IQWiG Reports – Commission No. A19-06

Ribociclib (breast cancer) –

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

Extract

[1] Translation of Sections 2.1 to 2.8 of the dossier assessment *Ribociclib (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 April 2019). 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
EMA	European Medicines Agency
EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module
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)
NSAI	nonsteroidal aromatase inhibitor
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
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 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. 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 14 January 2019.

Research question

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

Depending on the line of treatment and the menopausal status of the patients, the G-BA distinguished between 4 different treatment situations and specified different ACTs for each of them. This resulted in 4 research questions for the present benefit assessment, each of which comprises the combination of ribociclib with aromatase inhibitors and the combination of ribociclib with fulvestrant. The research questions are shown in Table 2.

The present benefit assessment was carried out in the course of an extension of the therapeutic indication of ribociclib. The assessment of the added benefit of ribociclib as initial endocrine therapy in combination with an aromatase inhibitor in postmenopausal women was the subject of benefit assessment A17-45.

Table 2: Research questions of the benefit assessment of ribociclib

Research question	Subindication	ACT[a]
Women with HR-positive, HER2-negative locally advanced/metastatic breast cancer[b]		
A1	Postmenopausal women, initial endocrine therapy ▪ in combination with fulvestrant	Anastrozole or letrozole or fulvestrant or, if applicable, tamoxifen if aromatase inhibitors are unsuitable
A2	Pre- and perimenopausal women, initial endocrine therapy ▪ in combination with fulvestrant ▪ in combination with aromatase inhibitor	Tamoxifen in combination with suppression of the ovarian function
B1	Postmenopausal women who have received prior endocrine therapy ▪ in combination with fulvestrant ▪ in combination with aromatase inhibitor	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
B2	Pre- and perimenopausal women who have received prior endocrine therapy ▪ in combination with fulvestrant ▪ in combination with aromatase inhibitor	Endocrine therapy specified by the physician under consideration of the respective approval[d] Tamoxifen, letrozole, exemestane, megestrol acetate and medroxyprogesterone acetate are approved in the present therapeutic indication.

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 comparison.
d: It is assumed that ovarian suppression with a GnRH analogue is continued in the therapeutic indication B2. The available evidence for megestrol acetate and medroxyprogesterone acetate in the therapeutic indication B2 is considered inadequate for a concrete recommendation. In addition, the progestogens are explicitly approved only for the palliative treatment of breast cancer. It is assumed that there has been a change in treatment with respect to the drugs used for initial endocrine therapy.

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

The company followed the G-BA in the choice of the ACT for the research questions A1, B1 and B2. Deviating from the G-BA, the company considered letrozole and anastrozole as suitable comparator therapies besides tamoxifen for research question A2. This approach was inadequate. Hence, tamoxifen in combination with suppression of the ovarian function is the ACT for research question A2.

In the present assessment, "initial endocrine therapy" refers to the first-line treatment for the advanced or metastatic disease stage.

The subdivision according to lines of treatment for the advanced stage does not at first make any statement about a possible (neo)adjuvant therapy for an earlier disease stage. The present benefit assessment also comprises patients with (neo)adjuvant pretreatment. In their entirety, these patients cannot be clearly attributed to one research question. In these patients, the type of prior therapy is to be considered if recurrence occurred during or shortly after the end of (neo)adjuvant therapy. In this situation, not all options of the ACT are equally suitable in case of initial endocrine therapy.

The company presented analyses in which patients whose (neo)adjuvant therapy was terminated more than 12 months before the diagnosis of a recurrence were allocated to the group with initial endocrine therapy. Patients with recurrence during or ≤ 12 months after completion of (neo)adjuvant endocrine therapy were allocated to the group with prior endocrine therapy, even if they were in first-line therapy for the advanced stage. This approach is adequate and was used for the present benefit assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results on added benefit

Evidence provided by the company

The company presented data only for part of the possible drug combinations. Table 3 shows an overview of the data presented by the company.

Table 3: Data presented by the company on the individual research questions

Research question G-BA	Subindication	Data presented by the company
Women with HR-positive, HER2-negative advanced or metastatic breast cancer		
A1	Postmenopausal women, initial endocrine therapy ▪ in combination with fulvestrant	 ▪ RCT (MONALEESA-3)
A2	Pre- and perimenopausal women, initial endocrine therapy ▪ in combination with aromatase inhibitor ▪ in combination with fulvestrant	 ▪ RCT (MONALEESA-7) ▪ No data
B1	Postmenopausal women who have received prior endocrine therapy ▪ in combination with aromatase inhibitor ▪ in combination with fulvestrant	 ▪ No data ▪ RCT (MONALEESA-3)
B2	Pre- and perimenopausal women who have received prior endocrine therapy ▪ in combination with aromatase inhibitor ▪ in combination with fulvestrant	 ▪ RCT (MONALEESA-7) ▪ No data
HER2: human epidermal growth factor receptor 2; HR: hormone receptor; RCT: randomized controlled trial		

The studies presented by the company were not relevant for all research questions. Details can be found in the sections on the individual research questions.

Research question A1 (postmenopausal women, initial endocrine therapy)

Study pool and study characteristics

The MONALEESA-3 study was included in the benefit assessment for research question A1.

The MONALEESA-3 study was a randomized controlled trial (RCT) comparing a combination of ribociclib + fulvestrant with placebo + fulvestrant. A total of 726 patients 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. Group allocation was stratified according to the presence of lung and liver metastases (yes/no) and prior endocrine therapy. All women in the study were postmenopausal.

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).

Only the subpopulation of patients with initial endocrine therapy was relevant for the assessment of the added benefit in research question A1. All other study participants constituted another subpopulation, which was considered in research question B1 (patients who have already received endocrine therapy).

Treatment was administered continuously in 28-day cycles until disease progression. 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.

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes at study level was low. The outcome-specific risk of bias was low only for the outcomes "overall survival" and "discontinuation due to AEs". All patient-reported outcomes, overall rates of serious AEs (SAEs) and severe AEs, as well as specific AEs, were affected by the different durations of observation periods in the treatment arms, and the results for these outcomes had a high risk of bias.

Results

Mortality – overall survival

The subpopulation considered here showed no statistically significant difference between the treatment groups for the outcome "overall survival".

In the present data situation, the results for the outcome "overall survival" in the total population were additionally used for the derivation of the added benefit. A statistically significant difference in favour of ribociclib was shown here, which would result in an indication of an added benefit for the total population. Due to the consistency of the direction of the effect and the position of the point estimates between the subpopulations A1 and B1 as well as of the total population of the MONALEESA-3 study, it is justified in the present data situation to transfer the results of the total population to the subpopulation when interpreting the results. Hence, a hint of an added benefit was derived in research question A1 for the outcome "overall survival" in this data constellation.

Morbidity – symptoms, recorded using the EORTC QLQ-C30 (symptom scales)

No statistically significant difference between the treatment groups was shown for any of the symptom scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30). This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant. Hence, an added benefit of ribociclib + fulvestrant is not proven for the outcomes of disease-specific symptoms.

Morbidity – health status (EQ-5D VAS)

There were no usable data for the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions questionnaire (EQ-5D) for the relevant subpopulation.

Morbidity – pain (BPI-SF)

There were no usable data for the Brief Pain Inventory-Short Form (BPI-SF) questionnaire for the relevant subpopulation.

Health-related quality of life – EORTC QLQ-C30 (functional scales)

No statistically significant difference between the treatment groups was shown for any of the functional scales of the EORTC QLQ-C30. This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant. Hence, an added benefit of ribociclib + fulvestrant is not proven for the outcomes of health-related quality of life.

Side effects – serious adverse events, severe adverse events and discontinuation due to adverse events

A statistically significant difference to the disadvantage of ribociclib was shown for each of the following outcomes: SAEs, severe AEs (Common Terminology Criteria for Adverse Events [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 in an indication of greater harm for severe AEs and discontinuation due to AEs.

Side effects – blood and lymphatic system disorders (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib was shown for the outcome "severe blood and lymphatic system disorders". Due to the size of the effect, there was an indication of greater harm of ribociclib + fulvestrant in comparison with fulvestrant despite the high risk of bias.

Research question A2 (pre- and perimenopausal women, initial endocrine therapy)

The company assessed the added benefit for pre- and perimenopausal women based on the MONALEESA-7 study (see section on research question B2 for a description of the study). This study investigated the comparison of ribociclib + aromatase inhibitor versus aromatase inhibitor; the company presented no data on the comparison of ribociclib + fulvestrant.

The MONALEESA-7 study comprised both women with initial endocrine therapy and women with progression under prior (neo)adjuvant endocrine therapy. Only some of the included patients can be allocated to the present research question based on their prior therapies.

In the MONALEESA-7 study, ribociclib was combined either with an aromatase inhibitor (letrozole or anastrozole) or with tamoxifen. The combination of ribociclib with tamoxifen is not approved, however. The tamoxifen combination was administered in about 26% of the total study population, and in 36% within the subpopulation with initial endocrine therapy. Hence, only the subgroup of patients treated with an aromatase inhibitor could be used for the assessment of research question A2.

The company specified tamoxifen as ACT for pre- and perimenopausal women receiving initial endocrine therapy. A relevant comparison for the derivation of the added benefit therefore requires the combination of ribociclib + aromatase inhibitor (or fulvestrant) as intervention and tamoxifen as comparator therapy. No such randomised comparison was available, however. Hence, no relevant data were available for the derivation of an added benefit of ribociclib + aromatase inhibitor in pre- and perimenopausal patients receiving initial endocrine therapy.

The company presented no data for the combination of ribociclib + fulvestrant for research question A2. This resulted in no hint of an added benefit of ribociclib + aromatase inhibitor and for ribociclib + fulvestrant in comparison with the ACT for this research question. An added benefit for research question A2 is not proven.

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

Study pool and study characteristics

The MONALEESA-3 study was included in the benefit assessment for research question B1. This study investigated the comparison of ribociclib + fulvestrant versus fulvestrant; the company presented no data on the comparison of ribociclib + aromatase inhibitor. The subpopulation of women with prior endocrine therapy was relevant for the assessment.

The relevant subpopulation comprised 236 women in the ribociclib arm and 109 women in the comparator arm (2:1 randomization). This corresponds to almost half of the 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. Hence, it is no ACT for a majority of the patients in this subpopulation. The study was therefore unsuitable to derive an added benefit of ribociclib for research question B1. In accordance with the G-BA's note on the ACT, however, studies in which fulvestrant was also used after pretreatment with aromatase inhibitors were also considered. The results of this subpopulation are therefore described below.

Risk of bias and certainty of conclusions of the results

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

Results

Mortality – overall survival

The subpopulation considered here showed no statistically significant difference between the treatment groups for the outcome "overall survival". The total population of the MONALEESA-3 study showed a statistically significant difference in favour of ribociclib for this outcome. Due to the consistency of the direction of the effect and the position of the point estimates between the subpopulations A1 and B1 as well as of the total population of the MONALEESA-3 study, it is justified in the present data situation to transfer the results of the total population to the subpopulation when interpreting the results. Hence, an advantage of ribociclib was derived in research question B1 for the outcome "overall survival" in this data constellation.

Side effects – severe adverse events (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib + fulvestrant versus fulvestrant was shown for the outcome "severe AEs". Due to the size of the effect, there was a high certainty of results for this outcome despite high risk of bias.

Side effects – discontinuation due to adverse events

A statistically significant difference to the disadvantage of ribociclib + fulvestrant versus fulvestrant was shown for the outcome "discontinuation due to AEs".

Side effects – blood and lymphatic system disorders (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib + fulvestrant versus fulvestrant was shown for the outcome "severe blood and lymphatic system disorders". Due to the size of the effect, there was a high certainty of results for this outcome despite high risk of bias.

Other outcomes

There were no statistically significant differences for all other outcomes of the categories "mortality", "morbidity", "health-related quality of life" and "side effects".

Research question B2 (pre- and perimenopausal women who have received prior endocrine therapy)

The MONALEESA-7 study was included in the benefit assessment for research question B2. This study investigated the comparison of ribociclib + aromatase inhibitor versus aromatase inhibitor; the company presented no data on the comparison of ribociclib + fulvestrant.

Study pool and study characteristics

MONALEESA-7 is an RCT comparing a combination of ribociclib + nonsteroidal aromatase inhibitor (NSAI) or ribociclib + tamoxifen with placebo + NSAI or placebo + tamoxifen. A total of 672 patients with HR-positive, HER2-negative, advanced or metastatic breast cancer were included. Randomization was in a 1:1 ratio and was stratified according to the presence of liver or lung metastases (yes/no), prior chemotherapy for advanced disease (yes/no) and endocrine combination partner (tamoxifen + goserelin or NSAI + goserelin). All patients in the study were pre- or perimenopausal. Their tumours had to be not amenable to resection or radiotherapy with curative intent. In addition, the patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1 at baseline.

