IQWiG Reports – Commission No. A20-22

Ribociclib (breast cancer, combination with fulvestrant) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Ribociclib (Mammakarzinom, Kombination mit Fulvestrant) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 May 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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[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
BPI-SF	Brief Pain Inventory-Short Form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
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 ribociclib in combination with fulvestrant. 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 3 March 2020. The company submitted a first dossier of the drug to be evaluated on 14 January 2019 for the early benefit assessment. In this procedure, by decision of 4 July 2019, the G-BA limited its decision until 1 March 2020.

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 ribociclib in combination with fulvestrant in comparison with the appropriate comparator therapy (ACT) in postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.

The research questions A1 and B1 presented in Table 2 resulted from the ACTs specified by the G-BA (designation according to the first assessment A19-06 and the corresponding addendum A19-45).

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

Research question	Subindication	ACT[a]
Women with HR-positive, HER2-negative advanced/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 have received prior endocrine therapy	Another endocrine therapy in dependence on the pretreatment with: ▪ tamoxifen or ▪ anastrozole or ▪ fulvestrant; only for patients with recurrence or progression following anti-oestrogen therapy[c] or ▪ letrozole; only for patients with recurrence or progression following anti-oestrogen therapy or ▪ exemestane; only for patients with progression following anti-oestrogen therapy or ▪ everolimus in combination with exemestane; only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor

a. Presentation of the respective ACT specified by the G-BA.
b. It is assumed for the present therapeutic indications that (if applicable, another) endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
c. In therapeutic indication B1, the approval of fulvestrant provides for use of the drug only after prior anti-oestrogen therapy. In this respect, there is a discrepancy with the use of fulvestrant recommended in guidelines and established in health care, which do not focus exclusively on previous therapy with anti-oestrogens, but also on previous therapy with aromatase inhibitors. In this special therapeutic and health care situation, the G-BA sees a medical reason that, in the present case, exceptionally justifies considering fulvestrant as a comparator.

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

The company followed the ACTs specified by the G-BA for both research questions.

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.

Results on added benefit

Study pool

The MONALEESA-3 study was identified for the benefit assessment of ribociclib in combination with fulvestrant. This RCT included both women who were to receive the first

endocrine therapy (for the advanced stage) (research question A1) and women who had already received endocrine therapy (for the advanced stage) (research question B1).

The relevance of the MONALEESA-3 study for both research questions A1 and B1 is described below. The MONALEESA-3 study is already known from the previous benefit assessment of ribociclib in the present therapeutic indication; with the current dossier, the company presented data on a further data cut-off.

Research question A1 (postmenopausal women, initial endocrine therapy for the advanced stage)

Relevant subpopulation and study characteristics

From the MONALEESA-3 study, the subpopulation of patients with initial endocrine therapy in the advanced stage was relevant for the assessment of the added benefit in research question A1 (subpopulation A1). The relevant subpopulation comprised 374 patients in the ribociclib + fulvestrant arm and 198 patients in the placebo + fulvestrant arm. All other study participants constituted another subpopulation, which was considered in research question B1 (patients who have already received endocrine therapy for the advanced stage).

The MONALEESA-3 study was an RCT comparing a combination of ribociclib + fulvestrant with placebo + fulvestrant. A total of 727 women with HR-positive, HER2-negative, advanced or metastatic breast cancer were included in a 2:1 randomization. The included patients had received either no or at most 1 endocrine therapy for the advanced stage. All women in the study were postmenopausal.

Treatment was administered continuously in 28-day cycles until disease progression, unacceptable toxicity or discontinuation of treatment for other reasons. The drugs used in the study were largely administered in compliance with the current Summaries of Product Characteristics (SPCs). Switching treatments, particularly from placebo to ribociclib, was not possible.

Primary outcome of the study was progression-free survival (PFS). Patient-relevant secondary outcomes were overall survival, symptoms, health status, health-related quality of life, and adverse events (AEs).

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes (study level) was low. The outcome-specific risk of bias was low only for the outcome “overall survival”. Due to incomplete observations for potentially informative reasons, there was a high risk of bias for all patient-reported outcomes, serious AEs (SAEs) and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3–4), as well as for the specific AEs. The certainty of results for the outcome “discontinuation due to AEs” was limited despite a low risk of bias.

On the basis of the available data, at most an indication, e.g. of an added benefit, can regularly be determined for the outcome "overall survival", and at most hints for all other outcomes. Due to the size of the observed effect, the outcome-specific certainty of the results may not be downgraded, however.

Mortality – overall survival

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

Morbidity – symptoms, recorded with the symptom scales of the EORTC QLQ-C30

No statistically significant difference between the treatment groups was shown for any of the 8 symptom scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). In each case, this resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

Morbidity – health status, recorded using the EQ-5D VAS

No usable analyses were available for the outcome "health status" recorded with the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D) questionnaire. This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

Morbidity – pain, recorded using the BPI-SF

There were no usable analyses for the outcome "pain" recorded with the Brief Pain Inventory-Short Form (BPI-SF). This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

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

No statistically significant difference between the treatment groups was shown for global health status or for the 5 functional scales. In each case, this resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

Side effects – SAEs, severe AEs (CTCAE grade 3–4) and discontinuation due to AEs

A statistically significant difference to the disadvantage of ribociclib + fulvestrant was shown for each of the outcomes "SAEs", "severe AEs (CTCAE grade 3–4)" and "discontinuation due to AEs". This resulted in a hint of greater harm of ribociclib + fulvestrant in comparison with fulvestrant for SAEs and discontinuation due to AEs, and, due to the size of the observed effect, in an indication of greater harm for severe AEs.

Side effects – specific AEs

Severe AEs (CTCAE grade 3–4): blood and lymphatic system disorders (including: neutropenia) and investigations

A statistically significant difference to the disadvantage of ribociclib + fulvestrant was shown for the specific severe AEs (CTCAE grade 3–4) "blood and lymphatic system disorders" (including: "neutropenia") and "investigations". Due to the size of the observed effects in each case, this resulted in an indication of greater harm of ribociclib + fulvestrant in comparison with fulvestrant for these outcomes.

AEs: eye disorders and skin and subcutaneous tissue disorders

Statistically significant differences to the disadvantage of ribociclib + fulvestrant were shown for each of the specific AEs "eye disorders" and "skin and subcutaneous tissue disorders". This resulted in hints of greater harm of ribociclib + fulvestrant in comparison with fulvestrant for each of these outcomes.

Research question B1 (postmenopausal women who have received prior endocrine therapy for the advanced stage)

Relevant subpopulation and study characteristics

From the MONALEESA-3 study, the subpopulation of patients who have received prior endocrine therapy for the advanced stage was relevant for research question B1 (subpopulation B1). The relevant subpopulation comprised 100 patients in the ribociclib + fulvestrant arm and 39 patients in the placebo + fulvestrant arm. This was about 19% of the total study population.

Fulvestrant, which was administered as comparator intervention in the MONALEESA-3 study, is only approved for patients with recurrence or progression following anti-oestrogen therapy. This requirement was not met for all patients included in the MONALEESA-3 study. Thus, fulvestrant was not an ACT for these patients of subpopulation B1. However, the G-BA saw a medical reason for research question B1, which, in the present case, exceptionally justified considering fulvestrant, which was used in the MONALEESA-3 study also after pretreatment with aromatase inhibitors, as a comparator. Thus, the results of the total subpopulation B1 for the comparison of ribociclib + fulvestrant versus fulvestrant (hereinafter referred to as "comparator") are relevant.

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes (study level) and the outcome-specific risk of bias are analogous to research question A1.

On the basis of the available data, at most an indication, e.g. of an added benefit, can regularly be determined for the outcome "overall survival", and at most hints for all other outcomes. Due to the size of the observed effect, the outcome-specific certainty of the results may not be downgraded, however.

Mortality – overall survival

The subpopulation B1 considered here showed no statistically significant difference between the treatment groups for the outcome "overall survival". This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant for this outcome; an added benefit is therefore not proven. However, there was a specific data constellation for this outcome, which was considered in the overall consideration of the added benefit for subpopulation B1.

Morbidity – symptoms, recorded with the symptom scales of the EORTC QLQ-C30

No statistically significant difference between the treatment groups was shown in any of the 8 EORTC QLQ-C30 symptom scales. In each case, this resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

Morbidity – health status, recorded with the EQ-5D VAS

No usable analyses were available for the outcome "health status" recorded with the EQ-5D VAS. This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

Morbidity – pain, recorded with the BPI-SF

There were no usable analyses for the outcome "pain" recorded with the BPI-SF. This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

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

Global health status, cognitive functioning, physical functioning, role functioning and social functioning

There was no statistically significant difference between the treatment groups for global health status or for the 4 functional scales of cognitive functioning, physical functioning, role functioning and social functioning. This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant for any of these outcomes; an added benefit is therefore not proven.

Emotional functioning

There was a statistically significant difference between the treatment groups for the symptom scale "emotional functioning". There was an effect modification by the characteristic "age", however. This resulted in a hint of an added benefit of ribociclib + fulvestrant in patients ≥ 65 years of age for emotional functioning. For patients < 65 years of age, there was no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

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 ribociclib + fulvestrant in comparison with fulvestrant for this outcome; greater or lesser harm is therefore not proven.

Severe AEs (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib + fulvestrant was shown for the outcome "severe AEs (CTCAE grade 3–4)". This resulted in a hint of greater harm of ribociclib + fulvestrant in comparison with fulvestrant for this outcome.

Discontinuation due to AEs

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

Side effects – specific AEs

Severe AEs (CTCAE grade 3–4): blood and lymphatic system disorders (including: neutropenia)

A statistically significant difference to the disadvantage of ribociclib + fulvestrant was shown for the specific severe AEs (CTCAE grade 3–4) "blood and lymphatic system disorders" (including: "neutropenia"). Due to the size of the observed effects in each case, this resulted in an indication of greater harm of ribociclib + fulvestrant in comparison with fulvestrant for these outcomes.

AEs: skin and subcutaneous tissue disorders

A statistically significant difference to the disadvantage of ribociclib + fulvestrant was shown for the specific AE "skin and subcutaneous tissue disorders". This resulted in a hint of greater harm of ribociclib + fulvestrant in comparison with fulvestrant for this outcome.

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 ribociclib in combination with fulvestrant in comparison with the ACT are assessed as follows:

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

Research question A1 (initial endocrine therapy for the advanced stage)

In the overall consideration, there is a positive effect of considerable extent in the outcome "overall survival", which is accompanied by a number of serious and severe side effects (CTCAE grade 3–4) of mostly considerable or major extent.

In the present subpopulation A1, the side effects were particularly evident in all superordinate AE outcomes (SAEs, severe AEs [CTCAE grade 3–4] and discontinuation due to AEs). The severe side effects (CTCAE grade 3–4) were mostly severe blood and lymphatic system disorders, including mainly neutropenia.

The negative effects did not completely outweigh the advantage in overall survival, but resulted in a downgrading of the extent of the added benefit.

In summary, there is an indication of a minor added benefit of ribociclib in combination with fulvestrant versus the ACT for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer in initial endocrine therapy.

Research question B1 (postmenopausal women who have received prior endocrine therapy for the advanced stage)

The overall consideration showed a positive effect of major extent for the functional scale of emotional functioning in the outcome category of health-related quality of life, but only for patients aged 65 years and older. This was accompanied by mostly severe side effects (CTCAE grade 3–4) of considerable or major extent for patients both aged 65 years and older and younger than 65 years.

