6 HR: 0.93 [0.27; 3.23] p = 0.907	Lesser benefit/added benefit not proven
Sexual enjoyment	No usable data	
Future perspective	Median: NA vs. 36.9 HR: 0.32 [0.05; 2.06] p = 0.208	Lesser benefit/added benefit not proven
Side effects		
SAEs	Median: NA vs. NA HR: 4.33 [0.52; 36.10] p = 0.140	Greater/lesser harm not proven
Severe AEs (CTCAE grade ≥ 3)	Median: 3.0 vs. 27.4 HR: 5.75 [1.94; 17.06] HR[e]: 0.17 [0.06; 0.52] p < 0.001 probability: “hint”	Outcome category: severe/serious side effects CI_u < 0.75; risk ≥ 5% greater harm, extent: “major”
Discontinuation due to AEs[f]	Median: NA vs. NA HR: –[g] p = 0.213	Greater/lesser harm not proven
Neutropenia (PT, CTCAE grade ≥ 3)	No usable data	
Diarrhoea (PT, CTCAE grade ≥ 3)	No usable data	

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
d. Although the upper limit of the confidence interval cited by the company in Module 4 B is 1.03, the presence of an effect is assumed due to the statistically significant p-value.
e. Institute’s calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
f. Discontinuation of at least one of both drugs.
g. No meaningful estimation of HR possible (no event in the control arm).

Table 29: Extent of added benefit at outcome level: abemaciclib + fulvestrant vs. placebo + fulvestrant (research question B2: pre- and perimenopausal women who received prior endocrine therapy) (multipage table)

Outcome category **Outcome** **Subscale** **Effect modifier** **Subgroup**	**Abemaciclib + fulvestrant vs. placebo + fulvestrant** **Median time to event in months** **Effect estimation [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; 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; EQ-5D-5L: European Quality of Life-5 Dimensions 5 Levels; HR: hazard ratio; mBPI-SF: modified Brief Pain Inventory-Short Form; NA: not achieved; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus		

2.6.3.2 Overall conclusion on added benefit

Table 30 summarizes the results considered in the overall conclusion about the extent of added benefit.

Table 30: Positive and negative effects from the assessment of abemaciclib + fulvestrant in comparison with placebo + fulvestrant (research question B2: pre- and perimenopausal women who received prior endocrine therapy)

Positive effects	**Negative effects**
–	Serious/severe side effects ▪ severe AEs (CTCAE grade ≥ 3): hint of greater harm – extent: “major”
No (usable) data are available for neutropenia (CTCAE grade ≥ 3), diarrhoea (CTCAE grade ≥ 3) and, if applicable, further specific AEs.	
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events	

In the overall consideration, there is only a negative effect of abemaciclib in combination with fulvestrant in comparison with fulvestrant on the basis of the results of the MONARCH 2 study (subpopulation B2). This is a hint of greater harm with major extent in severe/serious side effects (CTCAE grade ≥ 3). There were no usable analyses on specific AEs.

In summary, there is therefore a hint of lesser benefit of abemaciclib in combination with fulvestrant versus fulvestrant alone for pre- and perimenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer who received prior endocrine therapy (research question B2).

The assessment described above deviates from that of the company, which derived a considerable added benefit, without determining a concrete probability, for the patients of research question B2 based on the results of the MONARCH 2 study and under consideration of further outcomes.

2.7 Probability and extent of added benefit – summary

Table 31 shows a summary of the probability and extent of the added benefit of abemaciclib in combination with fulvestrant.

Table 31: Abemaciclib in combination with fulvestrant – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
Women with HR-positive, HER2-negative locally advanced or metastatic breast cancer[b]			
A1	Postmenopausal women, initial endocrine therapy	Anastrozole or letrozole or **fulvestrant** or, if applicable, tamoxifen if aromatase inhibitors are unsuitable	Hint of lesser benefit[c]
B1	Postmenopausal women who received prior endocrine therapy	Further endocrine therapy depending on prior therapy with: ▪ tamoxifen or ▪ anastrozole or ▪ **fulvestrant** (only for patients with recurrence or progression following antioestrogen therapy) or ▪ letrozole; only for patients with recurrence or progression following antioestrogen therapy, or ▪ exemestane; only for patients with progression following antioestrogen therapy, or everolimus in combination with exemestane; only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor	Indication of minor added benefit[c, d]
B2	Pre- and perimenopausal women who received prior endocrine therapy	Endocrine therapy specified by the physician under consideration of the respective approval[e]	Hint of lesser benefit[c, d]

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could 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. Furthermore, it is assumed that ovarian function is suppressed by oophorectomy or with a GnRH analogue in pre- and perimenopausal patients.
c. Only patients with an ECOG PS of 0 or 1 were included in the MONARCH 2 study. 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 Section 2.2).
e. Tamoxifen, letrozole, exemestane, megestrol acetate and medroxyprogesterone acetate are approved in the present therapeutic indication.

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

The approach for deriving 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.

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