The subpopulation of patients with recurrence during or ≤ 12 months after completion of (neo)adjuvant endocrine therapy were relevant for the assessment in research question B2. Patients with second-line treatment were not included in the study. The assessment considered these patient groups to be similar as the same ACT (letrozole) was adequate for both.

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

Risk of bias and certainty of conclusions of the results for research question B2

The outcome-specific risk of bias in the MONALEESA-7 study was low only for the outcomes "overall survival" and "discontinuation due to AEs". All patient-reported outcomes, overall rates of SAEs and severe AEs, as well as specific AEs, were affected by the different durations of observation periods in the treatment arms. In addition, there was no information on observation periods for both relevant subpopulations of the study. Hence, it cannot be assessed whether differences in observation periods were even more or possibly less pronounced in a subpopulation.

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

Mortality – overall survival

There was no statistically significant difference between the treatment groups for the outcome "overall survival". This resulted in no hint of an added benefit of ribociclib + letrozole in comparison with letrozole. An added benefit for this outcome is therefore not proven.

Morbidity – symptoms, recorded using the EORTC QLQ-C30 and the EORTC QLQ-BR23 (symptom scales)

Symptom outcomes were recorded with the symptom scales of the disease-specific instruments EORTC QLQ-C30 and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module (EORTC QLQ-BR23). In each case, the proportion of patients with definitive deterioration by ≥ 10 points was considered.

Fatigue, pain, symptoms in the chest region

Statistically significant differences, each in favour of ribociclib + letrozole, were shown between the treatment groups for the outcomes "fatigue" and "pain". This resulted in a hint of an added benefit of ribociclib + letrozole in comparison with letrozole for both outcomes.

There was also a statistically significant difference in favour of ribociclib for the outcome "symptoms in the chest region". This effect was no more than marginal, however. This resulted in no hint of an added benefit of ribociclib + letrozole in comparison with letrozole for this outcome.

Nausea/vomiting, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, side effects of systemic treatment, symptoms in the arm region, upset by hair loss

No statistically significant difference between the treatment groups was shown for each of the following outcomes: nausea/vomiting, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, side effects of systemic treatment, and symptoms in the arm region. There were no usable data for the outcome "upset by hair loss". In each case, this resulted in no hint of an added benefit of ribociclib + letrozole in comparison with letrozole. An added benefit for these outcomes is therefore not proven.

Morbidity – health status (EQ-5D VAS)

There were no usable data for the VAS of the EQ-5D questionnaire for the relevant subpopulation.

Health-related quality of life – EORTC QLQ-C30 and EORTC QLQ-BR23 (functional scales)

A statistically significant difference between the treatment groups was only shown for one outcome in the functional scales of the EORTC questionnaires:

Future perspective

A statistically significant difference in favour of ribociclib + letrozole was shown for the outcome "future perspective". This resulted in a hint of an added benefit of ribociclib + letrozole in comparison with letrozole.

Further functional scales

No statistically significant differences between the treatment groups were shown for each of the following outcomes: general health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, body image, and sexual activity. There were no usable data for the outcome "enjoyment of sex". In each case, this resulted in no hint of an added benefit of ribociclib + letrozole in comparison with letrozole. An added benefit for these outcomes is therefore not proven.

Side effects – overall rate of serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs". This resulted in no hint of an added benefit of ribociclib + letrozole in comparison with letrozole. An added benefit for this outcome is therefore not proven.

Side effects – overall rate of severe adverse events (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib + letrozole was shown for the outcome "severe AEs". Due to the size of the effect, there was an indication of greater harm of ribociclib + letrozole in comparison with letrozole despite the high risk of bias.

Side effects – overall rate of discontinuations due to AEs

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of an added benefit of ribociclib + letrozole in comparison with letrozole. An added benefit for this outcome is therefore not proven.

Side effects – blood and lymphatic system disorders (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib + letrozole was shown for the outcome "severe blood and lymphatic system disorders". Due to the size of the effect, there was an indication of greater harm of ribociclib + letrozole in comparison with letrozole despite the high risk of bias.

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

On the basis of the results presented, probability and extent of the added benefit of the drug ribociclib compared with the ACT are assessed as follows:

Research question A1

On the one hand, there were advantages of ribociclib in the outcome category "mortality" and, on the other, disadvantages in the outcome category "serious/severe side effects" for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer in initial endocrine therapy.

In the overall assessment, there is a hint of a minor added benefit for the outcome "overall survival" and an indication of greater harm of major extent in severe and serious side effects.

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

Research question A2

No relevant data were available for research question A2.

Research question B1

Since there was no comparison of ribociclib with an ACT in the relevant subpopulation of the MONALEESA-3 study, an added benefit of ribociclib in research question B1 is not proven.

In summary, the results of the MONALEESA-3 study led to both advantages and disadvantages of ribociclib + fulvestrant in comparison with placebo + fulvestrant regarding the following outcomes:

- Advantage in mortality (overall survival)
- Disadvantages in AE outcomes:
  - Severe AEs (CTCAE grade 3–4), including particularly blood and lymphatic system disorders (neutropenia): Due to the size of the effect, there was a high certainty of results for this outcome despite high risk of bias.

[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].

- Discontinuation due to AEs

In the overall assessment, this resulted neither in an advantage nor in a disadvantage of ribociclib + fulvestrant in comparison with placebo + fulvestrant.

Research question B2

There was an indication of lesser benefit of ribociclib + letrozole versus letrozole for pre- and perimenopausal patients who have received prior endocrine therapy. This conclusion only refers to part of research question B2, i. e. pre- and perimenopausal patients with (neo)adjuvant tamoxifen pretreatment and with recurrence during or within 12 months after completion of (neo)adjuvant treatment.

Table 4 presents a summary of probability and extent of the added benefit of ribociclib.

Table 4: Ribociclib – 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	▪ *Combination with fulvestrant:* added benefit not proven
A2: pre- and perimenopausal women, initial endocrine therapy	Tamoxifen in combination with suppression of the ovarian function	▪ *Combination with fulvestrant:* added benefit not proven ▪ *Combination with aromatase inhibitor:* added benefit not proven
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[d] 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	▪ *Combination with fulvestrant:* added benefit not proven[c] ▪ *Combination with aromatase inhibitor:* added benefit not proven
B2: pre- and perimenopausal women who have received prior endocrine therapy	Endocrine therapy specified by the physician under consideration of the respective approval[e] Tamoxifen, letrozole, exemestane, megestrol acetate and medroxyprogesterone acetate are approved in the present therapeutic indication.	▪ *Combination with fulvestrant:* added benefit not proven ▪ *Combination with aromatase inhibitor:* ▫ indication of lesser benefit[f, g]

(continued)

Table 4: Ribociclib – probability and extent of added benefit (continued)

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 the overall assessment, the results of the MONALEESA-3 study led neither to an advantage nor to a disadvantage of ribociclib + fulvestrant versus placebo + fulvestrant.
d: 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 comparison.
e: It is assumed that ovarian suppression with a GnRH analogue is continued in the therapeutic indication B2. The available evidence for megestrol acetate and medroxyprogesterone acetate in the therapeutic indication B2 is considered inadequate for a concrete recommendation. In addition, the progestogens are explicitly approved only for the palliative treatment of breast cancer.
f: Only patients with an ECOG PS of 0 or 1 were included in the MONALEESA-7 study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
g: This conclusion only refers to part of research question B2, i. e. pre- and perimenopausal patients with (neo)adjuvant tamoxifen pretreatment and with recurrence during or within 12 months after completion of (neo)adjuvant treatment.
ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone

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 was to assess the added benefit of ribociclib in combination with an aromatase inhibitor or fulvestrant in comparison with the ACT in patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer.

Depending on the line of treatment and the menopausal status of the patients, the G-BA distinguished between 4 different treatment situations and specified different ACTs for each of them. This resulted in 4 research questions for the present benefit assessment, each of which comprises the combination of ribociclib with aromatase inhibitors and the combination of ribociclib with fulvestrant. The research questions are shown in Table 5.

The present benefit assessment was carried out in the course of an extension of the therapeutic indication of ribociclib. The assessment of the added benefit of ribociclib as initial endocrine therapy in combination with an aromatase inhibitor in postmenopausal women was the subject of benefit assessment A17-45 [3].

Table 5: Research questions of the benefit assessment of ribociclib

Research question	Subindication	ACT[a]
Women with HR-positive, HER2-negative locally advanced/metastatic breast cancer[b]		
A1	Postmenopausal women, initial endocrine therapy ▪ in combination with fulvestrant	Anastrozole or letrozole or fulvestrant or, if applicable, tamoxifen if aromatase inhibitors are unsuitable
A2	Pre- and perimenopausal women, initial endocrine therapy ▪ in combination with fulvestrant ▪ in combination with aromatase inhibitor	Tamoxifen in combination with suppression of the ovarian function
B1	Postmenopausal women who have received prior endocrine therapy ▪ in combination with fulvestrant ▪ in combination with aromatase inhibitor	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
B2	Pre- and perimenopausal women who have received prior endocrine therapy ▪ in combination with fulvestrant ▪ in combination with aromatase inhibitor	Endocrine therapy specified by the physician under consideration of the respective approval[d] Tamoxifen, letrozole, exemestane, megestrol acetate and medroxyprogesterone acetate are approved in the present therapeutic indication.

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 comparison.
d: It is assumed that ovarian suppression with a GnRH analogue is continued in the therapeutic indication B2. The available evidence for megestrol acetate and medroxyprogesterone acetate in the therapeutic indication B2 is considered inadequate for a concrete recommendation. In addition, the progestogens are explicitly approved only for the palliative treatment of breast cancer. It is assumed that there has been a change in treatment with respect to the drugs used for initial endocrine therapy.

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

The company followed the G-BA in the choice of the ACT for the research questions A1, B1 and B2. Deviating from the G-BA, the company considered letrozole and anastrozole as suitable comparator therapies besides tamoxifen for research question A2. This approach was inadequate (see Section 2.9.1 of the full dossier assessment). Hence, tamoxifen in combination with suppression of the ovarian function was the G-BA's ACT for research question A2.

In the present assessment, "initial endocrine therapy" refers to the first-line treatment for the advanced or metastatic disease stage.

The subdivision according to lines of treatment for the advanced stage does not at first make any statement about a possible (neo)adjuvant therapy for an earlier disease stage. The present benefit assessment also comprises patients with (neo)adjuvant pretreatment. In their entirety, these patients cannot be clearly attributed to one research question. In these patients, the type of prior therapy is to be considered if recurrence occurred during or shortly after the end of (neo)adjuvant therapy. In this situation, not all options of the ACT are equally suitable in case of initial endocrine therapy.

The company presented analyses in which patients whose (neo)adjuvant therapy was terminated more than 12 months before the diagnosis of a recurrence were allocated to the group with initial endocrine therapy. The company allocated patients with recurrence during or ≤ 12 months after completion of (neo)adjuvant endocrine therapy to the group with prior endocrine therapy, even if they were in first-line therapy for the advanced stage. This approach is adequate. A detailed description and explanation of the approach for patients with (neo)adjuvant pretreatment can be found in Section 2.9.3.2 of the full dossier assessment and in the descriptions of the studies assessed (see Sections 2.4.2 and 2.7.2).

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

Information retrieval

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

Sources of the company in the dossier:

- study list on ribociclib (status: 26 November 2018)
- bibliographical literature search on ribociclib (last search on 23 November 2018)
- search in trial registries for studies on ribociclib (last search on 23 November 2018)

To check the completeness of the study pool:

- search in trial registries for studies on ribociclib (last search on 24 January 2019)

The check identified no additional relevant study.

Evidence provided by the company

The company presented data only for part of the possible drug combinations. Table 6 shows an overview of the data presented by the company.

Table 6: Data presented by the company on the individual research questions

Research question G-BA	Subindication	Data presented by the company
Women with HR-positive, HER2-negative advanced or metastatic breast cancer		
A1	Postmenopausal women, initial endocrine therapy ▪ in combination with fulvestrant	 ▪ RCT (MONALEESA-3)
A2	Pre- and perimenopausal women, initial endocrine therapy ▪ in combination with aromatase inhibitor ▪ in combination with fulvestrant	 ▪ RCT (MONALEESA-7) ▪ No data
B1	Postmenopausal women who have received prior endocrine therapy ▪ in combination with aromatase inhibitor ▪ in combination with fulvestrant	 ▪ No data ▪ RCT (MONALEESA-3)
B2	Pre- and perimenopausal women who have received prior endocrine therapy ▪ in combination with aromatase inhibitor ▪ in combination with fulvestrant	 ▪ RCT (MONALEESA-7) ▪ No data
HER2: human epidermal growth factor receptor 2; HR: hormone receptor; RCT: randomized controlled trial		

The studies presented by the company were not relevant for all research questions. Further details can be found in Sections 2.4, 2.5, 2.6 and 2.7.