If only the results of the subpopulation were considered, balancing benefit and harm would initially result in lesser benefit of ribociclib + fulvestrant versus fulvestrant. In the present specific data constellation, however, the results of the total population of the MONALEESA-3 study were additionally considered in the overall consideration. In the total population of the MONALEESA-3 study, a statistically significant effect in favour of ribociclib + fulvestrant was shown for the outcome "overall survival". At the present data cut-off, 78% of the deaths planned for the final analysis had been reached (275 of 351). The subpopulation B1 comprised only 19% of the study population. However, there was a consistency of the direction of the effect and the position of the point estimations between the subpopulations A1 and B1 available here. A similar situation was already shown in the earlier data cut-off of the first assessment, which was based on a notably lower number of deaths. In the present data constellation, no lesser benefit was derived in the overall consideration despite the clear negative effects.

In summary, there is therefore no hint of an added benefit of ribociclib in combination with fulvestrant versus the comparator fulvestrant for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy; an added benefit is therefore not proven.

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

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

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Women with HR-positive, HER2-negative advanced/metastatic breast cancer[b]		
A1: postmenopausal women, initial endocrine therapy	Anastrozole or letrozole or fulvestrant or, if applicable, tamoxifen if aromatase inhibitors are unsuitable	Indication of minor added benefit[d]
B1: postmenopausal women who have received prior endocrine therapy	Another endocrine therapy in dependence on the pretreatment with: ▪ tamoxifen or ▪ anastrozole or ▪ fulvestrant; only for patients with recurrence or progression following anti-oestrogen therapy[c] or ▪ letrozole; only for patients with recurrence or progression following anti-oestrogen therapy or ▪ exemestane; only for patients with progression following anti-oestrogen therapy or ▪ everolimus in combination with exemestane; only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor	Added benefit not proven[d]

a. Presentation of the respective ACT specified by the G-BA.
b. It is assumed for the present therapeutic indications that (if applicable, another) endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
c. In therapeutic indication B1, the approval of fulvestrant provides for use of the drug only after prior anti-oestrogen therapy. In this respect, there is a discrepancy with the use of fulvestrant recommended in guidelines and established in health care, which do not focus exclusively on previous therapy with anti-oestrogens, but also on previous therapy with aromatase inhibitors. In this special therapeutic and health care situation, the G-BA sees a medical reason that, in the present case, exceptionally justifies considering fulvestrant as a comparator.
d. The MONALEESA-3 study only contains data on the comparison with fulvestrant. In addition, only patients with an ECOG PS of 0 or 1 were included. It remains unclear whether the observed results can be transferred to patients with an ECOG PS of ≥ 2. Almost all patients included in the study had stage IV disease (breast cancer with distant metastasis).

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 ribociclib in combination with fulvestrant in comparison with the ACT in postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer.

The research questions A1 and B1 presented in Table 4 resulted from the ACTs specified by the G-BA (designation according to the first assessment A19-06 [3] and the corresponding addendum A19-45 [4]).

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

Research question	Subindication	ACT[a]
Women with HR-positive, HER2-negative advanced/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 have received prior endocrine therapy	Another endocrine therapy in dependence on the pretreatment with: ▪ tamoxifen or ▪ anastrozole or ▪ fulvestrant; only for patients with recurrence or progression following anti-oestrogen therapy[c] or ▪ letrozole; only for patients with recurrence or progression following anti-oestrogen therapy or ▪ exemestane; only for patients with progression following anti-oestrogen therapy or ▪ everolimus in combination with exemestane; only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor

a. Presentation of the respective ACT specified by the G-BA.
b. It is assumed for the present therapeutic indications that (if applicable, another) endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
c. In therapeutic indication B1, the approval of fulvestrant provides for use of the drug only after prior anti-oestrogen therapy. In this respect, there is a discrepancy with the use of fulvestrant recommended in guidelines and established in health care, which do not focus exclusively on previous therapy with anti-oestrogens, but also on previous therapy with aromatase inhibitors. In this special therapeutic and health care situation, the G-BA sees a medical reason that, in the present case, exceptionally justifies considering fulvestrant as a comparator.

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

The company followed the ACTs specified by the G-BA for both research questions.

The subdivision according to lines of treatment for the advanced stage does not make any statement about a possible (neo)adjuvant endocrine therapy for an earlier disease stage. The present benefit assessment also comprises patients with (neo)adjuvant pretreatment. These are either patients with recurrence > 12 months after completion of prior (neo)adjuvant endocrine therapy or patients with recurrence during or shortly (i.e. ≤ 12 months) after completion of (neo)adjuvant endocrine therapy [3,4]. In accordance with the G-BA's approach in the previous benefit assessment procedure [5], both patient populations were allocated to research question A1 in the present 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.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on ribociclib (status: 14 January 2020)
- bibliographical literature search on ribociclib (last search on 4 December 2019)
- search in trial registries for studies on ribociclib (last search on 2 December 2019)

To check the completeness of the study pool:

- search in trial registries for studies on ribociclib (last search on 12 March 2020)

No additional relevant study was identified from the check.

The company conducted its information retrieval for all options of the ACT. With this approach, it identified one relevant study comparing ribociclib in combination with fulvestrant versus fulvestrant.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: ribociclib + 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 (yes/no [citation])
MONA-LEESA-3	Yes	Yes	No	No[c]	Yes [6-8]	Yes [3,4,9-11]

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. 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.

CSR: clinical study report; RCT: randomized controlled trial; vs.: versus

The MONALEESA-3 study, which directly compared the combination of ribociclib + fulvestrant with placebo + fulvestrant, was identified for the benefit assessment of ribociclib in combination with fulvestrant. This study is already known from the previous benefit assessment of ribociclib in the present therapeutic indication [3,4]; with the current dossier, the company presented data on a further data cut-off. This RCT included both women who were to receive the first endocrine therapy (for the advanced stage) and women who had already received endocrine therapy (for the advanced stage).

On the basis of this study, the company assessed the added benefit for all postmenopausal women, without differentiating between the lines of treatment according to research questions A1 and B1 of this benefit assessment (see Table 4). This approach does not concur with the specification of the G-BA. Instead, it had already described in its justification regarding the first assessment that it still considered it appropriate to consider data separately according to the subpopulations defined [5]. Deviating from the company's reasoning, the data of the respective subpopulation were therefore used for the present assessment.

The relevance of the MONALEESA-3 study for both research questions A1 and B1 is described in the Sections 2.4 and 2.5.

2.4 Research question A1: postmenopausal women, initial endocrine therapy for the advanced stage

2.4.1 Study characteristics

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

Table 6: Characteristics of the study included – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MONA-LEESA-3	RCT, double-blind, parallel	Postmenopausal women[b] with HR-positive, HER2-negative advanced breast cancer, no or at most one pretreatment with endocrine therapy in the advanced stage	Ribociclib + fulvestrant (N = 484)[c] placebo + fulvestrant (N = 242)[c] Relevant subpopulations thereof: ▪ Research question A1: postmenopausal women, initial endocrine therapy for the advanced stage ▫ ribociclib + fulvestrant (n = 374) ▫ placebo + fulvestrant (n = 198) ▪ Research question B1: postmenopausal women who have received prior endocrine therapy for the advanced stage ▫ ribociclib + fulvestrant (n = 100) ▫ placebo + fulvestrant (n = 39)	▪ Screening: 28 days ▪ Treatment: until progression of disease, unacceptable toxicity or treatment discontinuation following the physician's or patient's decision ▪ Observation[d]: outcome-specific, at most until death, discontinuation of participation in the study or end of study	175 centres in: Australia, Austria, Belgium, Bulgaria, Canada, Columbia, Czech Republic, Denmark, France, Germany, Hungary, Italy, Jordan, Korea, Lebanon, Malaysia, Mexico, Netherlands, Norway, Poland, Portugal, Russia, Sweden, Singapore, Spain, Switzerland, Thailand, Turkey, United Kingdom, USA 6/2015–ongoing First interim analysis: after 364 PFS events (3 November 2017) Second interim analysis: after 263 deaths (3 June 2019) Pending analysis: ▪ final analysis after 351 deaths	▪ Primary: PFS ▪ Secondary: overall survival, morbidity, 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. Men could also participate in the study; only women were enrolled, however.
c. A total of N = 727 women were randomized. One patient died before signing the consent and was not considered in the analyses.
d. Outcome-specific information is provided in Table 8.

AE: adverse event; HER2: human epidermal growth factor receptor 2, HR: hormone receptor; n: relevant subpopulation; N: number of randomized patients; PFS: progression-free survival; RCT: randomized controlled trial; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant

Study	Intervention	Comparison
MONA-LEESA-3	Ribociclib 600 mg capsules, orally, day 1-21 of a 28-day cycle + fulvestrant 500 mg IM, day 1 and day 15 of the first cycle, then on day 1 of each following cycle	Placebo capsules, orally, day 1-21 of a 28-day cycle + fulvestrant 500 mg IM, day 1 and day 15 of the first cycle, then on day 1 of each following cycle
	Dose adjustments: ribociclib/placebo: reduction (to 400 mg/day or 200 mg/day), interruption or discontinuation possible in case of toxicity fulvestrant: no adjustment allowed	
	Permitted pretreatment: ▪ endocrine therapy except fulvestrant ([neo]adjuvant or first-line for advanced stage)[a] ▪ neoadjuvant/adjuvant chemotherapy ▪ radiotherapy ≥ 4 weeks before baseline ▪ limited palliative radiotherapy ≥ 2 weeks before baseline ▪ systemic corticosteroids within 2 weeks before baseline **Non-permitted pretreatment:** ▪ chemotherapy, fulvestrant or CDK4/6 inhibitors ▪ any other anticancer therapy ▪ anthracyclines (doxorubicin ≥ 450 mg/m², epirubicin ≥ 900 mg/m²) **Permitted concomitant treatment:** ▪ any therapies for the treatment of AEs, cancer symptoms and accompanying diseases, unless noted otherwise ▪ corticosteroids as individual doses, topical administration (e.g. rash), inhaled sprays (e.g. obstructive airways disorder), eye drops or local injections (e.g. intraarticular) ▪ bisphosphonates/denosumab for the treatment of osteoporosis or for prevention of skeletal-related events for patients with bone metastases ▪ haematopoietic growth factors ▪ palliative radiotherapy (except for target lesions) ▪ short-term treatment (< 5 days) with a maximum total daily dose of 4 mg dexamethasone (e.g. in chronic obstructive pulmonary disease or antiemetic) **Non-permitted concomitant treatment:** ▪ warfarin or other coumarin-like anticoagulants ▪ the following substances if they could not be discontinued 7 days before cycle 1, day 1: ▫ strong inducers or inhibitors of CYP3A4/5, including grapefruit, grapefruit hybrids, shaddock, star fruit and bitter orange ▫ drugs with narrow therapeutic indices mainly metabolized by CYP3A4/5 ▫ drugs with known risk to prolong the QT interval ▫ herbal drugs, dietary supplements ≥ 7 days before baseline	

a. Subpopulation of patients in research question A1: endocrine therapy not permitted in the advanced stage; (neo)adjuvant endocrine therapy permitted regardless of the time point of recurrence after completion of this therapy (earlier or later than 12 months).

AE: adverse event; CDK: cyclin-dependent kinase; CYP: cytochrome P450; IM: intramuscular; RCT: randomized controlled trial; vs.: versus

The MONALEESA-3 study was an RCT comparing a combination of ribociclib + fulvestrant with placebo + fulvestrant. A total of 727 women with HR-positive, HER2-negative, advanced or metastatic breast cancer were included. Randomization was in a ratio of 2:1, stratified according to the presence of lung and liver metastases (yes/no) and prior endocrine therapy (see below). All women in the study were postmenopausal.

To be eligible for study inclusion, patients had to have received no or only one line of endocrine therapy in the advanced stage. Hence, both women who had already received one (neo)adjuvant endocrine therapy for the early disease stage and at most one endocrine therapy for the advanced stage, and women who had received a first-line treatment for the advanced stage as their first endocrine therapy could be included. Patients who had relapsed within 12 months from completion of (neo)adjuvant therapy and progressed after first-line endocrine treatment were not included in the study. Their tumours had to be not amenable to resection or radiotherapy with curative intent. In addition, the patients had to have a baseline Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1.