2.4 Research question A1: postmenopausal women, initial endocrine therapy

2.4.1 Studies included

The information retrieval of the company is described in Section 2.3. The study listed in the following table was included in the benefit assessment.

Table 7: Study pool – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women, initial endocrine therapy)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
MONALEESA-3	Yes	Yes	No
a: Study sponsored by the company. RCT: randomized controlled trial; vs.: versus			

Section 2.4.5 contains a reference list for the study included.

2.4.2 Study characteristics

Table 8 and Table 9 describe the study used for the benefit assessment.

Table 8: Characteristics of the study included – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women, initial endocrine therapy)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MONA-LEESA-3	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 for research question A1 (initial endocrine therapy): ribociclib + fulvestrant (n = 238) placebo + fulvestrant (n = 129)	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 data cut-off: after 364 PFS events (3 November 2017) Pending analyses: ▪ interim analysis after 263 deaths ▪ 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 exclusively 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 patients were randomized. One patient died before signing the consent and was not considered in the analyses.
d: Outcome-specific information is provided in Table 10.
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 9: Characteristics of the interventions – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women, initial endocrine therapy)

Study	Intervention	Comparison
MONALEESA-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: no endocrine therapy in the advanced stage, (neo)adjuvant therapy > 12 months before recurrence.

AE: adverse event; CDK: cyclin-dependent kinase; 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 726 patients with HR-positive, HER2-negative, advanced or metastatic breast cancer were included in a 2:1 randomization. Group allocation was 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 could be included 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. Patients who had relapsed within 12 months from completion of (neo)adjuvant therapy and progressed after endocrine first-line 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 ECOG PS of 0 or 1.

Only a subpopulation of the MONALEESA-3 study was relevant for the assessment of the added benefit (hereinafter referred to as "subpopulation A1"). Further details can be found below in the Section "Subpopulations of the MONALEESA-3 study relevant for the assessment".

According to the SPC, fulvestrant is used in patients not previously treated with endocrine therapy and in patients with disease relapse on or after adjuvant antioestrogen therapy [4]. This applies to 99 patients (77%) in the comparator arm of subpopulation A1. The most recent pretreatment of 29 patients (22%) in the comparator arm had been an aromatase inhibitor. These patients did not meet the preconditions for fulvestrant therapy. However, the G-BA named fulvestrant without restriction as ACT in this treatment situation. Hence, the total subpopulation was included for the derivation of the added benefit.

Treatment was administered continuously in 28-day cycles until disease progression. Apart from the pretreatment situation described above, the drugs used in the study were administered in compliance with the current SPCs [4,5]. Switching treatments, particularly from placebo to ribociclib, was not possible.

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 company derived the added benefit of ribociclib for postmenopausal patients on the basis of the total study population without differentiating between lines of treatment. This approach was inadequate. However, the G-BA distinguished between patients with initial endocrine therapy and patients with progression after prior endocrine therapy and partly specified different ACTs. In patients with prior endocrine therapy, fulvestrant is an ACT only under certain

conditions, i. e. after prior antioestrogen therapy. This condition was not met for pretreated patients in the MONALEESA-3 study. For this reason alone, the two subpopulations cannot be considered together. The added benefit of ribociclib is assessed separately for both subpopulations.

The company presented subgroup analyses in which it analysed the study population separately by prior endocrine therapy for the MONALEESA-3 study. The strata were:

- A: no treatment in the advanced setting
- B: at most one line of treatment in the advanced setting

Subpopulation A comprised:

  - patients who have never received endocrine therapy
  - patients who received a (neo)adjuvant endocrine therapy that must have been completed at least 12 months before diagnosis of recurrence

Subpopulation B comprised:

  - patients with recurrence during or ≤ 12 months after completion of (neo)adjuvant endocrine therapy
  - patients with recurrence > 12 months after completion of (neo)adjuvant endocrine therapy and another progression after (first-line) endocrine therapy for the advanced stage
  - patients with initial diagnosis of metastatic breast cancer who progressed after first-line endocrine therapy for this stage

This division was adopted for the present benefit assessment. See Section 2.9.3.2 of the full dossier assessment for more details. Hence, subpopulation A of the MONALEESA-3 study was used for the research question A1 considered here. All following information in this section refers to the relevant subpopulation of the study, unless otherwise noted.

Subpopulation B of the study is considered in research question B1 and is explained in detail in Section 2.6.

Data cut-offs

A first data cut-off was planned after 364 events of the primary outcome PFS and was conducted on 3 November 2017. The present assessment was based on this data cut-off. A further analysis of overall survival was to be conducted after the death of 263 patients, and a final analysis after 351 deaths.

Table 10 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 10: Planned duration of follow-up observation – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (total population)

Study **Outcome category** **Outcome**	**Planned follow-up observation**
MONALEESA-3	
Mortality	
Overall survival	Every 12 weeks until death, end of study, loss to follow-up or premature study discontinuation
Morbidity	
Symptoms (EORTC QLQ-C30, EQ-5D VAS)	Every 8 weeks in the first 18 months, then every 12 weeks until progression, death, withdrawal of consent, or loss to follow-up
Health-related quality of life	
EORTC QLQ-C30	Every 8 weeks in the first 18 months, then every 12 weeks until progression, death, withdrawal of consent, or loss to follow-up
Side effects	
All outcomes in the category “side effects”	Until up to 30 days after the end of treatment
AE: adverse event; 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 survival.

Characteristics of the study population

Table 11 shows the characteristics of the patients in the relevant subpopulation of the MONALEESA-3 study.

Table 11: Characteristics of the study population – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women, initial endocrine therapy)

Study Characteristics Category	**Ribociclib + fulvestrant**	**Placebo + fulvestrant**
MONALEESA-3	N[a] = 238	N[a] = 129
Age [years], mean (SD)	64.3 (9.68)	64.5 (9.65)
Region, n (%)		
Asia	24 (10.1)	10 (7.8)
Europe and Australia	154 (64.7)	91 (70.5)
Latin America	3 (1.3)	3 (2.3)
North America	45 (18.9)	20 (15.5)
Other	12 (5.0)	5 (3.9)
ECOG PS, n (%)		
0	142 (59.7)	90 (69.8)
1	96 (40.3)	39 (30.2)
Disease stage on study entry, n (%)		
II	1 (0.4)	0 (0.0)
III	2 (0.8)	2 (1.6)
IV	235 (98.7)	127 (98.4)
Disease-free interval, n (%)		
De novo	94 (39.5)	42 (32.6)
Not de novo	144 (60.5)	87 (67.4)
≤ 12 months	4 (1.7)	1 (0.8)
> 12 months	140 (58.8)	86 (66.7)
Previous drug treatment, n (%)		
No	109 (45.8)	48 (37.2)
Yes	129 (54.2)	81 (62.8)
Type of most recent treatment, n (%)		
Chemotherapy	13 (5.5)	14 (10.9)
Endocrine therapy	55 (23.1)	38 (29.5)
Radiotherapy	62 (26.1)	35 (27.1)
Surgery (not biopsy)	44 (18.5)	27 (20.9)
Other	0 (0.0)	1 (0.8)
Setting of most recent treatment, n (%)		
Adjuvant	90 (37.8)	62 (48.1)
Neoadjuvant	3 (1.3)	2 (1.6)
Therapeutic	5 (2.1)	3 (2.3)
Palliative	28 (11.8)	12 (9.3)
Not applicable[b]	44 (18.5)	27 (20.9)

(continued)

Table 11: Characteristics of the study population – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women, initial endocrine therapy) (continued)

Study Characteristics Category	Ribociclib + fulvestrant	Placebo + fulvestrant
Location of metastases, n (%)		
Soft tissue	13 (5.5)	9 (7.0)
Breast	1 (0.4)	0 (0.0)
Bone	177 (74.4)	90 (69.8)
Bone only	49 (20.6)	25 (19.4)
Visceral	137 (57.6)	77 (59.7)
Lung	84 (35.3)	45 (34.9)
Liver	47 (19.7)	23 (17.8)
Lung or liver	110 (46.2)	62 (48.1)
CNS	4 (1.7)	1 (0.8)
Other	50 (21.0)	27 (20.9)
Skin	11 (4.6)	4 (3.1)
Lymph nodes	117 (49.2)	67 (51.9)
None	2 (0.8)	0 (0.0)
Treatment discontinuation[c], n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a: Number of randomized patients in the relevant subpopulation. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Apparently, these are patients with surgery as their most recent treatment.
c: Discontinuation of entire study medication.
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

The subpopulation relevant for research question A1 showed no important imbalances between the treatment groups. The study population only consisted of women.

The mean age of the patients was 64 years and most of them were from Europe. With few exceptions, all patients were in the metastatic stage of the disease. Slightly more than a third were diagnosed only after the occurrence of metastases, almost all others were disease-free for more than 12 months after the resection of the primary tumour. At baseline, metastases were mainly present in the lymph nodes, lungs, liver or bones.

The most recent treatment before baseline was endocrine therapy or radiotherapy, each in about one quarter of the patients. Surgery was the most recent intervention in just under one fifth of the patients. Chemotherapy was not common (< 8%).

Table 12 shows the mean/median treatment duration of the patients and the mean/median observation period for individual outcomes. This information was only available for the total population of the MONALEESA-3 study.

Table 12: Information on the course of the study – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (total population)

Study **Duration of the study phase** **Outcome category**	**Ribociclib + fulvestrant**	**Placebo + fulvestrant**
MONALEESA-3	N = 483	N = 241
Treatment duration[a] [months]		
Median [min; max]	15.8 [0.9; 27.4]	12.0 [0.9; 25.9]
Mean (SD)	13.3 (7.90)	11.9 (7.75)
Observation period [months]		
Overall survival		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Symptoms/health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	13.7 [−0.7; 25.9][b]	11.1 [−0.2; 24.9][b]
Mean (SD)	12.0 (7.73)	10.6 (7.62)
Side effects		
Median [min; max]	16.6 [1.0; 27.5]	12.3 [1.0; 25.9]
Mean (SD)	13.6 (7.77)	12.3 (7.58)

a: The information on treatment duration refers to any study medication.
b: Negative numbers in the observation period are due to the fact that the recording of patient-reported outcomes was first conducted at screening with the time point of randomization serving as reference.
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; max.: maximum; min: minimum; N: number of patients; NA: not achieved; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The median treatment duration for the total population was about 25% longer in the ribociclib arm than in the placebo arm. The observation periods of most relevant outcomes differed between the study arms in a comparable magnitude. This is due to the fact that patient-reported outcomes were only observed until progression, and AEs up to 30 days after the end of treatment.

Risk of bias across outcomes (study level)

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

Table 13: Risk of bias across outcomes (study level) – RCT, direct comparison: 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							

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

2.4.3 Results on added benefit

2.4.3.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.9.4.3.2 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms, recorded with the EORTC QLQ-C30 symptom scales
  - health status, measured using the EQ-5D VAS
  - pain, recorded using the BPI-SF
- Health-related quality of life
  - EORTC QLQ-C30 (functional scales)
- Side effects
  - overall rate of SAEs
  - overall rate of severe AEs (CTCAE grade 3–4)
  - overall rate of discontinuations due to AEs
  - blood and lymphatic system disorders (System Organ Class [SOC]; CTCAE grade 3–4)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4 A) (see Section 2.9.4.3.2 of the full dossier assessment).

Table 14 shows for which outcomes data were available in the study included.

Table 14: Matrix of outcomes – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women, initial endocrine therapy)

Study	Outcomes								
	Overall survival	EORTC QLQ-C30 (symptom scales)	Health status (EQ-5D VAS)	Pain (BPI-SF)	Health-related quality of life (EORTC QLQ-C30, functional scales)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3–4)	Blood and lymphatic system disorders (SOC; CTCAE grade 3–4)
MONALEESA-3	Y	Y	No[a]	No[a]	Y	Y	Y	Y	Y

a: 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; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus; Y: yes

2.4.3.2 Risk of bias

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

Table 15: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women, initial endocrine therapy)

Study	Study level	Outcomes								
		Overall survival	EORTC QLQ-C30 (symptom scales)	Health status (EQ-5D VAS)	Pain (BPI-SF)	Health-related quality of life (EORTC QLQ-C30, functional scales)	SAEs	Discontinuation due to AEs[a]	Severe AEs (CTCAE grade 3–4)	Blood and lymphatic system disorders (SOC, CTCAE grade 3–4)
MONALEESA-3	L	L	H[b]	-[c]	-[c]	H[b]	H[b]	L	H[b]	H[b]

a: Defined as AEs that have led to the discontinuation of treatment with ribociclib or placebo.
b: Differences in the observation periods between the treatment arms with potentially informative censoring in the total population; data on the observation periods for subpopulations A1 and B1 were not available.
c: No usable data available for the relevant subpopulation; see Section 2.9.4.3.2 of the full dossier assessment.
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; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

The outcome-specific risk of bias in the MONALEESA-3 study was low only for the results on the outcomes "overall survival" and "discontinuation due to AEs". The results on all patient-reported outcomes, overall rates of SAEs and severe AEs, as well as specific AEs, were affected by the different durations of observation periods in the treatment arms with potentially informative censoring. It should also be noted that no information was available on the observation periods for the relevant subpopulation A1 of the study. Hence, an unequivocal assessment of whether differences in observation periods were even more or possibly less pronounced in a subpopulation is not possible.

This largely concurs with the assessment of the company, which saw a high risk of bias also for the results on the outcome "discontinuation due to AEs", however.

2.4.3.3 Results

Table 16 summarizes the results for the comparison of ribociclib + fulvestrant with fulvestrant as initial endocrine therapy in patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. Results on common AEs, SAEs and severe AEs (CTCAE grade 3–4) are presented in Appendix B.1 of the full dossier assessment. Kaplan-

Meier curves on the presented event time analyses can be found in Appendix C.1 of the full dossier assessment.

Table 16: (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women, initial endocrine therapy)

Study **Outcome category**	**Ribociclib + fulvestrant**		**Placebo + fulvestrant**		**Ribociclib + fulvestrant vs. placebo + fulvestrant**
Outcome **Time point**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI][a]; p-value[b]**
MONALEESA-3					
First data cut-off 3 November 2017					
Mortality					
Overall survival	238	NA [NA; NA] 19 (8.0)	129	NA [NA; NA] 17 (13.2)	0.61 [0.31; 1.17]; 0.129
Morbidity					
Symptoms					
EORTC QLQ-C30 (symptom scales)[c]					
Fatigue	238	NA [22.1; NA] 57 (23.9)	129	NA [19.4; NA] 30 (23.3)	1.00 [0.64; 1.56]; 0.999
Nausea/ vomiting	238	NA [NA; NA] 10 (4.2)	129	NA [NA; NA] 3 (2.3)	1.66 [0.45; 6.08]; 0.435
Pain	238	NA [22.3; NA] 38 (16.0)	129	NA [NA; NA] 15 (11.6)	1.34 [0.74; 2.45]; 0.332
Dyspnoea	238	NA [NA; NA] 10 (4.2)	129	NA [NA; NA] 8 (6.2)	0.66 [0.26; 1.66]; 0.370
Insomnia	238	NA [NA; NA] 16 (6.7)	129	NA [24.9; NA] 8 (6.2)	1.05 [0.45; 2.45]; 0.914
Appetite loss	238	NA [NA; NA] 15 (6.3)	129	NA [NA; NA] 3 (2.3)	2.73 [0.79; 9.43]; 0.097
Constipation	238	NA [NA; NA] 10 (4.2)	129	NA [NA; NA] 4 (3.1)	1.28 [0.40; 4.09]; 0.682
Diarrhoea	238	NA [NA; NA] 6 (2.5)	129	NA [NA; NA] 0 (0)	-[d]; 0.083
Health status					
EQ-5D VAS	No usable data				
Pain					
BPI-SF	No usable data				

(continued)

Table 16: (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women, initial endocrine therapy) (continued)

Study Outcome category	Ribociclib + fulvestrant		Placebo + fulvestrant		Ribociclib + fulvestrant vs. placebo + fulvestrant
Outcome Time point	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value[b]
Health-related quality of life					
EORTC QLQ-C30 (general health status and functional scales)[f]					
General health status	238	NA [22.1; NA] 56 (23.5)	129	22.4 [17.0; NA] 40 (31.0)	0.73 [0.48; 1.09]; 0.124
Physical functioning	238	NA [20.4; NA] 60 (25.2)	129	NA [19.5; NA] 29 (22.5)	1.09 [0.70; 1.70]; 0.693
Role functioning	238	NA [22.1; NA] 57 (23.9)	129	NA [22.3; NA] 25 (19.4)	1.22 [0.76; 1.95]; 0.415
Emotional functioning	238	22.3 [22.1; NA] 60 (25.2)	129	22.4 [19.6; NA] 31 (24.0)	1.02 [0.66; 1.57]; 0.941
Cognitive functioning	238	NA [20.3; NA] 64 (26.9)	129	22.4 [22.4; NA] 32 (24.8)	1.12 [0.73; 1.72]; 0.602
Social functioning	238	NA [NA; NA] 49 (20.6)	129	NA [22.1; NA] 24 (18.6)	1.12 [0.69; 1.83]; 0.650
Side effects					
AEs (additional information)	238	ND 235 (98.7)	129	ND 123 (95.3)	–
SAEs	238	NA [NA; NA] 62 (26.1)	129	NA [NA; NA] 18 (14.0)	1.91 [1.13; 3.22]; 0.014
Severe AEs (CTCAE grade ≥ 3)	238	1.9 [1.51; 3.12]; 184 (77.3)	129	NA [20.30; NA] 34 (26.4)	5.10 [3.53; 7.38]; < 0.001
Discontinuation due to AEs[g]	238	NA [26.02; NA] 38 (16.0)	129	NA [NA; NA] 8 (6.2)	2.58 [1.20; 5.55]; 0.012
Blood and lymphatic system disorders (SOC, CTCAE grade 3–4)	238	19.3 [10.18; NA] 107 (45.0)	129	NA [NA; NA] 0 (0.0)	-[d]; < 0.001
Including:	238	ND	129	ND	-
Neutropenia (PT, CTCAE grade 3–4)		105 (44.1)		0 (0.0)	

(continued)

Table 16: (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women, initial endocrine therapy) (continued)

a: Cox proportional hazards model stratified by the presence of liver and/or lung metastases, based on an extension of the Cox regression model with the corresponding subgroup variable and the interaction term treatment*subgroup variable.
b: Two-sided log-rank test stratified by the presence of liver and/or lung metastases.
c: An increase in score by ≥ 10 points compared with baseline was considered definitive deterioration if this also applied to all subsequent values. Deaths were not recorded as events.
d: Effect estimation not meaningfully interpretable.
f: A decrease in score by 10 points compared with baseline was considered definitive deterioration if this also applied to all subsequent values. Deaths were not recorded as events.
g: Defined as AEs that led to discontinuation of treatment 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; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Based on the available data, indications, e.g. of an added benefit, can be determined for the outcomes “overall survival” and “discontinuation due to AEs”. There was a high risk of bias of the results for the further outcomes; for the specific outcomes, however, the certainty of conclusions of the results was not always downgraded (see description of the results below and Section 2.9.4.2 of the full dossier assessment).

Mortality

Overall survival

The subpopulation considered here showed no statistically significant difference between the treatment groups for the outcome “overall survival”.

In the present data situation, the results for the outcome “overall survival” in the total population were additionally used for the derivation of the added benefit. A statistically significant difference in favour of ribociclib was shown here (see Appendix A of the full dossier assessment). Due to the consistency of the direction of the effect and the position of the point estimates between the subpopulations A1 and B1 (see Section 2.6.3.3) as well as of the total population of the MONALEESA-3 study, it is justified in the present data situation to transfer the results of the total population to the subpopulation when interpreting the results. Hence, a hint of an added benefit was derived in research question A1 for the outcome “overall survival” in this data constellation.

This deviates from the approach of the company, which derived an added benefit of ribociclib for overall survival based solely on the results on the total population of the study.

Morbidity

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

No statistically significant difference between the treatment groups was shown for any of the symptom scales of the EORTC QLQ-C30. This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant. Hence, an added benefit of ribociclib + fulvestrant is not proven for the outcomes of disease-specific symptoms.

This concurs with the assessment of the company, which used the total population for this, however.

Health status (EQ-5D VAS)

There were no usable data for the VAS of the EQ-5D questionnaire for the relevant subpopulation.

Pain (BPI-SF)

There were no usable data for the BPI-SF questionnaire for the relevant subpopulation.

Health-related quality of life

EORTC QLQ-C30 (functional scales)

No statistically significant difference between the treatment groups was shown for any of the functional scales of the EORTC QLQ-C30. This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant. Hence, an added benefit of ribociclib + fulvestrant is not proven for the outcomes of health-related quality of life.

This concurs with the assessment of the company, which used the total population for this, however.

Side effects

Serious adverse events

A statistically significant difference to the disadvantage of ribociclib 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, which used the total population for this, however, and made no statement on the certainty of conclusions.

Severe adverse events (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib was shown for the outcome “severe AEs (CTCAE grade 3–4)”. Due to the size of the effect, there was an indication of greater harm of ribociclib + fulvestrant in comparison with fulvestrant despite the high risk of bias.

This concurs with the assessment of the company, which used the total population for this, however, and made no statement on the certainty of conclusions.

Discontinuation due to adverse events

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

This concurs with the assessment of the company, which used the total population for this, however, and made no statement on the certainty of conclusions.

Blood and lymphatic system disorders (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib was shown for the outcome "severe blood and lymphatic system disorders". Due to the size of the effect, there was an indication of greater harm of ribociclib + fulvestrant in comparison with fulvestrant despite the high risk of bias.

This concurs with the assessment of the company, which used the total population for this, however, and made no statement on the certainty of conclusions.

Further specific adverse events

There were no complete usable data for further specific AEs. Due to the differences in observation periods in the study arms, AEs can only be interpreted if event time analyses are available (see Section 2.4.3.2). The company provided these event time analyses only for the AEs chosen by the company itself.

The company also saw greater harm from ribociclib for the side effect outcomes, but did not downgrade the added benefit because of this. This approach was not followed, see Section 2.4.4.2.

2.4.3.4 Subgroups and other effect modifiers

The assessment of the added benefit was conducted on the basis of a subpopulation of the MONALEESA-3 study. In its dossier, the company presented the results for the relevant subpopulation only in the framework of subgroup analyses because it itself assessed the added benefit on the basis of the total population. There were no data on subgroups of the relevant subpopulation for research question A1.

2.4.4 Probability and extent of added benefit

The derivation of probability and extent of the added benefit per subpopulation is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

2.4.4.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.4.3 (see Table 17).

Determination of the outcome category for the outcomes on side effects

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were serious/severe or non-serious/non-severe. The categorization of the outcome "discontinuation due to AEs" is justified below.

There were no analyses for the relevant subpopulation for the outcome "discontinuation due to AEs". The results of the total population showed, however, that more than half of all events were CTCAE grade 3 or 4 events. The outcome was therefore allocated to the category of serious/severe side effects.