A subpopulation of the MONALEESA-3 study was relevant for research question A1 (see below), which hereinafter is referred to as “subpopulation A1”.

According to the SPC, fulvestrant is used either in patients not previously treated with endocrine therapy or in patients with disease relapse on or after adjuvant antioestrogen therapy [12]. No information is available on the number of patients in subpopulation A1 who did not meet this precondition because they last received pretreatment with an aromatase inhibitor. These patients would not have met the preconditions for fulvestrant therapy. However, the G-BA named 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 in Module 4 B of the company’s dossier also showed that there was no effect modification from the characteristic of prior therapy with an aromatase inhibitor (yes versus no).

Treatment was administered continuously in 28-day cycles until disease progression, unacceptable toxicity or discontinuation of treatment for other reasons. Apart from the pretreatment situation described above, the drugs used in the study were administered in compliance with the current SPCs [12,13].

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

Subpopulations of the MONALEESA-3 study relevant for the assessment

The G-BA differentiated between patients with initial endocrine therapy in the advanced stage (research question A1) and patients with progression after prior endocrine therapy in the advanced stage (research question B1) [5], and specified partly different ACTs (see Table 4).

The added benefit of ribociclib in combination with fulvestrant in postmenopausal women was therefore assessed separately for the research questions A1 and B1.

This approach deviates from that of the company, which derived the added benefit of ribociclib in combination with fulvestrant for postmenopausal patients together on the basis of the total study population of the MONALEESA-3 study (i.e. without differentiating between lines of treatment). Nevertheless, the company presented the results separately for research questions A1 and B1 as supplementary information.

The company presented the following definition of the patient populations in the dossier:

- Patient group A1:
  - patients who have never received endocrine therapy, and
  - patients who received a (neo)adjuvant endocrine therapy that must have been completed at least 12 months before diagnosis of recurrence, and
  - patients with recurrence during or ≤ 12 months after completion of (neo)adjuvant endocrine therapy
- Patient group B1:
  - patients with recurrence > 12 months after completion of (neo)adjuvant endocrine therapy and another progression after (first-line) endocrine therapy for the advanced stage, and
  - patients with initial diagnosis of metastatic breast cancer who progressed after (first-line) endocrine therapy for this stage

This division was in line with the definitions of the patient populations according to the specification of the G-BA in the previous benefit assessment procedure on ribociclib in combination with fulvestrant in postmenopausal women [5] and was therefore relevant for the present benefit assessment. There was a marginal numerical discrepancy between the information provided by the company on the number of randomized patients for the 2 subpopulations A1 and B1 between the addendum to the first assessment [4] and the present limitation of the decision, which was not explained by the company. Since the deviations only concerned individual patients, they had no consequence for the assessment, however.

Hence, the subpopulation A1 according to the company's definition was used for the research question A1 considered here. This subpopulation comprised 374 patients in the intervention arm and 198 patients in the control arm. All following information in this section refers to subpopulation A1, unless otherwise noted.

Subpopulation B1 is relevant for research question B1 (see Section 2.5).

Data cut-offs

The MONALEESA-3 study has not yet been completed; analyses of 2 data cut-offs are available to date:

- first data cut-off (3 November 2017): planned interim analysis after 364 PFS events
- second data cut-off (3 June 2019): planned interim analysis after 263 deaths

The final analysis of the MONALEESA-3 study is planned for the time point after 351 deaths.

Results for the second data cut-off on all patient-relevant outcomes were available for the present benefit assessment. These results were used for the benefit assessment.

Planned duration of follow-up observation

Table 8 shows the planned duration of follow-up observation in the MONALEESA-3 study for the individual outcomes.

Table 8: Planned duration of follow-up observation – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant

Study **Outcome category** **Outcome**	**Planned follow-up observation**
MONALEESA-3	
Mortality	
Overall survival	▪ Until death, end of study, loss to follow-up or premature study discontinuation
Morbidity	
Symptoms (EORTC QLQ-C30)	▪ Until progression, death, withdrawal of consent, or loss to follow-up
Health status (EQ-5D VAS)	▪ Until progression, death, withdrawal of consent, or loss to follow-up
Pain (BPI-SF)	▪ Until progression, death, withdrawal of consent, or loss to follow-up
Health-related quality of life (EORTC QLQ-C30)	▪ Until progression, death, withdrawal of consent, or loss to follow-up
Side effects	
All outcomes in the category of side effects	▪ Until up to 30 days after the end of treatment

BPI-SF: Brief Pain Inventory-Short Form; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; VAS: visual analogue scale; vs.: versus

The observation periods for the outcomes “morbidity”, “health-related quality of life” and “side effects” were systematically shortened because they were recorded at most until progression (symptoms, health-related quality of life) or for the period of treatment with the study medication (plus 30 days) (side effects). 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.

Characteristics of the study population

Table 9 shows the characteristics of the patients in subpopulation A1 of the MONALEESA-3 study.

Table 9: Characteristics of the study population – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine therapy for the advanced stage) (multipage table)

Study Characteristics Category	**Ribociclib + fulvestrant N[a] = 374**	**Placebo + fulvestrant N[a] = 198**
MONALEESA-3		
Age [years], mean (SD)	63 (10)	63 (11)
Region, n (%)		
Asia	34 (9.1)	14 (7.1)
Europe/Australia[b]	258 (69.0)	143 (72.2)
Latin America	5 (1.3)	3 (1.5)
North America	59 (15.8)	31 (15.7)
Other	18 (4.8)	7 (3.5)
ECOG PS, n (%)		
0	232 (62.0)	137 (69.2)
1	141 (37.7)	61 (30.8)
Missing	1 (0.3)	0 (0)
Disease stage on study entry, n (%)		
II	ND	ND
III	ND	ND
IV	ND	ND
Disease-free interval, n (%)		
De novo	ND	ND
Not de novo	ND	ND
≤ 12 months	ND	ND
> 12 months	ND	ND
Type of most recent treatment, n (%)		
Chemotherapy	ND	ND
Endocrine therapy	ND	ND
Radiotherapy	ND	ND
Surgery (not biopsy)	ND	ND
Other	ND	ND

Table 9: Characteristics of the study population – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine therapy for the advanced stage) (multipage table)

Study **Characteristics** **Category**	**Ribociclib + fulvestrant** **N[a] = 374**	**Placebo + fulvestrant** **N[a] = 198**
Setting of most recent treatment, n (%)		
Adjuvant	ND	ND
Neoadjuvant	ND	ND
Therapeutic	ND	ND
Palliative	ND	ND
Not applicable	ND	ND
Location of metastases, n (%)		
Soft tissue	ND	ND
Breast	ND	ND
Bone	ND	ND
Bone only	ND	ND
Visceral	ND	ND
Lung	ND	ND
Liver	ND	ND
Lung or liver	ND	ND
CNS	ND	ND
Other	ND	ND
Skin	ND	ND
Lymph nodes	ND	ND
None	ND	ND
Treatment discontinuation[c], n (%)	276 (73.8[d])	169 (85.4[d])
Study discontinuation, n (%)	ND	ND

a. Number of analysed patients; no information as to whether this concurs with the number of randomized patients.
b. There is no information separately for Europe and Australia.
c. Discontinuation of the entire study medication; data cut-off on 3 June 2019; no information available on whether deaths are included or on patients who did not start therapy; no information available on the reasons for treatment discontinuation for subpopulation A1; in the total population, disease progression was the main reason for treatment discontinuation for both treatment arms.
d. Institute's calculation.

CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group Performance Status; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

For patients with initial endocrine therapy for the advanced stage (subpopulation A1), the company presented information exclusively on the characteristics of age, region and general condition (recorded using the ECOG PS). These were comparable between the treatment groups. The mean age of the patients was 63 years and the vast majority of them were in Europe or Australia. The general condition of most patients on study entry was without restriction

(ECOG PS of 0) and otherwise with mild restriction (ECOG PS of 1). The study population only consisted of women.

Regarding all other characteristics, the company did not provide any information for the relevant subpopulation A1 in Module 4 B of its dossier, although these characteristics had already been presented in the previous assessments of ribociclib in combination with fulvestrant [3,4]. The patient characteristics of the total study population of the MONALEESA-3 study can be found in Appendix A of the addendum to the first assessment [4].

Information on the course of the study

Table 10 shows the median observation period in patients with initial endocrine therapy in the advanced stage (subpopulation A1) for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine therapy for the advanced stage)

Study **Duration of the study phase** **Outcome category**	**Ribociclib + fulvestrant** **N = 374[a]**	**Placebo + fulvestrant** **N = 198**
MONALEESA-3		
Treatment duration	ND	ND
Observation period [months]		
Overall survival	ND	ND
Symptoms and health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	14.7 [ND]	11.2 [ND]
Mean (SD)	ND	ND
Pain (BPI-SF)		
Median [min; max]	13.8 [ND]	10.4 [ND]
Mean (SD)	ND	ND
Health status (EQ-5D VAS)	12.9 [ND]	9.2 [ND]
Side effects		
Median [min; max]	16.8 [ND]	12.7 [ND]
Mean (SD)	ND	ND

a. N = 373 for side effects, this number of patients received at least one dose of the study medication.

BPI-SF: Brief Pain Inventory-Short Form; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

There is no information on treatment duration for the new data cut-off from 3 June 2019. The observation periods of the outcomes on symptoms, pain, health-related quality of life, health status and side effects were longer in the ribociclib + fulvestrant arm than in the placebo + fulvestrant arm. Since these outcomes were recorded until progression or end of treatment, it

can be assumed that the treatment duration was longer in the ribociclib + fulvestrant arm than in the placebo + fulvestrant arm. As for treatment duration, there was no information on the observation period of the outcome "overall survival".

Information on subsequent therapies

After discontinuation of the study medication, patients in both study arms could start subsequent treatment. Switching treatments, particularly from placebo to ribociclib, was not possible.

At the time point of the second data cut-off, in subpopulation A1, a total of 226 of the patients in the ribociclib + fulvestrant arm and 146 of the patients in the placebo + fulvestrant arm had received subsequent therapy. Thus, of those patients who discontinued therapy during the study period (ribociclib + fulvestrant: n = 276; placebo + fulvestrant: n = 169), 82% in the intervention arm and 86% in the control arm received subsequent therapy. A presentation of any subsequent antineoplastic therapy by type of therapy for subpopulation A1 can be found in Appendix A.3 of the full dossier assessment. A list of the drugs administered is only available for the total population of the MONALEESA-3 study and can be found in Appendix D.1 of the full dossier assessment.

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: ribociclib + 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			
MONALEESA-3	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

For the MONALEESA-3 study, the risk of bias across outcomes was rated as low. This concurs with the company's assessment.

Transferability of the study results to the German health care context

In Module 4 B, the company described that the results of the MONALEESA-3 study were fully transferable to the German health care context, since well over 80% of the patients came from countries with a high standard of health care and were of Caucasian family origin. According to the company, there were also no effect modifications by the characteristic "family origin",

and the study results of the subgroup of patients residing in Europe, Australia or North America did not deviate from those of the total population.

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

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms, recorded with the symptom scales of the EORTC QLQ-C30 instrument
  - health status, recorded with the VAS of the EQ-5D questionnaire
  - pain, recorded with the BPI-SF
- Health-related quality of life
  - recorded with the global health status and the functional scales of the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade 3–4)
  - discontinuation due to AEs
  - neutropenia (Preferred Term [PT], CTCAE grade 3–4)
  - 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 (patients with initial endocrine therapy in the advanced stage) were available in the study included.