Table 17: Extent of added benefit at outcome level: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women, initial endocrine therapy)

Outcome category **Outcome**	**Ribociclib + fulvestrant vs. placebo + fulvestrant** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	NA vs. NA HR: 0.61 [0.31; 1.17] p = 0.129 probability: "hint"	Outcome category "mortality" added benefit, extent: "minor"[c]
Morbidity		
EORTC QLQ-C30 (symptom scales)		
Fatigue	NA vs. NA HR: 1.00 [0.64; 1.56] p = 0.999	Lesser benefit/added benefit not proven
Nausea/vomiting	NA vs. NA HR: 1.66 [0.45; 6.08] p = 0.435	Lesser benefit/added benefit not proven
Pain	NA vs. NA HR: 1.34 [0.74; 2.45] p = 0.332	Lesser benefit/added benefit not proven
Dyspnoea	NA vs. NA HR: 0.66 [0.26; 1.66] p = 0.370	Lesser benefit/added benefit not proven
Insomnia	NA vs. NA HR: 1.05 [0.45; 2.45] p = 0.914	Lesser benefit/added benefit not proven
Appetite loss	NA vs. NA HR: 2.73 [0.79; 9.43] p = 0.097	Lesser benefit/added benefit not proven
Constipation	NA vs. NA HR: 1.28 [0.40; 4.09] p = 0.682	Lesser benefit/added benefit not proven
Diarrhoea	NA vs. NA HR: -[d] p = 0.083	Lesser benefit/added benefit not proven
Health status		
EQ-5D VAS	No usable data available	
Pain		
BPI-SF	No usable data available	

(continued)

Table 17: Extent of added benefit at outcome level: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women, initial endocrine therapy) (continued)

Outcome category **Outcome**	**Ribociclib + fulvestrant vs. placebo + fulvestrant** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Health-related quality of life		
EORTC QLQ-C30 (functional scales)		
General health status	NA vs. 22.4 HR: 0.73 [0.48; 1.09] p = 0.124	Lesser benefit/added benefit not proven
Physical functioning	NA vs. NA HR: 1.09 [0.70; 1.70] p = 0.693	Lesser benefit/added benefit not proven
Role functioning	NA vs. NA HR: 1.22 [0.76; 1.95] p = 0.415	Lesser benefit/added benefit not proven
Emotional functioning	22.3 vs. 22.4 HR: 1.02 [0.66; 1.57] p = 0.941	Lesser benefit/added benefit not proven
Cognitive functioning	NA vs. 22.4 HR: 1.12 [0.73; 1.72] p = 0.602	Lesser benefit/added benefit not proven
Social functioning	NA vs. NA HR: 1.12 [0.69; 1.83] p = 0.650	Lesser benefit/added benefit not proven
Side effects		
SAEs	NA vs. NA HR: 1.91 [1.13; 3.22] HR: 0.52 [0.31; 0.88][e] p = 0.014 probability: “hint”	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent: “considerable”
Severe AEs (CTCAE grade 3–4)	1.9 vs. NA HR: 5.10 [3.53; 7.38] HR: 0.20 [0.14; 0.28][e] p < 0.001 probability: “indication”	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent: “major”

(continued)

Table 17: Extent of added benefit at outcome level: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women, initial endocrine therapy) (continued)

Outcome category **Outcome**	**Ribociclib + fulvestrant vs. placebo + fulvestrant** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Discontinuation due to AEs	NA vs. NA HR: 2.58 [1.20; 5.55] HR: 0.39 [0.18; 0.83][e] p = 0.012 probability: "indication"	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ added benefit, extent "considerable"
Blood and lymphatic system disorders (SOC, CTCAE grade 3–4)	19.3 vs. NA proportions of events: 107 (45.0%) vs. 0 (0.0%) HR: -[d] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent: "major"[f]

a: Probability provided if there is a statistically significant and relevant effect.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: An indication of a minor added benefit is shown for the total population of the MONALEESA-3 study (see Appendix A of the full dossier assessment). Hence, a hint of a minor added benefit is derived for subpopulation A1. The extent cannot be quantified, but is no more than "minor" due to the results in the total population.
d: Effect estimation not meaningfully interpretable.
e: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.
f: Derivation of extent possible based on the proportions of events as a large proportion of events occurred only in the ribociclib arm, versus no events in the comparator arm.

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-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module; 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; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.4.4.2 Overall conclusion on added benefit

Table 18 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 18: Positive and negative effects from the assessment of ribociclib + fulvestrant in comparison with fulvestrant (postmenopausal women, initial endocrine therapy)

Positive effects	**Negative effects**
Mortality ▪ overall survival: hint of added benefit – extent "minor"[a]	Serious/severe side effects ▪ severe AEs (CTCAE grade 3–4): indication of greater harm – extent: "major" ▫ including in particular: SOC blood and lymphatic system disorders ▪ discontinuation due to AEs: indication of greater harm – extent: "considerable" ▪ SAEs: hint of greater harm – extent: "considerable"
a: An indication of a minor added benefit is shown for the total population of the MONALEESA-3 study (see Appendix A of the full dossier assessment). Hence, a hint of a minor added benefit is derived for subpopulation A1. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event; SOC: System Organ Class	

Both positive and negative effects of ribociclib were shown for the subpopulation of postmenopausal women with initial endocrine therapy. There were advantages in the outcome category "mortality" (overall survival) and disadvantages in the outcome category "serious/ severe side effects (SAEs, severe AEs and discontinuation due to AEs).

A hint of an added benefit, which was based on the results of the total population, was shown for the outcome "overall survival". Hence, the extent of added benefit for subpopulation A1 was no more than "minor".

Due to the size and the certainty of conclusions of the effects in severe CTCAE grade 3–4 AEs, these determined the derivation of harm. These events were mainly blood and lymphatic system disorders, particularly severe neutropenia. Despite the outcome-specific high risk of bias, these outcomes had a high certainty of conclusions because effects of this magnitude cannot be explained solely by differences in observation periods in the treatment arms. In addition, the effects occurred already early in the course of the study. Hence, an indication of greater harm of major extent can be derived for these outcomes.

In the overall assessment of research question A1, there is therefore a hint of a minor added benefit for the outcome "overall survival" and an indication of greater harm of major extent.

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

This deviates from the assessment of the company, which – based on the total population of the MONALEESA-3 study – derived considerable added benefit with high certainty of conclusions for postmenopausal patients.

2.4.5 List of included studies

MONALEESA-3

Novartis. MONALEESA-3: a randomized double-blind, placebocontrolled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment; study CLEE011F2301 (MONALEESA-3); clinical study report [unpublished]. 2018.

Novartis. MONALEESA-3: a randomized double-blind, placebocontrolled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment; study CLEE011F2301 (MONALEESA-3); Zusatzanalysen [unpublished]. 2018.

Novartis Pharma Services. MONALEESA-3: a randomized double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment [online]. In: EU Clinical Trials Register. [Accessed: 08.02.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2015-000617-43.

Novartis Pharmaceuticals. Study of efficacy and safety of LEE011 in men and postmenopausal women with advanced breast cancer: (MONALEESA-3); study details [online]. In: ClinicalTrials.gov. 11.01.2019 [Accessed: 08.02.2019]. URL: https://ClinicalTrials.gov/show/NCT02422615.

Novartis Pharmaceuticals. Study of efficacy and safety of LEE011 in men and postmenopausal women with advanced breast cancer: (MONALEESA-3); study results [online]. In: ClinicalTrials.gov. 11.01.2019 [Accessed: 08.02.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT02422615.

Slamon DJ, Neven P, Chia S, Fasching PA, De Laurentiis M, Im SA et al. Phase III randomized study of ribociclib and fulvestrant in hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced breast cancer: MONALEESA-3. J Clin Oncol 2018; 36(24): 2465-2472.

2.5 Research question A2: pre- and perimenopausal women, initial endocrine therapy

2.5.1 Study pool

Details on the information retrieval of the company can be found in Section 2.3 of the present assessment.

The company presented no data on the added benefit of ribociclib in combination with fulvestrant in pre- and perimenopausal patients with initial endocrine therapy. The company

presented the MONALEESA-7 study for the combination of ribociclib + aromatase inhibitor. This study was not relevant for the derivation of an added benefit in research question A2, however. The reasons are explained below.

MONALEESA-7 is an RCT comparing a combination of ribociclib + NSAI or ribociclib + tamoxifen with placebo + NSAI or placebo + tamoxifen (see Section 2.7.5 for references). This study comprised both women with initial endocrine therapy and women with progression under prior (neo)adjuvant endocrine therapy. A subpopulation was therefore relevant for the assessment of the added benefit in research question A2. The characteristics and interventions of the study are described in Section 2.7.2 of the present benefit assessment (see Table 24 and Table 25).

Combination with tamoxifen not approved

In the MONALEESA-7 study, ribociclib was combined either with an aromatase inhibitor (letrozole or anastrozole) or with tamoxifen. The combination of ribociclib with tamoxifen is not approved, however [5]. As described by the company, no application for approval of the combination with tamoxifen has been submitted to the European Medicines Agency (EMA) because there was an increased risk for QT interval prolongation in this constellation [6]. Hence, only the subpopulation of the study who received ribociclib together with an aromatase inhibitor was relevant for the benefit assessment. The tamoxifen combination was administered in about 26% of the total study population, and in 36% within the subpopulation with initial endocrine therapy. Hence, not the total subpopulation of the patients with initial treatment could be used for the derivation of the added benefit, but only the subgroup of patients treated with an aromatase inhibitor.

No randomized comparison in the relevant subpopulation

The company specified tamoxifen as ACT for pre- and perimenopausal women receiving initial endocrine therapy (see Section 2.2). A relevant comparison for the derivation of the added benefit therefore requires the combination of ribociclib + aromatase inhibitor (or fulvestrant) as intervention and tamoxifen as comparator therapy. There was no such randomized comparison in the MONALEESA-7 study, however. The MONALEESA-7 study did also not allow for the operationalization of a subpopulation that was in compliance with the approval on the intervention side (ribociclib + aromatase inhibitor), implemented the specified ACT on the comparator side (placebo + tamoxifen) and also constituted a randomized comparison.

This could also not be fulfilled by the sensitivity analyses presented by the company, showing results for ribociclib + tamoxifen and ribociclib + aromatase inhibitor separately in comparison with the total placebo group (placebo + aromatase inhibitor or tamoxifen). This also constituted no randomized comparison, and therefore allowed no derivation of an added benefit, particularly as the ACT and the patients' pretreatments were not considered.

However, a relevant subpopulation for research question B2 (pre- and perimenopausal women with prior endocrine therapy) could be operationalized from the MONALEESA-7 study for the

present assessment. These were women with (neo)adjuvant pretreatment with progression either under the (neo)adjuvant treatment or within 12 months after completion of this therapy (see Section 2.7.1 and Section 2.9.3.2 of the full dossier assessment).

Summary

In summary, no relevant data were available for the derivation of an added benefit in pre- and perimenopausal patients receiving initial endocrine therapy.

2.5.2 Results on added benefit

The company presented no relevant data for research question A2. This resulted in no hint of an added benefit of ribociclib in comparison with the ACT for this research question. An added benefit for this research question is not proven.

2.5.3 Probability and extent of added benefit

The company presented no relevant data for the assessment of the added benefit of ribociclib in combination with an aromatase inhibitor or fulvestrant as initial endocrine therapy in pre- and perimenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer. An added benefit for these patients is therefore not proven.

This deviates from the assessment of the company, which – based on the total population of the MONALEESA-7 study – derived considerable added benefit with high certainty of conclusions for pre- and perimenopausal patients.

2.5.4 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment. Information on the MONALEESA-7 study can be found in Section 2.7.5.

2.6 Research question B1: postmenopausal women who have received prior endocrine therapy

2.6.1 Studies used by the company

Details on the information retrieval of the company can be found in Section 2.3 of the present assessment.

The company used the MONALEESA-3 study for research question B1. This study investigated the comparison of ribociclib + fulvestrant versus fulvestrant; the company presented no data on the comparison of ribociclib + aromatase inhibitor.

The MONALEESA-3 study was not relevant for the assessment of the added benefit of ribociclib, however, as fulvestrant did not constitute an ACT for a decisive proportion of the patients in the present situation. Nonetheless, the results of the study are presented below as the G-BA saw a medical reason in this special therapeutic and health care situation, which, in the present case, exceptionally justified considering fulvestrant, which was used also after

pretreatment with aromatase inhibitors in the MONALEESA-3 study, as a comparison for research question B1 (see also Section 2.2).

2.6.2 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 2.4.2. This section also describes the operationalization of the subpopulations of the study after endocrine pre-treatment.

The MONALEESA-3 study comprised a subpopulation of women with endocrine pretreatment, which in principle corresponds to research question B1. This subpopulation comprised 236 women in the ribociclib arm and 109 women in the comparator arm (2:1 randomization). This corresponds to almost half of the study population. 75 (69%) of these patients had received an aromatase inhibitor as most recent endocrine therapy before enrolment; the remaining patients had received the antioestrogen tamoxifen.

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. Hence, it is no ACT for a majority of the patients in this subpopulation. The study was therefore unsuitable to derive conclusions on the added benefit of ribociclib for research question B1. In accordance with the G-BA's note on the ACT, however, studies in which fulvestrant was also used after pretreatment with aromatase inhibitors were also considered as comparison (see Section 2.2). The results of the subpopulation are therefore presented below.

Table 19: Characteristics of the study population – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women who have received prior endocrine therapy)

Study Characteristics Category	**Ribociclib + fulvestrant**	**Placebo + fulvestrant**
MONALEESA-3	N[a] = 236	N[a] = 109
Age [years], mean (SD)	62.5 (9.90)	61.0 (11.52)
Region, n (%)		
Asia	16 (6.8)	6 (5.5)
Europe and Australia	185 (78.4)	79 (72.5)
Latin America	3 (1.3)	0 (0.0)
North America	23 (9.7)	22 (20.2)
Other	9 (3.8)	2 (1.8)
ECOG PS, n (%)		
0	160 (67.8)	66 (60.6)
1	75 (31.8)	43 (39.4)
No data	1 (0.4)	0 (0.0)
Disease stage on study entry, n (%)		
II	1 (0.4)	0 (0.0)
III	1 (0.4)	0 (0.0)
IV	234 (99.2)	109 (100.0)
Disease-free interval, n (%)		
De novo	2 (0.8)	0 (0.0)
Not de novo	234 (99.2)	109 (100.0)
≤ 12 months	18 (7.6)	8 (7.3)
> 12 months	216 (91.5)	101 (92.7)
Progression in the course of treatment		
Recurrence during or ≤ 12 months after (neo)adjuvant endocrine therapy, without endocrine therapy for advanced stage	137 (58.1)	71 (65.1)
Progression after endocrine therapy for advanced stage, with or without (neo)adjuvant endocrine therapy	99 (41.9)	38 (34.9)

(continued)

Table 19: Characteristics of the study population – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women who have received prior endocrine therapy) (continued)

Study **Characteristics** **Category**	**Ribociclib + fulvestrant**	**Placebo + fulvestrant**
Type of most recent treatment, n (%)		
Chemotherapy	1 (0.4)	0 (0.0)
Endocrine therapy	145 (61.4)	59 (54.1)
Targeted therapy	2 (0.8)	1 (0.9)
Radiotherapy	69 (29.2)	39 (35.8)
Surgery (not biopsy)	19 (8.1)	10 (9.2)
Other	4 (1.7)	0 (0.0)
Setting of most recent treatment		
Adjuvant	110 (46.6)	48 (44.0)
Neoadjuvant	0 (0.0)	2 (1.8)
Therapeutic	71 (30.1)	29 (26.6)
Palliative	36 (15.3)	20 (18.3)
Not applicable[b]	19 (8.1)	10 (9.2)
Location of metastases, n (%)		
Soft tissue	10 (4.2)	5 (4.6)
Breast	2 (0.8)	1 (0.9)
Bone	184 (78.0)	88 (80.7)
Bone only	51 (21.6)	25 (22.9)
Visceral	151 (64.0)	67 (61.5)
Lung	59 (25.0)	26 (23.9)
Liver	85 (36.0)	39 (35.8)
Lung or liver	127 (53.8)	57 (52.3)
CNS	2 (0.8)	1 (0.9)
Other	50 (21.2)	24 (22.0)
Skin	9 (3.8)	4 (3.7)
Lymph nodes	81 (34.3)	47 (43.1)
Treatment discontinuation[c], n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a: Number of randomized patients in the relevant subpopulation. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Apparently, these are patients with surgery as their most recent treatment.
c: Discontinuation of entire study medication.

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

The subpopulation considered showed only few imbalances between the treatment groups. It is noticeable that the proportion of patients from North America was more than twice as high in the placebo arm. The study population only consisted of women.

The mean age of the patients was 62 years and most of them were from Europe. With individual exceptions, all patients were in the metastatic stage of the disease. The cancer disease had been diagnosed already at an early stage in almost all patients. More than 90% of the patients had been disease-free for more than 12 months after resection of the primary tumour. The main sites of metastasis at baseline were bone (almost 79%), but also lung or liver (53%) and lymph nodes (37%). 40% of the women in the subpopulation had already received endocrine therapy for the advanced stage, whereas 60% had recurrence during or within 12 months after completion of (neo)adjuvant therapy.

The most recent treatment before baseline was endocrine therapy in almost 60% of the patients, and radiotherapy in just over 30%. Surgery was the most recent intervention in just under 8% of the patients.

Regarding treatment durations and observation periods in the MONALEESA-3 study, the dossier only contained information on the total population. These are presented in Table 12 of the present benefit assessment.

Risk of bias across outcomes (study level)

The risk of bias across outcomes (risk of bias at study level) is described in Table 13 of the present benefit assessment.

2.6.3 Results on the study used by the company

2.6.3.1 Patient-relevant outcomes considered

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.9.4.3.2 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms, recorded using the EORTC QLQ-C30 (symptom scales)
  - health status, measured using the EQ-5D VAS
  - pain, recorded using the BPI-SF
- Health-related quality of life
  - EORTC QLQ-C30 (functional scales)
- Side effects

- overall rate of SAEs
- overall rate of severe AEs (CTCAE grade 3–4)
- overall rate of discontinuations due to AEs
- blood and lymphatic system disorders (SOC; CTCAE grade 3–4)
- if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.9.4.3.2 of the full dossier assessment).

Table 20 shows for which outcomes data were available in the MONALEESA-3 study.

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

Study	Outcomes								
	Overall survival	EORTC QLQ-C30 (symptom scales)	Health status (EQ-5D VAS)	Pain (BPI-SF)	Health-related quality of life (EORTC QLQ-C30, functional scales)	SAEs	Discontinuation due to AEs	Severe AEs (CTCAE grade 3–4)	Blood and lymphatic system disorders (SOC; CTCAE grade 3–4)
MONALEESA-3	Y	Y	No[a]	No[a]	Y	Y	Y	Y	Y

a: No usable data available for the considered 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; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus; Y: yes

2.6.3.2 Risk of bias

Table 21 describes the risk of bias for the results of the relevant outcomes.

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

Study	Study level	Outcomes								
		Overall survival	EORTC QLQ-C30 (symptom scales)	Health status (EQ-5D VAS)	Pain (BPI-SF)	Health-related quality of life (EORTC QLQ-C30, functional scales)	SAEs	Discontinuation due to AEs[a]	Severe AEs (CTCAE grade 3–4)	Blood and lymphatic system disorders (SOC, CTCAE grade 3–4)
MONALEESA-3	L	L	H[b]	-[c]	-[c]	H[b]	H[b]	L	H[b]	H[b]

a: Defined as AEs that have led to the discontinuation of treatment with ribociclib or placebo.
b: Differences in the observation periods between the treatment arms with potentially informative censoring in the total population; data on the observation periods for subpopulations A1 and B1 were not available.
c: No usable data available for subpopulation B1; see Section 2.9.4.3.2 of the full dossier assessment.

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; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

The outcome-specific risk of bias for the subpopulation considered here corresponds to that for patients with initial endocrine therapy (research question A1). Further information can be found in Section 2.4.3.2.

2.6.3.3 Results

The results on the comparison of ribociclib + fulvestrant with fulvestrant in postmenopausal women with HR-positive, HER2-negative advanced or 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. Results on common AEs, SAEs and severe AEs (CTCAE grade 3–4) are presented in Appendix B.2 of the full dossier assessment. Kaplan-Meier curves on the presented event time analyses can be found in Appendix C.2 of the full dossier assessment.

Table 22: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women who have received prior endocrine therapy)

Study **Outcome category**	**Ribociclib + fulvestrant**		**Placebo + fulvestrant**		**Ribociclib + fulvestrant vs. placebo + fulvestrant**
Outcome **Time point**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI][a]; p-value[b]**
MONALEESA-3					
First data cut-off 3 November 2017					
Mortality					
Overall survival	236	NA [NA; NA] 50 (21.1)	109	NA [NA; NA] 32 (29.4)	0.68 [0.44; 1.07]; 0.093
Morbidity					
Symptoms					
EORTC QLQ-C30 (symptom scales)[c]					
Fatigue	236	19.7 [14.7; NA] 76 (32.2)	109	16.8 [9.3; NA] 34 (31.2)	0.83 [0.55; 1.24]; 0.358
Nausea/ vomiting	236	NA [NA; NA] 3 (1.3)	109	NA [NA; NA] 3 (2.8)	0.35 [0.07; 1.77]; 0.185
Pain	236	NA [22.0; NA] 49 (20.8)	109	21.3 [16.6; NA] 23 (21.1)	0.74 [0.45; 1.22]; 0.229
Dyspnoea	236	NA [NA; NA] 12 (5.1)	109	NA [19.5; NA] 7 (6.4)	0.57 [0.22; 1.46]; 0.234
Insomnia	236	NA [NA; NA] 20 (8.5)	109	NA [19.5; NA] 9 (8.3)	0.83 [0.38; 1.83]; 0.642
Appetite loss	236	NA [NA; NA] 10 (4.2)	109	NA [NA; NA] 2 (1.8)	1.98 [0.43; 9.06]; 0.372
Constipation	236	NA [NA; NA] 11 (4.7)	109	NA [NA; NA] 4 (3.7)	1.19 [0.38; 3.74]; 0.768
Diarrhoea	236	NA [NA; NA] 1 (0.4)	109	NA [NA; NA] 0 (0)	-[d]; 0.617
Health status					
EQ-5D VAS				No usable data	
Pain					
BPI-SF				No usable data	

(continued)

Table 22: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women who have received prior endocrine therapy) (continued)

Study Outcome category	Ribociclib + fulvestrant		Placebo + fulvestrant		Ribociclib + fulvestrant vs. placebo + fulvestrant
Outcome Time point	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]; p-value[b]
Health-related quality of life					
EORTC QLQ-C30 (general health status and functional scales)[f]					
General health status	236	22.4 [16.6; NA] 75 (31.8)	109	16.7 [12.9; NA] 34 (31.2)	0.85 [0.56; 1.28]; 0.423
Physical functioning	236	22.0 [19.4; NA] 66 (28.0)	109	14.9 [11.1; NA] 31 (28.4)	0.73 [0.47; 1.13]; 0.151
Role functioning	236	22.0 [16.5; NA] 75 (31.8)	109	16.8 [16.6; NA] 27 (24.8)	1.03 [0.66; 1.61]; 0.895
Emotional functioning	236	23.1 [19.4; NA] 59 (25.0)	109	19.4 [16.8; 22.6] 30 (27.5)	0.70 [0.45 1.09]; 0.110
Cognitive functioning	236	19.4 [15.0; 23.1] 79 (33.5)	109	19.4 [14.8; NA] 25 (22.9)	1.21 [0.77 1.90]; 0.418
Social functioning	236	22.4 [18.5; NA] 64 (27.1)	109	21.3 [14.9; NA] 24 (22.0)	0.94 [0.58 1.50]; 0.783
Side effects					
AEs (additional information)	235	ND 234 (99.6)	109	ND 105 (96.3)	–
SAEs	235	NA [NA; NA] 73 (31.1)	109	NA [NA; NA] 22 (20.2)	1.47 [0.91 2.37]; 0.115
Severe AEs (CTCAE grade ≥ 3)	235	1.2 [0.95; 1.87] 187 (79.6)	109	NA [11.56; NA] 37 (33.9)	3.64 [2.55; 5.19]; < 0.001
Discontinuation due to AEs[g]	235	NA [NA; NA] 43 (18.3)	109	NA [NA; NA] 7 (6.4)	2.81 [1.26 6.26]; 0.008
Blood and lymphatic system disorders (SOC, CTCAE grade 3–4)	235	13.8 [7.39; NA] 108 (46.0)	109	NA [NA; NA] 5 (4.6)	13.05 [5.32; 32.03]; < 0.001
Including: Neutropenia (CTCAE grade 3–4)	235	ND 95 (40.4)	109	ND 0 (0.0)	-

(continued)

Table 22: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (postmenopausal women who have received prior endocrine therapy) (continued)

a: Cox proportional hazards model stratified by the presence of liver and/or lung metastases, based on an extension of the Cox regression model with the variable prior therapy (no treatment in the advanced setting vs. at most one line of treatment in the advanced setting) and the corresponding interaction term with treatment.
b: Two-sided log-rank test stratified by the presence of liver and/or lung metastases.
c: An increase in score by ≥ 10 points compared with baseline was considered definitive deterioration if this also applied to all subsequent values.
d: Effect estimation not meaningfully interpretable.
f: A decrease in score by 10 points compared with baseline was considered definitive deterioration if this also applied to all subsequent values.
g: Defined as AEs that led to discontinuation of treatment 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; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; ND: no data; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

Patient-relevant outcomes with statistically significant differences in the MONALEESA-3 study

Mortality

Overall survival

The subpopulation considered here showed no statistically significant difference between the treatment groups for the outcome “overall survival”. The total population of the MONALEESA-3 study showed a statistically significant difference in favour of ribociclib for this outcome (see Appendix A of the full dossier assessment). Due to the consistency of the direction of the effect and the position of the point estimates between the subpopulations A1 (see Section 2.4.3.3) and B1 as well as of the total population of the MONALEESA-3 study, it is justified in the present data situation to transfer the results of the total population to the subpopulation when interpreting the results. Hence, an advantage of ribociclib was derived in research question B1 for the outcome “overall survival” in this data constellation.

Side effects

Severe adverse events (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib was shown for the outcome “severe AEs”. Due to the size of the effect, there was a high certainty of results for this outcome despite high risk of bias.