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

Study	Outcomes									
	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Pain (BPI-SF)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs (CTCAE grade 3–4)	Discontinuation due to AEs	Neutropenia (PT, CTCAE grade 3–4)	Further specific AEs[a]
MONALEESA-3	Yes	Yes	No[b]	No[b]	Yes	Yes	Yes	Yes	Yes	Yes

a. The following events are considered (MedDRA coding): eye disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade 3–4]), and investigations (SOC, severe AEs [CTCAE grade 3–4]).
b. No usable data available for the relevant subpopulation.

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

No usable analyses were available for the following patient-relevant outcomes:

- Health status (recorded using the EQ-5D VAS): The recording of the health status by means of a VAS is generally regarded as patient-relevant. However, referring to the work of Pickard 2007 [14], the company presented responder analyses for the time to definitive deterioration by ≥ 7 or ≥ 10 points in the dossier. The response criteria chosen by the company are not validated, and their analyses are therefore not usable [15]. A supplementary presentation of the results can be found in Appendix C.1 of the full dossier assessment. No analyses of the change from baseline were available.
- Pain (recorded using the BPI-SF):
  - Worst pain (Item 3): The recording of worst pain using the BPI-SF is regarded as patient-relevant. The analyses presented by the company were not usable, however, as the company only presented responder analyses for the time to definitive deterioration by ≥ 2 points. The company chose this response criterion post hoc. In particular, the company did not present the prespecified analysis of the change from baseline for worst pain. As already described in the first assessment [3], this approach is inadequate.

- Pain intensity (Items 3–6) and pain interference (Items 9 a–g): The recording of pain intensity and pain interference using the BPI-SF is regarded as patient-relevant. As described in the first assessment, the analysis of the change from baseline was prespecified for the MONALEESA-3 study. The company presented 2 analyses on the change from baseline each for pain intensity and pain interference, but there was no documentation of the methodological approach for any of the analyses. Depending on the analysis, there was no information on the model used, the test used or the time reference of the effects estimated by the company, for example. For the analysis using a linear mixed model in particular, it is unclear whether positive or negative effects indicate an advantage for the intervention. The presented analyses were therefore not usable.

2.4.2.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes in subpopulation A1 (patients with initial endocrine therapy in the advanced stage).

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine therapy for the advanced stage)

Study	Study level	Outcomes									
		Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Pain (BPI-SF)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs (CTCAE grade 3–4)	Discontinuation due to AEs	Neutropenia (PT, CTCAE grade 3-4)	Further specific AEs[a]
MONALEESA-3	L	L	H[b]	–[c]	–[c]	H[b]	H[b]	H[b]	L[d]	H[b]	H[b]

a. The following events are considered (MedDRA coding): eye disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade 3–4]), and investigations (SOC, severe AEs [CTCAE grade 3–4]).
b. Incomplete observations for potentially informative reasons.
c. No usable data for the relevant subpopulation available; see Section 2.4.2.1 for reasons.
d. Despite the low risk of bias, limited certainty of results is assumed for the outcome "discontinuation due to AEs".

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

The risk of bias of the result for overall survival was rated as low.

Due to incomplete observations for potentially informative reasons, there was a high risk of bias for the results of the following outcomes: symptoms, health-related quality of life, SAEs, severe AEs (CTCAE grade 3–4), neutropenia (CTCAE grade 3–4), and further specific AEs.

Although the risk of bias for the outcome "discontinuation due to AEs" was low, the certainty of results for this outcome was limited. 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.

This assessment concurs with that of the company, which assessed the risk of bias on the basis of the total population of the MONALEESA-3 study, however.

2.4.2.3 Results

The results of the comparison of ribociclib + fulvestrant with placebo + fulvestrant as initial endocrine therapy in postmenopausal women with HR-positive, HER2-negative metastatic breast cancer are summarized in Table 14. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves on the event time analyses are presented in Appendix A.1 of the full dossier assessment. The tables with the results on common AEs, SAEs, severe AEs (CTCAE grade 3–4) and discontinuations due to AEs can be found in Appendix A.2 of the full dossier assessment.

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

Study Outcome category	Ribociclib + fulvestrant		Placebo + fulvestrant		Ribociclib + fulvestrant vs. placebo + fulvestrant
Outcome	**N**	**Median time to event in months [95% CI][a] Patients with event n (%)**	**N**	**Median time to event in months [95% CI][a] Patients with event n (%)**	**HR [95% CI][b]; p-value[c]**
MONALEESA-3 (data cut-off 3 June 2019)					
Mortality					
Overall survival	374	NA [42.48; NC] 123 (32.9)	198	40.0 [37.42; 45.08] 89 (44.9)	0.71 [0.54; 0.94]; 0.015
Morbidity					
Symptoms					
EORTC QLQ-C30 symptom scales, time to definitive deterioration[d, e]					
Fatigue	374	38.8 [35.81; NC] 108 (28.9)	198	36.0 [28.42; NC] 57 (28.8)	0.89 [0.64; 1.22]; 0.467
Nausea/vomiting	374	NA 12 (3.2)	198	NA 4 (2.0)	1.34 [0.43; 4.18]; 0.610
Pain	374	41.9 [39.82; NC] 79 (21.1)	198	NA 31 (15.7)	1.19 [0.79; 1.81]; 0.409
Dyspnoea	374	NA 20 (5.3)	198	41.4 [38.90; NC] 13 (6.6)	0.70 [0.35; 1.41]; 0.313
Insomnia	374	NA 32 (8.6)	198	NA [38.90; NC] 14 (7.1)	1.02 [0.55; 1.92]; 0.940
Appetite loss	374	NA 23 (6.1)	198	NA 5 (2.5)	2.20 [0.83; 5.79]; 0.103
Constipation	374	NA 17 (4.5)	198	NA 6 (3.0)	1.40 [0.55; 3.56]; 0.479
Diarrhoea	374	NA 6 (1.6)	198	NA 0 (0)	–[f]; 0.082
Health status					
EQ-5D VAS	No usable data				
Pain					
BPI-SF	No usable data				

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

Study Outcome category	Ribociclib + fulvestrant		Placebo + fulvestrant		Ribociclib + fulvestrant vs. placebo + fulvestrant
Outcome	**N**	**Median time to event in months [95% CI][a] Patients with event n (%)**	**N**	**Median time to event in months [95% CI][a] Patients with event n (%)**	**HR [95% CI][b]; p-value[c]**
Health-related quality of life					
EORTC QLQ-C30 global health status and functional scales, time to definitive deterioration[e, g]					
Global health status	374	35.9 [30.42; 42.35] 124 (33.2)	198	33.4 [24.87; 35.98]; 63 (31.8)	0.90 [0.67; 1.23]; 0.509
Physical functioning	374	38.7 [34.60; NC] 107 (28.6)	198	35.9 [27.63; NC] 57 (28.8)	0.84 [0.61; 1.17]; 0.305
Role functioning	374	37.7 [33.08; 41.43] 122 (32.6)	198	35.9 [30.62; NC] 48 (24.2)	1.18 [0.84; 1.65]; 0.334
Emotional functioning	374	38.2 [35.91; 41.86] 109 (29.1)	198	33.1 [27.66; 41.72] 58 (29.3)	0.81 [0.59; 1.12]; 0.197
Cognitive functioning	374	39.6 [33.91; NC] 114 (30.5)	198	36.1 [34.89; NC] 51 (25.8)	1.10 [0.79; 1.54]; 0.571
Social functioning	374	41.4 [35.91; NC] 99 (26.5)	198	38.8 [34.89; NC] 40 (20.2)	1.15 [0.80; 1.66]; 0.457
Side effects					
AEs (supplementary information)	374	0.3 [0.16; 0.30] 369 (98.9)	198	0.4 [0.33; 0.49] 190 (96.0)	_
SAEs	374	44.2 [36.24; NC] 122 (32.7)	198	NA 41 (20.7)	1.50 [1.05; 2.14]; 0.024
Severe AEs (CTCAE grade 3–4)	374	1.9 [1.12; 1.97] 305 (81.8)	198	28.1 [21.85; NC] 72 (36.4)	3.90 [3.01; 5.05]; < 0.001
Discontinuation due to AEs[h]	374	NA 58 (15.5)	198	NA 13 (6.6)	2.39 [1.31; 4.36]; 0.003
Blood and lymphatic system disorders (SOC, CTCAE grade 3–4)	373	15.7 [10.15; 34.07] 180 (48.3)	198	NA 6 (3.0)	21.28 [9.43; 48.02]; < 0.001
including: neutropenia (PT, CTCAE grade 3–4)	373	20.1 [11.99; NC] 171 (45.8)	198	NA 2 (1.0)	59.73 [14.82; 240.85]; < 0.001
Investigations (SOC, CTCAE grade 3–4)	373	NA [34.04; NC] 136 (36.5)	198	NA 13 (6.6)	6.36 [3.60; 11.23]; < 0.001
Eye disorders (SOC, AEs)	373	NA 86 (23.1)	198	NA 20 (10.1)	2.29 [1.41; 3.73]; < 0.001
Skin and subcutaneous tissue disorders (SOC, AEs)	373	5.1 [3.91; 8.25] 223 (59.8)	198	NA [31.67; NC] 56 (28.3)	2.81 [2.09; 3.77]; < 0.001

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

Study Outcome category	Ribociclib + fulvestrant		Placebo + fulvestrant		Ribociclib + fulvestrant vs. placebo + fulvestrant
Outcome	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95% CI][b]; p-value[c]

a. Median time to event and corresponding 95% CI were estimated using the Kaplan-Meier method.
b. Effect and CI: Cox proportional hazards model, stratified by the presence of liver and/or lung metastases according to IRT.
c. p-value: log-rank test stratified by the presence of liver and/or lung metastases according to IRT.
d. An increase by at least 10 points on the respective score was considered to be a clinically relevant deterioration if this also applied to all subsequent values or if the deterioration occurred at the patient's last documentation time.
e. Deaths were not recorded as deterioration.
f. Effect estimation not meaningfully interpretable.
g. A decrease by at least 10 points on the respective score was considered to be a clinically relevant deterioration if this also applied to all subsequent values or if the deterioration occurred at the patient's last documentation time.
h. Termination of therapy with ribociclib or placebo; termination of fulvestrant treatment alone was not allowed in the framework of the study.

AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; IRT: interactive response technology; 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; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

Based on the available data, at most an indication, e.g. of an added benefit, can be determined for the outcome "overall survival". For the other outcomes, there was a high risk of bias of the results (or in the case of discontinuation due to AEs, the certainty of results was limited); the outcome-specific certainty of conclusions of the results may not be downgraded, however (see description of the results below).

Mortality

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

This concurs with the assessment of the company insofar as the company arrived at the same result on the basis of the results of the total population of the MONALEESA-3 study.

Morbidity

Symptoms, recorded using the EORTC QLQ-C30 symptom scales

In the MONALEESA-3 study, symptom outcomes were recorded using the symptom scales of the EORTC QLQ-C30. The time to definitive deterioration by ≥ 10 points was considered in each case.

No statistically significant difference between the treatment groups was shown for any of the symptom scales of the EORTC QLQ-C30. In each case, this resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This concurs with the assessment of the company, which arrived at this result on the basis of the results of the total population, however.

Health status (EQ-5D VAS)

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

This concurs with the assessment of the company, which arrived at this result on the basis of the results of the total population used by the company, however.

Pain (BPI-SF)

There were no usable analyses for the outcome "pain" recorded with the BPI-SF (see Section 2.4.2.1). This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This concurs with the assessment of the company, which arrived at this result on the basis of the results of the total population used by the company, however.

Health-related quality of life

Global health status and functional scales recorded using the EORTC QLQ-C30

Health-related quality of life was recorded using the global health status and the functional scales of the EORTC QLQ-C30. The time to definitive deterioration by ≥ 10 points was considered in each case.