Discontinuation due to adverse events

A statistically significant difference to the disadvantage of ribociclib was shown for the outcome “discontinuation due to AEs”.

Blood and lymphatic system disorders (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib was shown for the outcome "severe blood and lymphatic system disorders". Due to the size of the effect, there was a high certainty of results for this outcome despite high risk of bias.

Other outcomes

There were no statistically significant differences for all other outcomes of the categories "mortality", "morbidity", "health-related quality of life" and "side effects".

2.6.3.4 Subgroups and other effect modifiers

In its dossier, the company presented the results for the subpopulation of patients with prior endocrine therapy only in the framework of subgroup analyses because it itself assessed the added benefit for postmenopausal patients on the basis of the total population. There were no data on subgroups of the considered subpopulation for research question B1.

2.6.4 Summarizing assessment of the results

In summary, the results of the MONALEESA-3 study led to both advantages and disadvantages of ribociclib + fulvestrant in comparison with placebo + fulvestrant regarding the following outcomes:

- Advantage in mortality (overall survival)
- Disadvantages in AE outcomes:
  - Severe AEs (CTCAE grade 3–4), including particularly blood and lymphatic system disorders (neutropenia): Due to the size of the effect, there was a high certainty of results for this outcome despite high risk of bias.
  - Discontinuation due to AEs

In the overall assessment, this resulted neither in an advantage nor in a disadvantage of ribociclib + fulvestrant in comparison with placebo + fulvestrant.

2.6.5 List of the studies included by the company

Information on the MONALEESA-3 study can be found in Section 2.4.5.

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

2.7.1 Studies included

Details on the information retrieval of the company can be found in Section 2.3 of the present assessment. The study listed in the following table was included in the benefit assessment.

The company presented the study listed in the following table for research question B2 on the combination of ribociclib + aromatase inhibitor. It was included in the present benefit assessment.

This study investigated the comparison of ribociclib + aromatase inhibitor versus aromatase inhibitor; the company presented no data on the comparison of ribociclib + fulvestrant.

Table 23: Study pool – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women who have received prior endocrine therapy)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
MONALEESA-7	Yes	Yes	No
a: Study sponsored by the company. RCT: randomized controlled trial; vs.: versus			

Section 2.7.5 contains a reference list for the studies included.

2.7.2 Study characteristics

Table 24 and Table 25 describe the study used for the benefit assessment.

Table 24: Characteristics of the study included – RCT, direct comparison: ribociclib + NSAI/tamoxifen vs. placebo + NSAI/tamoxifen

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MONA-LEESA-7	Double-blind, parallel	Pre- and perimenopausal women (≥ 18 and < 60 years) with HR-positive, HER2-negativ advanced breast cancer, no or adjuvant pretreatment with endocrine therapy	Ribociclib + goserelin + tamoxifen or NSAI (N = 335) placebo + goserelin + tamoxifen or NSAI (N = 337) Relevant subpopulation thereof[b]: ribociclib + goserelin + letrozole (N = 100)[c] placebo + goserelin + letrozole (N = 105)[c]	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	188 centres in Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Columbia, France, Germany, Greece, Hong Kong, Hungary, India, Italy, Korea, Lebanon, Malaysia, Mexico, Poland, Portugal, Russia, Saudi Arabia, Switzerland, Singapore, Spain, Taiwan, Thailand, Turkey, United Arab Emirates, USA 11/2014–ongoing First data cut-off: after 329 PFS events (20 Aug 2017) Pending analyses: ▪ interim analysis after 189 deaths ▪ final analysis after 252 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: Patients with recurrence during or within 1 year after completion of (neo)adjuvant treatment.
c: About 19% of the patients in the relevant subpopulation were not treated with letrozole, but with tamoxifen or anastrozole.
d: Outcome-specific information is provided in Table 26.

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

Table 25: Characteristics of the interventions – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole

Study	Intervention	Comparison
MONA-LEESA-7	Ribociclib 600 mg capsules, orally, day 1–21 of a 28-day cycle, + goserelin 3.6 mg, subcutaneous implant, day 1 of a 28-day cycle, + letrozole 2.5 mg, orally, once daily[a]	Placebo capsules, orally, day 1–21 of a 28-day cycle, + goserelin 3.6 mg, subcutaneous implant, day 1 of a 28-day cycle, + letrozole 2.5 mg, orally, once daily[a]
	Dose adjustments: ribociclib/placebo: reduction (to 400 mg/day or 200 mg/day), interruption or discontinuation possible in case of toxicity goserelin and letrozole: no adjustment allowed	
	Permitted pretreatment: ▪ (neo)adjuvant endocrine therapy ▪ goserelin (e.g. for endometriosis) ≤ 28 days before baseline ▪ at most one chemotherapy until 28 days before baseline ▪ systemic corticosteroids within 2 weeks before baseline ▪ radiotherapy ≥ 4 weeks or local palliative radiotherapy ≥ 2 weeks before baseline **Non-permitted pretreatment:** ▪ CDK4/6 inhibitors ▪ hormonal anticancer therapy for advanced stage (except for short-term use of less than 14 or 28 days prior to randomization) ▪ any other anticancer therapy **Permitted concomitant treatment:** ▪ corticosteroids as individual doses, topical administration (e.g. rash), inhaled sprays (e.g. obstructive airways disorder), eye drops or local injections (e.g. intraarticular) ▪ short-term treatment (< 5 days) with a maximum total daily dose of 4 mg dexamethasone (e.g. in chronic obstructive pulmonary disease or antiemetic) ▪ drugs for the treatment of AEs, cancer symptoms and accompanying diseases, and supportive drugs (e.g. analgesics, antiemetics, antidiarrhoeal drugs) ▪ 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 target lesions) **Non-permitted concomitant treatment:** ▪ 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 known risk to prolong the QT interval ▫ drugs with narrow therapeutic indices mainly metabolized by CYP3A4/5 ▫ strong CYP2D6 inducers or inhibitors for patients with tamoxifen treatment ▫ herbal drugs, dietary supplements ▪ warfarin or other coumarin-like anticoagulants	

a: In addition, about 19% of the patients in the relevant subpopulation were treated with tamoxifen or anastrozole.

CDK: cyclin-dependent kinase; CYP: cytochrome P450; NSAI: nonsteroidal aromatase inhibitor; RCT: randomized controlled trial; vs.: versus

The MONALEESA-7 study was an RCT comparing a combination of ribociclib + NSAI or ribociclib + tamoxifen with placebo + NSAI or placebo + tamoxifen. The combination of ribociclib + tamoxifen is not approved, but this was not relevant for the assessment of the added benefit in research question B2 (see Section 2.9.4.1 of the full dossier assessment). A total of 672 patients with HR-positive, HER2-negative, advanced or metastatic breast cancer were included. Randomization was in a 1:1 ratio and was stratified according to the presence of liver or lung metastases (yes/no), prior chemotherapy for advanced disease (yes/no) and endocrine combination partner (tamoxifen + goserelin or NSAI + goserelin). Their tumours had to be not amenable to resection or radiotherapy with curative intent. In addition, the patients had to have an ECOG PS of 0 or 1 at baseline.

Treatment was to be administered continuously in 28-day cycles until disease progression. Apart from the combination of tamoxifen with ribociclib, which is not in compliance with the approval, the drugs used in the study were administered in compliance with the current SPCs [4,5]. Switching treatments, particularly from placebo to ribociclib, was not possible.

Primary outcome of the study was PFS. Patient-relevant secondary outcomes were overall survival, symptoms, health status, health-related quality of life, and side effects.

All patients in the study were pre- or perimenopausal and had not yet received prior endocrine therapy in the advanced stage. Hence, there were no patients in second-line treatment in the study. Nonetheless, a subpopulation of the study was relevant for the benefit assessment, i.e. for whom a comparison of ribociclib with the ACT is adequate for research question B2. This is explained in the following sections.

Determination of the combination partner for ribociclib/placebo in the MONALEESA-7 study

Whether a patient in the study received tamoxifen or an NSAI in addition to ribociclib/placebo depended, among other things, on the duration since the end of the previous endocrine therapy:

- In patients without prior endocrine therapy and in patients whose (neo)adjuvant endocrine therapy was ≥ 12 months ago, the investigator decided whether the patient should receive tamoxifen or an NSAI (letrozole or anastrozole). These patients are comprised by research question A2, they are therefore not considered further here.
- Patients whose (neo)adjuvant endocrine therapy was < 12 months before randomization received endocrine therapy depending on their prior therapy:
  - After prior therapy with tamoxifen or fulvestrant, the patient received an NSAI (letrozole or anastrozole, at the investigator’s choice).
  - After prior therapy with letrozole, anastrozole or exemestane, the patient received tamoxifen.

In patients with early recurrence after (neo)adjuvant therapy, the endocrine therapy was thus determined by the (unsuccessful) prior therapy both in the intervention group and in the comparator group. This had consequences for the ACT in this subpopulation, as explained below.

Subpopulation of the MONALEESA-7 study relevant for the assessment

The MONALEESA-7 study included patients with or without prior (neo)adjuvant endocrine therapy who had not yet received endocrine therapy for the advanced disease stage.

Although all patients in the study were treated in first-line treatment for the advanced disease stage, a population of patients can be identified that is relevant for research question B2. This resulted from the company's differentiation between 2 therapeutic situations in its dossier:

- patients without prior endocrine therapy or with progression > 12 months after completion of (neo)adjuvant endocrine therapy, and
- patients with progression during or within 12 months after completion of (neo)adjuvant endocrine therapy.

The group of patients with progression during or within 12 months after completion of (neo)adjuvant endocrine therapy was included for the assessment of research question B2. With few exceptions, these patients had received (neo)adjuvant pretreatment with tamoxifen. According to guidelines, subsequent treatment with the same drug is not adequate in patients with recurrence shortly after completion of the adjuvant endocrine therapy (see Section 2.9.3.2 of the full dossier assessment). Repeated tamoxifen treatment (which is the ACT for patients with initial endocrine therapy) is therefore not a regular option as comparator therapy.

In the present study, these patients received an aromatase inhibitor (letrozole or anastrozole). Of the aromatase inhibitors, anastrozole is not approved for pre- and perimenopausal patients [6]. Hence, only patients who received letrozole together with ribociclib or placebo were relevant for the assessment of the added benefit. Data on these patients were not available in the dossier. However, they constituted 81% of the subpopulation of patients with progression during or within 12 months after completion of (neo)adjuvant endocrine therapy. This proportion was large enough to use the total subpopulation for the present assessment. See Section 2.9.3.2 of the full dossier assessment for more details. Unless noted otherwise, all further information refers to the described subpopulation.

Treatment of physician's choice

The G-BA specified endocrine therapy of physician's choice as ACT for pre- and perimenopausal patients with prior endocrine therapy. The current approvals have to be taken into account.

Tamoxifen, letrozole, exemestane, megestrol acetate and medroxyprogesterone acetate are approved in the therapeutic indication. In this case, tamoxifen was not a meaningful option as,

according to the company, almost all patients in the relevant subpopulation had already been pretreated with tamoxifen. According to the G-BA, the evidence for megestrol acetate and medroxyprogesterone acetate in the therapeutic indication B is considered inadequate for a concrete recommendation. In addition, the progestogens are approved only for the palliative treatment of breast cancer. Hence, letrozole and exemestane are the only available approved drugs. Correspondingly, the consistent use of letrozole in the relevant subpopulation is considered a therapy in the sense of a treatment of physician's choice (see Section 2.9.3.2 of the full dossier assessment). A conclusion on the added benefit can therefore only be drawn for patients for whom letrozole constitutes an adequate therapy.

Data cut-offs

A first data cut-off was planned after 329 PFS events and was conducted on 20 August 2017. The present assessment was based on this data cut-off. A further analysis of overall survival was to be conducted after the death of 189 patients, and the final analysis after 252 deaths.

Duration of follow-up

Table 26 shows the planned duration of follow-up observation of the patients for the individual outcomes.

Table 26: Planned duration of follow-up observation – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women who have received prior endocrine therapy)

Study **Outcome category** **Outcome**	**Planned follow-up observation**
MONALEESA-7	
Mortality	
Overall survival	Every 12 weeks until death, end of study, premature discontinuation of study or loss to follow-up
Morbidity	
Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23, EQ-5D VAS)	Every 8 weeks in the first 18 months, then every 12 weeks until progression, death, withdrawal of consent, or loss to follow-up
Health-related quality of life	
EORTC QLQ-C30, EORTC QLQ-BR23	Every 8 weeks in the first 18 months, then every 12 weeks until progression, death, withdrawal of consent, or loss to follow-up
Side effects	
All outcomes in the category "side effects"	Until up to 30 days after the end of treatment

AE: adverse event; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module; 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; NSAI: nonsteroidal aromatase inhibitor; 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 survival.