A statistically significant difference between the treatment groups was shown neither for any of the 5 functional scales nor for global health status. In each case, this resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an added benefit for emotional functioning on the basis of the results of the total population, and assumed a high certainty of results for this scale despite high risk of bias.

Side effects

SAEs

A statistically significant difference to the disadvantage of ribociclib + fulvestrant compared with placebo + fulvestrant was shown for the outcome "SAEs". This resulted in a hint of greater harm from ribociclib + fulvestrant in comparison with fulvestrant.

This concurs with the assessment of the company insofar as the company also derived greater harm on the basis of the results for the total population.

Severe AEs (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib + fulvestrant was shown for the outcome "severe AEs (CTCAE grade 3–4)". Due to the size of the observed effect and the early occurrence of the events in the course of the study (see Figure 17 of the full dossier assessment), there was an indication of greater harm of ribociclib + fulvestrant in comparison with fulvestrant for this outcome despite the high risk of bias.

This concurs with the assessment of the company insofar as the company also derived greater harm on the basis of the results for the total population.

Discontinuation due to AEs

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

This concurs with the assessment of the company insofar as the company also derived greater harm on the basis of the results for the total population.

Specific AEs

Severe AEs (CTCAE grade 3–4): blood and lymphatic system disorders (including: neutropenia) and investigations

A statistically significant difference to the disadvantage of ribociclib + fulvestrant in comparison with placebo + fulvestrant was shown for the specific severe AEs (CTCAE grade 3–4) "blood and lymphatic system disorders" (including: "severe neutropenia") and "investigations". Due to the size of the observed effects in each case, and the early occurrence of the events in the course of the study (see Figure 19, Figure 20 and Figure 21 of the full dossier assessment), there was an indication of greater harm of ribociclib + fulvestrant in comparison with fulvestrant for each of these outcomes despite the high risk of bias.

AEs: eye disorders and skin and subcutaneous tissue disorders

Statistically significant differences to the disadvantage of ribociclib + fulvestrant in comparison with placebo + fulvestrant were shown for each of the specific AEs "eye disorders" and "skin and subcutaneous tissue disorders". This resulted in hints of greater harm of ribociclib + fulvestrant in comparison with fulvestrant for each of these outcomes.

This deviates from the assessment of the company, which considered other specific AEs.

2.4.2.4 Subgroups and other effect modifiers

The following subgroup characteristic was considered in the present 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.

The company considered the total population and did not use the results from the subgroup analyses for the derivation of an added benefit for it in any outcome.

The subgroup results of ribociclib + fulvestrant in comparison with placebo + fulvestrant are summarized in Table 15. The Kaplan-Meier curves on the event time analyses in the respective subgroups are presented in Appendix A.1 of the full dossier assessment.

Table 15: Subgroups (side effects) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine therapy for the advanced stage)

Study Outcome	Ribociclib + fulvestrant		Placebo + fulvestrant		Ribociclib + fulvestrant vs. placebo + fulvestrant	
Characteristic Subgroup	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95% CI][b]	p-value[c]
MONALEESA-3 (data cut-off 3 June 2019)						
Severe AEs (CTCAE grade 3–4)						
Age						
< 65 years	210	1.9 [1.05; 1.97] 174 (82.9)	102	NA [22.97; NC] 28 (27.5)	5.33 [3.56; 7.97]	< 0.001
≥ 65 years	163	1.9 [0.95; 2.83] 131 (80.4)	96	28.0 [11.99; 33.45] 44 (45.8)	3.05 [2.14; 4.34]	< 0.001
Total					Interaction:	0.030[d]

a. Median time to event and corresponding 95% CI were estimated using the Kaplan-Meier method.
b. Effect and CI: Cox proportional hazards model, stratified by the presence of liver and/or lung metastases according to IRT.
c. p-value: log-rank test stratified by the presence of liver and/or lung metastases according to IRT.
d. p-value on the interaction term treatment*subgroup characteristic in a Cox proportional hazards model.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; IRT: interactive response technology; n: number of patients with event N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; vs.: versus

Side effects

Severe AEs (CTCAE grade 3–4)

There was an effect modification by the characteristic "age" for the outcome "severe AEs (CTCAE grade 3–4)". A statistically significant difference between the treatment groups to the disadvantage of ribociclib + fulvestrant was shown in both subgroups (< 65 years; ≥ 65 years). Probability and extent in both subgroups concurred with the results in the total relevant subpopulation A1. In the present constellation, the results of the total subpopulation A1 were therefore used for the derivation of the added benefit.

This concurs with the assessment of the company insofar as the company also identified no relevant effect modification by the characteristic of age on the basis of the results of the total population used by the company.

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 [1].

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

2.4.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.4.2 (see Table 24).

Determination of the outcome category for the outcomes on 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.

Discontinuation due to AEs

For the current data cut-off from 3 June 2019, no information on the proportion of SAEs or severe AEs (CTCAE grade 3–4) was available for the outcome "discontinuation due to AEs". In the first assessment A19-06 [3] on the earlier data cut-off (3 November 2017), the outcome "discontinuation due to AEs" was rated as serious/severe. This assessment was based on the fact that the events included in the outcome were mostly severe (CTCAE grade 3–4) in the total population. There was no information available that would justify a deviating classification for the present assessment. Hence, the outcome "discontinuation due to AEs" was allocated to the outcome category of serious/severe side effects.

The company did not allocate discontinuation due to AEs to an outcome category.

Specific AEs (eye disorders, skin and subcutaneous tissue disorders)

Most of the occurred events of the specific AEs "eye disorders" and "skin and subcutaneous tissue disorders" were non-serious/non-severe. The outcomes were therefore assigned to the outcome category of non-serious/non-severe side effects.

The company did not allocate the specific AEs used for the present assessment to an outcome category, as it considered different specific AEs in its assessment.

Table 16: Extent of added benefit at outcome level – RCT, direct comparison: ribociclib + fulvestrant vs. fulvestrant (research question A1: postmenopausal women, initial endocrine therapy for the advanced stage) (multipage table)

Outcome category **Outcome**	**Ribociclib + fulvestrant vs. fulvestrant** **Median time to event (months) or proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	NA vs. 40.0 HR: 0.71 [0.54; 0.94] p = 0.015 probability: "indication"	Outcome category: mortality $0.85 \leq CI_u < 0.95$ added benefit, extent: "considerable"
Morbidity		
Symptoms		
EORTC QLQ-C30 symptom scales, time to definitive deterioration		
Fatigue	38.8 vs. 36.0 HR: 0.89 [0.64; 1.22] p = 0.467	Lesser benefit/added benefit not proven
Nausea/vomiting	NA vs. NA HR: 1.34 [0.43; 4.18] p = 0.610	Lesser benefit/added benefit not proven
Pain	41.9 vs. NA HR: 1.19 [0.79; 1.81] p = 0.409	Lesser benefit/added benefit not proven
Dyspnoea	NA vs. 41.4 HR: 0.70 [0.35; 1.41] p = 0.313	Lesser benefit/added benefit not proven
Insomnia	NA vs. NA HR: 1.02 [0.55; 1.92] p = 0.940	Lesser benefit/added benefit not proven
Appetite loss	NA vs. NA HR: 2.20 [0.83; 5.79] p = 0.103	Lesser benefit/added benefit not proven
Constipation	NA vs. NA HR: 1.40 [0.55; 3.56] p = 0.479	Lesser benefit/added benefit not proven
Diarrhoea	NA vs. NA Proportions of events: 1.6% vs. 0% HR: –[c] p = 0.082	Lesser benefit/added benefit not proven[d]
Health status		
EQ-5D VAS	No usable data	
Pain		
BPI-SF	No usable data	

Table 16: Extent of added benefit at outcome level – RCT, direct comparison: ribociclib + fulvestrant vs. fulvestrant (research question A1: postmenopausal women, initial endocrine therapy for the advanced stage) (multipage table)

Outcome category **Outcome**	**Ribociclib + fulvestrant vs. fulvestrant** **Median time to event (months) or proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
EORTC QLQ-C30 global health status and functional scales, time to definitive deterioration		
Global health status	35.9 vs. 33.4 HR: 0.90 [0.67; 1.23] p = 0.509	Lesser benefit/added benefit not proven
Physical functioning	38.7 vs. 35.9 HR: 0.84 [0.61; 1.17] p = 0.305	Lesser benefit/added benefit not proven
Role functioning	37.7 vs. 35.9 HR: 1.18 [0.84; 1.65] p = 0.334	Lesser benefit/added benefit not proven
Emotional functioning	38.2 vs. 33.1 HR: 0.81 [0.59; 1.12] p = 0.197	Lesser benefit/added benefit not proven
Cognitive functioning	39.6 vs. 36.1 HR: 1.10 [0.79; 1.54] p = 0.571	Lesser benefit/added benefit not proven
Social functioning	41.4 vs. 38.8 HR: 1.15 [0.80; 1.66] p = 0.457	Lesser benefit/added benefit not proven
Side effects		
SAEs	44.2 vs. NA HR: 1.50 [1.05; 2.14] HR: 0.67 [0.47; 0.95][e] p = 0.024 probability: “hint”	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: “minor”
Severe AEs (CTCAE grade 3–4)	1.9 vs. 28.1 HR: 3.90 [3.01; 5.05] HR: 0.26 [0.20; 0.33][e] p < 0.001 probability: “indication”	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: “major”
Discontinuation due to AEs[f]	NA vs. NA HR: 2.39 [1.31; 4.36] HR: 0.42 [0.23; 0.76][e] p = 0.003 probability: “hint”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: “considerable”

Table 16: Extent of added benefit at outcome level – RCT, direct comparison: ribociclib + fulvestrant vs. fulvestrant (research question A1: postmenopausal women, initial endocrine therapy for the advanced stage) (multipage table)

Outcome category **Outcome**	**Ribociclib + fulvestrant vs. fulvestrant** **Median time to event (months) or proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Blood and lymphatic system disorders (SOC, CTCAE grade 3–4)	15.7 vs. NA HR: 21.28 [9.43; 48.02] HR: 0.05 [0.02; 0.11][e] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: "major"
including: neutropenia (PT, CTCAE grade 3-4)	20.1 vs. NA HR: 59.73 [14.82; 240.85] HR: 0.02 [0.00; 0.07][e] p < 0.001 probability: "indication"	
Investigations (SOC, CTCAE grade 3–4)	NA vs. NA HR: 6.36 [3.60; 11.23] HR: 0.16 [0.09; 0.28][e] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5% greater harm, extent: "major"
Eye disorders (SOC, AEs)	NA vs. NA HR: 2.29 [1.41; 3.73] HR: 0.44 [0.27; 0.71][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"
Skin and subcutaneous tissue disorders (SOC, AEs)	5.1 vs. NA HR: 2.81 [2.09; 3.77] HR: 0.36 [0.27; 0.48][e] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects CI_u < 0.80 greater harm, extent: "considerable"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Effect estimation not meaningfully interpretable.
d. The p-value is decisive for the derivation of the added benefit.
e. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
f. Termination of therapy with ribociclib or placebo; termination of fulvestrant treatment alone was not allowed in the framework of the study.

AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30:European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MD: difference of the mean change over time; NA: not achieved; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.4.3.2 Overall conclusion on added benefit

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

Table 17: Positive and negative effects from the assessment of ribociclib in combination with fulvestrant in comparison with fulvestrant (research question A1: postmenopausal women, initial endocrine therapy for the advanced stage)

Positive effects	**Negative effects**
Mortality ▪ Overall survival: indication of added benefit – extent: "considerable"	–
–	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: "minor" ▪ Discontinuation due to AEs: hint of greater harm – extent: "considerable" ▪ Severe AEs (CTCAE grade 3–4): indication of greater harm – extent: "major" ▫ Specific AEs (CTCAE grade 3–4): - blood and lymphatic system disorders (including: neutropenia) and investigations: in each case indication of greater harm – extent: "major"
–	Non-serious/non-severe side effects ▪ Specific AEs: ▫ eye disorders and skin and subcutaneous tissue disorders: in each case hint of greater harm – extent: "considerable"
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event	

In the overall consideration, there is a positive effect of considerable extent in the outcome "overall survival", which is accompanied by a number of serious and severe side effects (CTCAE grade 3–4) of mostly considerable or major extent.

In the present subpopulation A1, the side effects were particularly evident in all superordinate AE outcomes (SAEs, severe AEs [CTCAE grade 3–4] and discontinuation due to AEs). The severe side effects (CTCAE grade 3–4) were mostly severe blood and lymphatic system disorders, including mainly neutropenia. Furthermore, there was a hint of considerably greater harm in each of the outcomes "eye disorders" and "skin and subcutaneous tissue disorders".

The negative effects did not completely outweigh the advantage in overall survival, but resulted in a downgrading of the extent of the added benefit.

In summary, there is an indication of a minor added benefit of ribociclib in combination with fulvestrant versus the ACT for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer in initial endocrine therapy.

2.5 Research question B1: postmenopausal women who have received prior endocrine therapy for the advanced stage

2.5.1 Information retrieval and study pool

Details on the information retrieval and the study pool can be found in Section 2.3. The company also identified the MONALEESA-3 study on the comparison of ribociclib + fulvestrant versus fulvestrant for research question B1. Deviating from the company's assessment, only a subpopulation of the MONALEESA-3 study was relevant also for research question B1 (see Sections 2.3 and 2.4).

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 anti-oestrogen therapy. The company did not provide information on how many postmenopausal patients who had received prior endocrine therapy for the advanced stage had been pretreated in compliance with the approval. It is known from the first assessment, however, that there were also patients who had received an aromatase inhibitor as most recent endocrine therapy before enrolment. Although the assessment at that time referred to a different operationalization of the relevant subpopulation for the present research question, it can still be assumed that the approval requirements for therapy with fulvestrant were not fulfilled for all patients included in the MONALEESA-3 study, and that fulvestrant was not an ACT for these patients of subpopulation B1. However, the G-BA saw a medical reason for research question B1, which, in the present case, exceptionally justified considering fulvestrant, which was used in the MONALEESA-3 study also after pretreatment with aromatase inhibitors, as a comparator (see also Section 2.2). Thus, the results of the total subpopulation B1 for the comparison of ribociclib + fulvestrant versus fulvestrant (hereinafter referred to as "comparator") [5] are relevant. Subgroup analyses in Module 4 B of the company's dossier additionally showed that there was no effect modification from the characteristic of prior therapy with an aromatase inhibitor (yes versus no).

2.5.1.1 Study characteristics

The study characteristics, information on data cut-offs and the planned follow-up observation of outcomes in the MONALEESA-3 study are described in detail in Section 2.4.1. The operationalizations of the subpopulations A1 and B1 for the present benefit assessment are also described there.

The subpopulation B1 of patients with prior endocrine therapy in the advanced stage of the MONALEESA-3 study comprised 100 women in the ribociclib + fulvestrant arm and 39 women in the placebo + fulvestrant arm (2:1 randomization). This corresponds to about 19% of the study population in total (intervention arm: 21%; control arm: 16%).

Characteristics of the study population

Table 18 shows the characteristics of the patients in subpopulation B1 of the MONALEESA-3 study.

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

Study **Characteristics** **Category**	**Ribociclib + fulvestrant** **N[a] = 100**	**Placebo + fulvestrant** **N[a] = 39**
MONALEESA-3		
Age [years], mean (SD)	66 (9)	62 (11)
Region, n (%)		
Asia	6 (6.0)	2 (5.1)
Europe/Australia	81 (81.0)	26 (66.7)
Latin America	1 (1.0)	0 (0)
North America	9 (9.0)	11 (28.2)
Other	3 (3.0)	0 (0)
ECOG PS, n (%)		
0	71 (71.0)	19 (48.7)
1	29 (29.0)	20 (51.3)
Disease stage on study entry, n (%)		
II	ND	ND
III	ND	ND
IV	ND	ND
Disease-free interval, n (%)		
De novo	ND	ND
Not de novo	ND	ND
≤ 12 months	ND	ND
> 12 months	ND	ND
Type of most recent treatment, n (%)		
Chemotherapy	ND	ND
Endocrine therapy	ND	ND
Radiotherapy	ND	ND
Surgery (not biopsy)	ND	ND
Other	ND	ND
Setting of most recent treatment, n (%)		
Adjuvant	ND	ND
Neoadjuvant	ND	ND
Therapeutic	ND	ND
Palliative	ND	ND
Not applicable	ND	ND

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

Study **Characteristics** **Category**	**Ribociclib + fulvestrant** **N[a] = 100**	**Placebo + fulvestrant** **N[a] = 39**
Location of metastases, n (%)		
Soft tissue	ND	ND
Breast	ND	ND
Bone	ND	ND
Bone only	ND	ND
Visceral	ND	ND
Lung	ND	ND
Liver	ND	ND
Lung or liver	ND	ND
CNS	ND	ND
Other	ND	ND
Skin	ND	ND
Lymph nodes	ND	ND
None	ND	ND
Treatment discontinuation[b], n (%)	80 (80.0[c])	37 (94.9[c])
Study discontinuation, n (%)	ND	ND

a. Number of analysed patients; no information as to whether this concurs with the number of randomized patients.
b. Discontinuation of the entire study medication; data cut-off on 3 June 2019; no information available on whether deaths are included or on patients who did not start therapy; no information available on the reasons for treatment discontinuation for subpopulation B1; in the total population, disease progression was the main reason for treatment discontinuation for both treatment arms.
c. Institute's calculation.

CNS: central nervous system; ECOG PS: Eastern Cooperative Oncology Group Performance Status; n: number of patients in the category; N: number of randomized patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Also for patients who have received prior endocrine therapy for the advanced stage (subpopulation B1), the company presented information exclusively on the characteristics of age, region and general condition (recorded using the ECOG PS). These were sufficiently comparable between the treatment groups. The mean age of the patients was 65 years and the majority of them were in Europe or Australia. The general condition of the patients was either without restriction (ECOG PS of 0) or with mild restriction (ECOG PS of 1). The study population only consisted of women.

Regarding all other characteristics, the company did not provide any information for subpopulation B1 in Module 4 B of its dossier, although these characteristics had already been presented in the previous assessments of ribociclib in combination with fulvestrant [3,4]. The

patient characteristics of the total study population of the MONALEESA-3 study can be found in Appendix A of the addendum to the first assessment [4].

Information on the course of the study

Table 19 shows the median observation period in patients with prior endocrine therapy in the advanced stage (subpopulation B1) for individual outcomes.

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

Study **Duration of the study phase** **Outcome category**	**Ribociclib + fulvestrant** **N = 100**	**Placebo + fulvestrant** **N = 39**
MONALEESA-3		
Treatment duration	ND	ND
Observation period [months]		
Overall survival	ND	ND
Symptoms and health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	12.9 [ND]	7.4 [ND]
Mean (SD)	ND	ND
Pain (BPI-SF)		
Median [min; max]	11.2 [ND]	7.4 [ND]
Mean (SD)	ND	ND
Health status (EQ-5D VAS)	10.5 [ND]	7.4 [ND]
Side effects		
Median [min; max]	13.7 [ND]	10.2 [ND]
Mean (SD)	ND	ND

BPI-SF: Brief Pain Inventory-Short Form; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

There is no information on treatment duration for the new data cut-off from 3 June 2019. The observation periods of the outcomes on symptoms, pain, health-related quality of life, health status and side effects were longer in the ribociclib + fulvestrant arm than in the placebo + fulvestrant arm. Since these outcomes were recorded until progression or end of treatment, it can be assumed that the treatment duration was longer in the ribociclib + fulvestrant arm than in the placebo + fulvestrant arm. As for treatment duration, there was no information on the observation period of the outcome “overall survival”.

Information on subsequent therapies

The specifications on subsequent therapies for the MONALEESA-3 study are described in Section 2.4.1. A presentation of any subsequent antineoplastic therapy by type of therapy for subpopulation B1 can be found in Appendix B.3 of the full dossier assessment.

Risk of bias across outcomes (study level)

The risk of bias across outcomes (study level) for the MONALEESA-3 study was rated as low (see Section 2.4.1, Table 11).

Transferability of the study results to the German health care context

The company's reasoning regarding the transferability of the study results to the German health care context is described in Section 2.4.1.

2.5.2 Results on added benefit

2.5.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms, recorded with the symptom scales of the EORTC QLQ-C30 instrument
  - health status, recorded with the VAS of the EQ-5D questionnaire
  - pain, recorded with the BPI-SF
- Health-related quality of life
  - recorded with the global health status and the functional scales of the EORTC QLQ-C30
- Side effects
  - SAEs
  - severe AEs (CTCAE grade 3–4)
  - discontinuation due to AEs
  - neutropenia (PT, CTCAE grade 3-4)
  - 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 20 shows for which outcomes data for subpopulation B1 (patients with prior endocrine therapy in the advanced stage) were available in the study included.

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

Study	Outcomes									
	Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Pain (BPI-SF)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs (CTCAE grade 3–4)	Discontinuation due to AEs	Neutropenia (PT, CTCAE grade 3-4)	Further specific AEs[a]
MONALEESA-3	Yes	Yes	No[b]	No[b]	Yes	Yes	Yes	Yes	Yes	Yes

a. The following events are considered (MedDRA coding): skin and subcutaneous tissue disorders (SOC, AEs) and general blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade 3–4]).
b. No usable data available for the relevant subpopulation.

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

No usable analyses were available for the outcomes “health status” (EQ-5D VAS) and “pain” (BPI-SF) (see Section 2.4.2.1 for reasons). The supplementary presentation of results on health status for subpopulation B1 (patients with prior endocrine therapy in the advanced stage) can be found in Appendix C.2 of the full dossier assessment.

2.5.2.2 Risk of bias

Table 21 describes the risk of bias for the results of the relevant outcomes in subpopulation B1 (patients with prior endocrine therapy in the advanced stage).

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

Study	Study level	Outcomes									
		Overall survival	Symptoms (EORTC QLQ-C30)	Health status (EQ-5D VAS)	Pain (BPI-SF)	Health-related quality of life (EORTC QLQ-C30)	SAEs	Severe AEs (CTCAE grade 3–4)	Discontinuation due to AEs	Neutropenia (PT, CTCAE grade 3-4)	Further specific AEs[a]
MONALEESA-3	L	L	H[b]	–[c]	–[c]	H[b]	H[b]	H[b]	L[d]	H[b]	H[b]

a. The following events are considered (MedDRA coding): skin and subcutaneous tissue disorders (SOC, AEs) and general blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade 3–4]).
b. Incomplete observations for potentially informative reasons.
c. No usable data for the relevant subpopulation available; see Sections 2.4.2.1 and 2.5.2.1 for reasons.
d. Despite the low risk of bias, limited certainty of results is assumed for the outcome "discontinuation due to AEs".

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

The risk of bias of the result for overall survival was rated as low.

Due to incomplete observations for potentially informative reasons, there was a high risk of bias for the results of the following outcomes: symptoms, health-related quality of life, SAEs, severe AEs (CTCAE grade 3–4), neutropenia (CTCAE grade 3–4), and further specific AEs.

Although the risk of bias for the outcome "discontinuation due to AEs" was low, the certainty of results for this outcome was limited. 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.

This assessment concurs with that of the company, which assessed the risk of bias on the basis of the total population of the MONALEESA-3 study, however.

2.5.2.3 Results

The results of the comparison of ribociclib + fulvestrant with placebo + fulvestrant in postmenopausal women with HR-positive, HER2-negative metastatic breast cancer who have received prior endocrine therapy are summarized in Table 22. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves on the event time analyses are presented in Appendix B.1 of the full dossier assessment. The tables with the results on common AEs, SAEs, severe AEs (CTCAE grade 3–4) and discontinuations due to AEs can be found in Appendix B.2 of the full dossier assessment.

Table 22: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy for the advanced stage) (multipage table)

Study Outcome category Outcome	Ribociclib + fulvestrant N	Ribociclib + fulvestrant Median time to event in months [95% CI][a] Patients with event n (%)	Placebo + fulvestrant N	Placebo + fulvestrant Median time to event in months [95% CI][a] Patients with event n (%)	Ribociclib + fulvestrant vs. placebo + fulvestrant HR [95% CI][b]; p-value[c]
MONALEESA-3 (data cut-off 3 June 2019)					
Mortality					
Overall survival	100	NA [32.89; NC] 42 (42.0)	39	35.4 [20.50; NC] 18 (46.2)	0.70 [0.40; 1.24]; 0.226
Morbidity					
Symptoms					
EORTC QLQ-C30 symptom scales, time to definitive deterioration[d, e]					
Fatigue	100	38.7 [19.68; NC] 30 (30.0)	39	28.0 [9.20; NC] 9 (23.1)	0.90 [0.42; 1.93]; 0.779
Nausea/vomiting	100	NA 1 (1.0)	39	NA 2 (5.1)	0.21 [0.02; 2.38]; 0.165
Pain	100	NA [31.90; NC] 20 (20.0)	39	NA [12.98; NC] 9 (23.1)	0.61 [0.27; 1.36]; 0.227
Dyspnoea	100	NA 3 (3.0)	39	35.9 [19.32; 35.91] 3 (7.7)	0.29 [0.06; 1.50]; 0.120
Insomnia	100	NA 10 (10.0)	39	NA 4 (10.3)	0.80 [0.25; 2.62]; 0.714
Appetite loss	100	NA 3 (3.0)	39	NA 0 (0)	–[f]; 0.357
Constipation	100	NA 3 (3.0)	39	NA 2 (5.1)	0.36 [0.05; 2.61]; 0.291
Diarrhoea	100	NA 0 (0)	39	NA 0 (0)	–
Health status					
EQ-5D VAS	No usable data				
Pain					
BPI-SF	No usable data				
Health-related quality of life					
EORTC QLQ-C30 global health status and functional scales, time to definitive deterioration[e, g]					
Global health status	100	NA [19.35; NC] 26 (26.0)	39	16.7 [11.83; 35.91] 15 (38.5)	0.53 [0.28; 1.02]; 0.056
Physical functioning	100	38.7 [35.81; NC] 26 (26.0)	39	16.7 [13.90; NC] 12 (30.8)	0.52 [0.26; 1.07]; 0.072
Role functioning	100	30.5 [22.01; 38.74] 31 (31.0)	39	24.9 [14.95; NC] 9 (23.1)	0.93 [0.43; 1.99]; 0.873

Table 22: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy for the advanced stage) (multipage table)

Study Outcome category Outcome	Ribociclib + fulvestrant N	Ribociclib + fulvestrant Median time to event in months [95% CI][a] Patients with event n (%)	Placebo + fulvestrant N	Placebo + fulvestrant Median time to event in months [95% CI][a] Patients with event n (%)	Ribociclib + fulvestrant vs. placebo + fulvestrant HR [95% CI][b]; p-value[c]
Emotional functioning	100	NA [24.94; NC] 24 (24.0)	39	22.6 [9.23; 27.96] 15 (38.5)	0.46 [0.24; 0.88]; 0.017
Cognitive functioning	100	35.9 [22.11; NC] 29 (29.0)	39	30.4 [14.78; NC] 7 (17.9)	1.15 [0.49; 2.65]; 0.760
Social functioning	100	38.7 [30.92; NC] 26 (26.0)	39	16.7 [11.20; 27.96] 13 (33.3)	0.51 [0.26; 1.02]; 0.054
Side effects					
AEs (supplementary information)	100	0.3 [0.13; 0.49] 100 (100)	39	0.2 [0.07; 0.82] 37 (94.9)	–
SAEs	100	38.5 [22.28; NC] 36 (36.0)	39	NA 6 (15.4)	2.06 [0.86; 4.95]; 0.099
Severe AEs (CTCAE grade 3–4)	100	1.7 [0.95; 3.84] 81 (81.0)	39	NA [9.63; NC] 11 (28.2)	3.94 [2.08; 7.46]; < 0.001
Discontinuation due to AEs[h]	100	NA 24 (24.0)	39	NA 2 (5.1)	4.73 [1.11; 20.12]; 0.021
Blood and lymphatic system disorders (SOC, CTCAE grade 3–4)	100	15.7 [7.36; NC] 48 (48.0)	39	NA 2 (5.1)	11.74 [2.84; 48.47]; < 0.001
including: neutropenia (PT, CTCAE grade 3–4)	100	NA [15.70; NC] 39 (39.0)	39	NA 0 (0)	–[f]; < 0.001
Skin and subcutaneous tissue disorders (SOC, AEs)	100	7.2 [4.44; 11.76] 56 (56.0)	39	NA [21.82; NC] 8 (20.5)	2.91 [1.38; 6.13]; 0.003

a. Median time to event and corresponding 95% CI were estimated using the Kaplan-Meier method.
b. Effect and CI: Cox proportional hazards model, stratified by the presence of liver and/or lung metastases according to IRT.
c. p-value: log-rank test stratified by the presence of liver and/or lung metastases according to IRT.
d. An increase by at least 10 points on the respective score was considered to be a clinically relevant deterioration if this also applied to all subsequent values or if the deterioration occurred at the patient's last documentation time.
e. Deaths were not recorded as deterioration.
f. Effect estimation not meaningfully interpretable.
g. A decrease by at least 10 points on the respective score was considered to be a clinically relevant deterioration if this also applied to all subsequent values or if the deterioration occurred at the patient's last documentation time.
h. Termination of therapy with ribociclib or placebo; termination of fulvestrant treatment alone was not allowed in the framework of the study.

Table 22: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy for the advanced stage) (multipage table)

Study Outcome category Outcome	Ribociclib + fulvestrant N	Ribociclib + fulvestrant Median time to event in months [95% CI][a] Patients with event n (%)	Placebo + fulvestrant N	Placebo + fulvestrant Median time to event in months [95% CI][a] Patients with event n (%)	Ribociclib + fulvestrant vs. placebo + fulvestrant HR [95% CI][b]; p-value[c]
AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; IRT: interactive response technology; 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; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus					

Based on the available data, at most an indication, e.g. of an added benefit, can be determined for the outcome "overall survival". For the other outcomes, there was a high risk of bias of the results (or in the case of discontinuation due to AEs, the certainty of results was limited); the outcome-specific certainty of conclusions of the results may not be downgraded, however (see description of the results below).

Mortality

The subpopulation B1 considered here showed no statistically significant difference between the treatment groups for the outcome "overall survival". This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant for this outcome; an added benefit is therefore not proven.

However, there was a specific data constellation for this outcome, which was considered in the overall consideration of the added benefit for subpopulation B1 (see Section 2.5.3.2).

This deviates from the company's assessment insofar as the company did not consider subpopulation B1 in a separate research question, and derived an added benefit for all postmenopausal patients on the basis of the total population of the MONALEESA-3 study.

Morbidity

Symptoms, recorded using the EORTC QLQ-C30 symptom scales

In the MONALEESA-3 study, symptom outcomes were recorded using the symptom scales of the EORTC QLQ-C30. The time to definitive deterioration by ≥ 10 points was considered in each case.

No statistically significant difference between the treatment groups was shown for any of the symptom scales of the EORTC QLQ-C30. In each case, this resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This concurs with the assessment of the company, which arrived at this result on the basis of the results of the total population, however.

Health status (EQ-5D VAS)

No usable analyses were available for the outcome "health status" recorded with the EQ-5D VAS (see Sections 2.4.2.1 and 2.5.2.2). This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This concurs with the assessment of the company, which arrived at this result on the basis of the results of the total population used by the company, however.

Pain (BPI-SF)

There were no usable analyses for the outcome "pain" recorded with the BPI-SF (see Sections 2.4.2.1 and 2.5.2.2). This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This concurs with the assessment of the company, which arrived at this result on the basis of the results of the total population used by the company, however.

Health-related quality of life

Global health status and functional scales recorded using the EORTC QLQ-C30

Health-related quality of life was recorded using the global health status and the functional scales of the EORTC QLQ-C30. The time to definitive deterioration by ≥ 10 points was considered in each case.

Emotional functioning

There was a statistically significant difference between the treatment groups for the symptom scale "emotional functioning". There was an effect modification by the characteristic "age", however. This resulted in a hint of an added benefit of ribociclib + fulvestrant in patients ≥ 65 years of age for emotional functioning. For patients < 65 years of age, there was no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

This assessment concurs with that of the company insofar as the company also derived an added benefit for emotional functioning on the basis of the results of the total population, but assumed a high certainty of results for this scale despite high risk of bias.

All other scales

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

This concurs with the company's assessment.

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 ribociclib + fulvestrant in comparison with fulvestrant for this outcome; greater or lesser harm is therefore not proven.

This deviates from the assessment of the company, which derived greater harm on the basis of the results for the total population.

Severe AEs (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib + fulvestrant was shown for the outcome "severe AEs (CTCAE grade 3–4)". This resulted in a hint of greater harm of ribociclib + fulvestrant in comparison with fulvestrant for this outcome.

This deviates from the assessment of the company, which derived greater harm on the basis of the results for the total population.

Discontinuation due to AEs

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

This deviates from the assessment of the company, which derived greater harm on the basis of the results for the total population.

Specific AEs

Severe AEs (CTCAE grade 3–4): blood and lymphatic system disorders (including: neutropenia)

A statistically significant difference to the disadvantage of ribociclib + fulvestrant in comparison with placebo + fulvestrant was shown for the specific severe AEs (CTCAE grade 3–4) "blood and lymphatic system disorders" (including: "neutropenia"). Due to the size of the observed effects in each case, and the early occurrence of the events in the course of the study (see Figure 44 and Figure 45 of the full dossier assessment), there was an indication of

greater harm of ribociclib + fulvestrant in comparison with fulvestrant for each of these outcomes despite the high risk of bias.

AEs: skin and subcutaneous tissue disorders

A statistically significant difference to the disadvantage of ribociclib + fulvestrant in comparison with placebo + fulvestrant was shown for the specific AE "skin and subcutaneous tissue disorders". This resulted in a hint of greater harm of ribociclib + fulvestrant in comparison with fulvestrant for this outcome.

This deviates from the assessment of the company, which considered other specific AEs.

2.5.2.4 Subgroups and other effect modifiers

The following subgroup characteristic was considered in the present 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.

The company considered the total population and did not use the results from the subgroup analyses for the derivation of an added benefit for it in any outcome.

The subgroup results of ribociclib + fulvestrant in comparison with placebo + fulvestrant are summarized in Table 23. The Kaplan-Meier curves on the event time analyses in the respective subgroups are presented in Appendix B.1 of the full dossier assessment.

Table 23: Subgroups (health-related quality of life) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy for the advanced stage)

Study Outcome	Ribociclib + fulvestrant		Placebo + fulvestrant		Ribociclib + fulvestrant vs. placebo + fulvestrant	
Characteristic Subgroup	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95% CI][b]	p-value[c]
MONALEESA-3 (data cut-off 3 June 2019)						
EORTC QLQ-C30 global health status and functional scales, time to deterioration[d, e]						
Emotional functioning						
Age						
< 65 years	41	NA [11.3; NC] 12 (29.3)	23	28.0 [22.8; NC] 6 (26.1)	0.96 [0.35; 2.67]	0.944
≥ 65 years	59	NA [24.9; NC] 12 (20.3)	16	9.3 [1.9; 22.6] 9 (56.3)	0.19 [0.08; 0.48]	< 0.001
Total					Interaction:	0.012[f]

a. Median time to event and corresponding 95% CI were estimated using the Kaplan-Meier method.
b. Effect and CI: Cox proportional hazards model, stratified by the presence of liver and/or lung metastases according to IRT.
c. p-value: log-rank test stratified by the presence of liver and/or lung metastases according to IRT.
d. A decrease by at least 10 points on the respective score was considered to be a clinically relevant deterioration if this also applied to all subsequent values or if the deterioration occurred at the patient's last documentation time.
e. Deaths were not recorded as deterioration.
f. p-value on the interaction term treatment*subgroup characteristic in a Cox proportional hazards model.

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

Health-related quality of life

EORTC QLQ-C30 (functional scales)

Emotional functioning

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

This assessment concurs with that of the company insofar as the company also derived an added benefit for emotional functioning on the basis of the results of the total population, but assumed a high certainty of results for this scale despite high risk of bias.

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 [1].

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

2.5.3.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.5.2 (see Table 24).

Determination of the outcome category for the outcomes on 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.

Discontinuation due to AEs

For the current data cut-off from 3 June 2019, no information on the proportion of SAEs or severe AEs (CTCAE grade 3–4) was available for the outcome “discontinuation due to AEs”. In the first assessment A19-06 [3] on the earlier data cut-off (3 November 2017), the outcome “discontinuation due to AEs” was rated as serious/severe. This assessment was based on the fact that the events included in the outcome were mostly severe (CTCAE grade 3–4) in the total population. There was no information available that would justify a deviating classification for the present assessment. Hence, the outcome “discontinuation due to AEs” was allocated to the outcome category of serious/severe side effects.

The company did not allocate discontinuation due to AEs to an outcome category.

Specific AEs (skin and subcutaneous tissue disorders)

Most of the occurred events of the specific AE “skin and subcutaneous tissue disorders” were non-serious/non-severe. The outcome was therefore allocated to the outcome category “non-serious/non-severe side effects”.

The company did not allocate the specific AEs used for the present assessment to an outcome category, as it considered different specific AEs in its assessment.

Table 24: Extent of added benefit at outcome level – RCT, direct comparison: ribociclib + fulvestrant vs. fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy for the advanced stage) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ribociclib + fulvestrant vs. fulvestrant** **Median time to event (months) or proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	NA vs. 35.4 HR: 0.70 [0.40; 1.24] p = 0.226	Lesser benefit/added benefit not proven
Morbidity		
Symptoms		
EORTC QLQ-C30 symptom scales, time to definitive deterioration		
Fatigue	38.7 vs. 28.0 HR: 0.90 [0.42; 1.93] p = 0.779	Lesser benefit/added benefit not proven
Nausea/vomiting	NA vs. NA HR: 0.21 [0.02; 2.38] p = 0.165	Lesser benefit/added benefit not proven
Pain	NA vs. NA HR: 0.61 [0.27; 1.36] p = 0.227	Lesser benefit/added benefit not proven
Dyspnoea	NA vs. 35.9 HR: 0.29 [0.06; 1.50] p = 0.120	Lesser benefit/added benefit not proven
Insomnia	NA vs. NA HR: 0.80 [0.25; 2.62] p = 0.714	Lesser benefit/added benefit not proven
Appetite loss	NA vs. NA Proportions of events: 3.0% vs. 0% HR: –[c] p = 0.357	Lesser benefit/added benefit not proven[d]
Constipation	NA vs. NA HR: 0.36 [0.05; 2.61] p = 0.291	Lesser benefit/added benefit not proven
Diarrhoea	NA vs. NA Proportions of events: 0% vs. 0% HR: – p: –	Lesser benefit/added benefit not proven

Table 24: Extent of added benefit at outcome level – RCT, direct comparison: ribociclib + fulvestrant vs. fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy for the advanced stage) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ribociclib + fulvestrant vs. fulvestrant** **Median time to event (months) or proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Health status		
EQ-5D VAS	No usable data	
Pain		
BPI-SF	No usable data	
Health-related quality of life		
EORTC QLQ-C30 global health status and functional scales, time to definitive deterioration		
Global health status	NA vs. 16.7 HR: 0.53 [0.28; 1.02] p = 0.056	Lesser benefit/added benefit not proven
Physical functioning	38.7 vs. 16.7 HR: 0.52 [0.26; 1.07] p = 0.072	Lesser benefit/added benefit not proven
Role functioning	30.5 vs. 24.9 HR: 0.93 [0.43; 1.99] p = 0.873	Lesser benefit/added benefit not proven
Emotional functioning Age < 65 years	NA vs. 28.0 HR: 0.96 [0.35; 2.67] p = 0.944	Lesser benefit/added benefit not proven
≥ 65 years	NA vs. 9.3 HR: 0.19 [0.08; 0.48] p < 0.001 probability: “hint”	Outcome category: health-related quality of life CI_u < 0.75, risk ≥ 5% added benefit, extent: “major”
Cognitive functioning	35.9 vs. 30.4 HR: 1.15 [0.49; 2.65] p = 0.760	Lesser benefit/added benefit not proven
Social functioning	38.7 vs. 16.7 HR: 0.51 [0.26; 1.02] p = 0.054	Lesser benefit/added benefit not proven
Side effects		
SAEs	38.5 vs. NA HR: 2.06 [0.86; 4.95] p = 0.099	Greater/lesser harm not proven

Table 24: Extent of added benefit at outcome level – RCT, direct comparison: ribociclib + fulvestrant vs. fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy for the advanced stage) (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ribociclib + fulvestrant vs. fulvestrant** **Median time to event (months) or proportion of events (%) or MD** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Severe AEs (CTCAE grade 3–4)	1.7 vs. NA HR: 3.94 [2.08; 7.46] HR: 0.25 [0.13; 0.48][e] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Discontinuation due to AEs[f]	NA vs. NA HR: 4.73 [1.11; 20.12] HR: 0.21 [0.05; 0.90][e] p = 0.021	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Blood and lymphatic system disorders (SOC, CTCAE grade 3–4)	15.7 vs. NA HR: 11.74 [2.84; 48.47] HR: 0.09 [0.02; 0.35][e] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
including: neutropenia (PT, CTCAE grade 3–4)	NA vs. NA Proportions of events: 39.0% vs. 0% HR: –[c, d] p < 0.001 probability: "indication"	
Skin and subcutaneous tissue disorders (SOC, AEs)	7.2 vs. NA HR: 2.91 [1.38; 6.13] HR: 0.34 [0.16; 0.72][e] p = 0.003 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Effect estimation not meaningfully interpretable.
d. The p-value is decisive for the derivation of the added benefit.
e. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
f. Termination of therapy with ribociclib or placebo; termination of fulvestrant treatment alone was not allowed in the framework of the study.

AE: adverse event; BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; MD: difference of the mean change over time; NA: not achieved; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.5.3.2 Overall conclusion on added benefit

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

Table 25: Positive and negative effects from the assessment of ribociclib in combination with aromatase inhibitors in comparison with the comparator fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy for the advanced stage)

Positive effects	**Negative effects**
Health-related quality of life ▪ Emotional functioning ▫ age (≥ 65 years): hint of added benefit – extent: "major"	Serious/severe side effects ▪ Severe AEs (CTCAE grade 3–4): hint of greater harm – extent: "major" ▪ Discontinuation due to AEs: hint of greater harm – extent "minor" ▪ Specific AEs (CTCAE grade 3–4): ▫ blood and lymphatic system disorders (including: neutropenia): indication of greater harm – extent: "major"
–	Non-serious/non-severe side effects ▪ Specific AEs: ▫ skin and subcutaneous tissue disorders: hint of greater harm – extent: "considerable"
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events	

The overall consideration showed a positive effect of major extent for the functional scale of emotional functioning in the outcome category of health-related quality of life, but only for patients aged 65 years and older. This was accompanied by mostly severe side effects (CTCAE grade 3–4) of considerable or major extent for patients both aged 65 years and older and younger than 65 years.

Side effects in the present subpopulation B1 were particularly evident in severe AEs (CTCAE grade 3–4). There was a hint of greater harm with the extent "major" for the superordinate AE outcome "severe AEs (CTCAE grade 3–4)". In particular, these were severe blood and lymphatic system disorders, including mainly neutropenia (indication of greater harm of major extent).

If only the results of the subpopulation were considered, balancing benefit and harm would initially result in lesser benefit of ribociclib + fulvestrant versus fulvestrant. In the present specific data constellation, however, the results of the total population of the MONALEESA-3 study were additionally considered in the overall consideration. In the total population of the MONALEESA-3 study, a statistically significant effect in favour of ribociclib + fulvestrant was shown for the outcome "overall survival". At the present data cut-off, 78% of the deaths planned for the final analysis had been reached (275 of 351). The subpopulation B1 comprised only 19% of the study population. However, there was a consistency of the direction of the effect and the position of the point estimations between the subpopulations A1 and B1 available here. The situation was similar already at the earlier data cut-off of the first assessment, which was

based on a notably lower number of deaths (see Appendix D.2, Table 43, of the full dossier assessment). In the present data constellation, no lesser benefit was derived in the overall consideration despite the clear negative effects.

In summary, there is therefore no hint of an added benefit of ribociclib in combination with fulvestrant versus the comparator fulvestrant for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer who have received prior endocrine therapy; an added benefit is therefore not proven.

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

2.6 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of ribociclib in combination with fulvestrant in comparison with fulvestrant is summarized in Table 26.

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

Subindication	**ACT[a]**	**Probability and extent of added benefit**
Women with HR-positive, HER2-negative advanced/metastatic breast cancer[b]		
A1: postmenopausal women, initial endocrine therapy	Anastrozole or letrozole or fulvestrant or, if applicable, tamoxifen if aromatase inhibitors are unsuitable	Indication of minor added benefit[d]
B1: postmenopausal women who have received prior endocrine therapy	Another endocrine therapy in dependence on the pretreatment with: ▪ tamoxifen or ▪ anastrozole or ▪ fulvestrant; only for patients with recurrence or progression following anti-oestrogen therapy[c] or ▪ letrozole; only for patients with recurrence or progression following anti-oestrogen therapy or ▪ exemestane; only for patients with progression following anti-oestrogen therapy or ▪ everolimus in combination with exemestane; only for patients without symptomatic visceral metastases who have progressed after a non-steroidal aromatase inhibitor	Added benefit not proven[d]

a. Presentation of the respective ACT specified by the G-BA.
b. It is assumed for the present therapeutic indications that (if applicable, another) endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
c. In therapeutic indication B1, the approval of fulvestrant provides for use of the drug only after prior anti-oestrogen therapy. In this respect, there is a discrepancy with the use of fulvestrant recommended in guidelines and established in health care, which do not focus exclusively on previous therapy with anti-oestrogens, but also on previous therapy with aromatase inhibitors. In this special therapeutic and health care situation, the G-BA sees a medical reason that, in the present case, exceptionally justifies considering fulvestrant as a comparator.
d. The MONALEESA-3 study only contains data on the comparison with fulvestrant. In addition, only patients with an ECOG PS of 0 or 1 were included. It remains unclear whether the observed results can be transferred to patients with an ECOG PS of ≥ 2. Almost all patients included in the study had stage IV disease (breast cancer with distant metastasis).

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 assessment described above deviates from that of the company, which derived considerable added benefit with high certainty of conclusions for the total population of postmenopausal patients without differentiating between lines of treatment.

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.

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

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