Patient characteristics

Table 27 shows the characteristics of the patients included in the study.

Table 27: Characteristics of the study population – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women who have received prior endocrine therapy)

Study Characteristics Category	**Ribociclib + letrozole**	**Placebo + letrozole**
MONALEESA-7	N[a] = 100	N[a] = 105
Age [years], mean (SD)	41.6 (6.23)	43.8 (6.17)
Region, n (%)		
Asia	26 (26.0)	25 (23.8)
Europe and Australia	42 (42.0)	50 (47.6)
Latin America	9 (9.0)	8 (7.6)
North America	12 (12.0)	13 (12.4)
Other	11 (11.0)	9 (8.6)
ECOG PS, n (%)		
0	75 (75.0)	85 (81.0)
1	24 (24.0)	18 (17.1)
2	0 (0.0)	1 (1.0)
No data	1 (1.0)	1 (1.0)
Disease stage on study entry, n (%)		
IV	100 (100.0)	105 (100.0)
Disease-free interval, n (%)		
De novo	0 (0.0)	0 (0.0)
Not de novo	100 (100.0)	105 (100.0)
≤ 12 months	3 (3.0)	1 (1.0)
> 12 months	97 (97.0)	104 (99.0)
Drug combination with ribociclib/placebo		
Letrozole	80 (80.0)[b]	86 (81.9)[b]
Anastrozole	17 (17.0)[b]	15 (14.3)[b]
Tamoxifen	3 (3.0)[b]	4 (3.8)[b]
Type of most recent treatment, n (%)		
Chemotherapy	6 (6.0)	12 (11.4)
Endocrine therapy	51 (51.0)	47 (44.8)
Radiotherapy	36 (36.0)	40 (38.1)
Surgery (not biopsy)	10 (10.0)	8 (7.6)
Other	0 (0.0)	2 (1.9)

(continued)

Table 27: Characteristics of the study population – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women who have received prior endocrine therapy) (continued)

Study Characteristics Category	Ribociclib + letrozole	Placebo + letrozole
Setting of most recent treatment		
Adjuvant	75 (75.0)	72 (68.6)
Neoadjuvant	0 (0.0)	1 (1.0)
Palliative	11 (11.0)	13 (12.4)
Therapeutic	6 (6.0)	11 (10.5)
None[c]	10 (10.0)	8 (7.6)
Location of metastases, n (%)		
Soft tissue	6 (6.0)	7 (6.7)
Bone	70 (70.0)	69 (65.7)
Bone only	24 (24.0)	24 (22.9)
Visceral	62 (62.0)	65 (61.9)
Lung	31 (31.0)	33 (31.4)
Liver	36 (36.0)	47 (44.8)
Lung or liver	52 (52.0)	65 (61.9)
Other	17 (17.0)	8 (7.6)
Skin	5 (5.0)	3 (2.9)
Lymph nodes	32 (32.0)	40 (38.1)
Treatment discontinuation[d], n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a: Number of randomized patients in the relevant subpopulation. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Institute's calculation.
c: Apparently, these are patients with surgery as their most recent treatment.
d: Discontinuation of entire study medication.
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

The subpopulation relevant for research question B2 showed no important imbalances between the treatment groups. The study population only consisted of women.

The mean age of the patients was 43 years and most of them were from Europe, Australia and Asia. All patients were in the metastatic stage of the disease. The cancer disease had been diagnosed already at an early stage in all patients. With few exceptions, all patients had been disease-free for more than 12 months after resection of the primary tumour. The main sites of metastasis at baseline were bone (almost 68%), but also lung or liver (52% versus 62%) and lymph nodes (32% versus 38%).

The most recent treatment before baseline was endocrine therapy in almost 48% of the patients, and radiotherapy in about 37%. Surgery or chemotherapy were less common (each in about 10% of the patients).

Tamoxifen, letrozole and anastrozole were possible combination partners of ribociclib and placebo in the relevant subpopulation. The study medication was combined with letrozole in 81% of the patients, with anastrozole in 16%, and with tamoxifen in about 3%. Even though the population of patients receiving ribociclib or placebo in combination with letrozole represents the relevant subpopulation, the entire population of patients with recurrence ≤ 12 months after the end of adjuvant therapy could be used for the assessment.

Table 28 shows the mean/median treatment duration of the patients and the mean/median observation period for individual outcomes. The information refers to the total population of the MONALEESA-7 study because no information was available for the subpopulation.

Table 28: Information on the course of the study – RCT, direct comparison: ribociclib + NSAI/tamoxifen vs. placebo + NSAI/tamoxifen (total population)

Study **Duration of the study phase** **Outcome category**	**Ribociclib + NSAI/tamoxifen**	**Placebo + NSAI/tamoxifen**
MONALEESA-7	N = 335	N = 337
Treatment duration[a] [months]		
Median [min; max]	15.2 [0.0; 30.1]	12.0 [0.5; 30.1]
Mean (SD)	14.4 (7.22)	11.2 (7.36)
Observation period [months]		
Overall survival		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Symptoms/health-related quality of life		
EORTC QLQ-C30		
Median [min; max]	14.8 [−0.9; 27.7][b]	11.1 [−1.0; 27.6][b]
Mean (SD)	13.2 (7.00)	10.6 (6.97)
EORTC QLQ-BR23		
Median [min; max]	13.7 [−0.9; 27.7][b]	10.4 [−1.0; 27.6][b]
Mean (SD)	12.8 (7.13)	10.2 (7.11)
Side effects		
Median [min; max]	15.7 [1.0; 30.1]	12.4 [0.5; 30.1]
Mean (SD)	14.7 (7.00)	12.2 (7.09)

a: The information on treatment duration refers to any study medication.
b: Negative numbers in the observation period are due to the fact that the recording of patient-reported outcomes was first conducted at screening with the time point of randomization serving as reference.
AE: adverse event; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; max: maximum; min: minimum; ND: no data; NSAI: nonsteroidal aromatase inhibitor; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The median treatment duration was about 25% longer in the ribociclib arm than in the placebo arm. The observation periods of most relevant outcomes differed between the study arms in a comparable magnitude. This is due to the fact that patient-reported outcomes were only observed until progression, and AEs up to 30 days after the end of treatment.

Risk of bias across outcomes (study level)

Table 29 shows the risk of bias across outcomes (risk of bias at study level).

Table 29: Risk of bias across outcomes (study level) – RCT, direct comparison: ribociclib + NSAI/tamoxifen vs. placebo + NSAI/tamoxifen

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-7	Yes	Yes	Yes	Yes	Yes	Yes	Low
NSAI: nonsteroidal aromatase inhibitor; RCT: randomized controlled trial; vs.: versus							

The risk of bias across outcomes was rated as low for the MONALEESA-7 study. This concurs with the company's assessment.

2.7.3 Results on added benefit

2.7.3.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.9.4.3.2 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms, recorded with the EORTC QLQ-C30 and the EORTC QLQ-BR23 (symptom scales)
  - health status, measured using the EQ-5D VAS
- Health-related quality of life
  - EORTC QLQ-C30 and EORTC QLQ-BR23 (functional scales)
- Side effects
  - overall rate of SAEs
  - overall rate of severe AEs (CTCAE grade 3–4)
  - overall rate of discontinuations due to AEs
  - blood and lymphatic system disorders (SOC; CTCAE grade 3–4)
  - if applicable, further specific AEs

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in the dossier (Module 4) (see Section 2.9.4.3.2 of the full dossier assessment).

Table 30 shows for which outcomes data were available in the study included.

Table 30: Matrix of outcomes – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women who have received prior endocrine therapy)

Study	Outcomes									
	Overall survival	**EORTC QLQ-C30 (symptom scales)**	**EORTC QLQ-BR23 (symptom scales)**	**Health status (EQ-5D VAS)**	**Health-related quality of life (EORTC QLQ-C30, functional scales)**	**Health-related quality of life (EORTC QLQ-BR23, functional scales)**	**SAEs**	**Discontinuation due to AEs**	**Severe AEs (CTCAE grade 3–4)**	**Blood and lymphatic system disorders (SOC; CTCAE grade 3–4)**
MONALEESA-7	Y	Y	Y	No[a]	Y	Y	Y	Y	Y	Y

a: No usable data available for the relevant subpopulations.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module; 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; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus; Y: yes

2.7.3.2 Risk of bias

Table 31 describes the risk of bias for the results of the relevant outcomes.

Table 31: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women who have received prior endocrine therapy)

Study	Study level	Outcomes									
		Overall survival	EORTC QLQ-C30 (symptom scales)	EORTC QLQ-BR23 (symptom scales)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, functional scales)	Health-related quality of life (EORTC QLQ-BR23, functional scales)	SAEs	Discontinuation due to AEs[a]	Severe AEs (CTCAE grade 3–4)	Blood and lymphatic system disorders (SOC; CTCAE grade 3–4)
MONALEESA-7	L	L	H[b]	H[b]	-[c]	H[b]	H[b]	H[b]	L	H[b]	H[b]

a: Defined as AEs that have led to the discontinuation of treatment with ribociclib or placebo.
b: Differences in the observation periods between the treatment arms with potentially informative censoring in the total population; data for subpopulation B2 were not available.
c: No usable data available for the subpopulation; see Section 2.9.4.3.2 of the full dossier assessment.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module; 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; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

The outcome-specific risk of bias in the MONALEESA-7 study was low only for the results on the outcomes “overall survival” and “discontinuation due to AEs”. The results on all patient-reported outcomes, overall rates of SAEs and severe AEs, as well as specific AEs, were affected by the different durations of observation periods in the treatment arms. It should also be noted that no information was available on the observation periods for both relevant subpopulations of the study. Hence, an unequivocal assessment of whether differences in observation periods were even more or possibly less pronounced in a subpopulation is not possible.

This largely concurs with the assessment of the company, which saw a high risk of bias also for the results on the outcome “discontinuation due to AEs”, however.

2.7.3.3 Results

The results on the comparison of ribociclib + letrozole with placebo + letrozole in pre- and perimenopausal women with HR-positive, HER2-negative advanced or metastatic breast cancer who have progressed after endocrine therapy are summarized in Table 32. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company’s

dossier. Results on common AEs, SAEs and severe AEs (CTCAE grade 3–4) are only available for the total population of the study. They are presented in Appendix B.3 of the full dossier assessment. Kaplan-Meier curves on the presented event time analyses can be found in Appendix C.3 of the full dossier assessment.

Table 32: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women who have received prior endocrine therapy)

Study **Outcome category**	**Ribociclib + letrozole**		**Placebo + letrozole**		**Ribociclib + letrozole vs. placebo + letrozole**
Outcome **Time point**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI][a]; p-value[b]**
MONALEESA-7					
First data cut-off 20 August 2017					
Mortality					
Overall survival	100	NA [21.26; NA] 18 (18.0)	105	28.2 [28.19; NA] 21 (20.0)	0.89 [0.47 1.71]; 0.730
Morbidity					
Symptoms					
EORTC QLQ-C30 (symptom scales)[c]					
Fatigue	100	27.7 [19.4; 27.7] 22 (22.0)	105	16.6 [10.9; NA] 38 (36.2)	0.41 [0.24 0.71]; 0.001
Nausea/ vomiting	100	NA [NA; NA] 5 (5.0)	105	NA [NA; NA] 4 (3.8)	1.13 [0.30 4.25]; 0.862
Pain	100	NA [NA; NA] 12 (12.0)	105	NA [NA; NA] 24 (22.9)	0.44 [0.22 0.88]; 0.017
Dyspnoea	100	NA [NA; NA] 7 (7.0)	105	NA [NA; NA] 3 (2.9)	2.12 [0.54 8.28]; 0.267
Insomnia	100	24.9 [19.4; 24.9] 12 (12.0)	105	22.2 [22.2; NA] 5 (4.8)	2.34 [0.74 7.40]; 0.136
Appetite loss	100	NA [NA; NA] 8 (8.0)	105	NA [NA; NA] 6 (5.7)	1.17 [0.40 3.41]; 0.769
Constipation	100	NA [NA; NA] 8 (8.0)	105	NA [NA; NA] 4 (3.8)	1.50 [0.45 5.04]; 0.509
Diarrhoea	100	NA [NA; NA] 1 (1.0)	105	NA [NA; NA] 1 (1.0)	0.97 [0.06 15.52]; 0.981

(continued)

Table 32: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women who have received prior endocrine therapy) (continued)

Study **Outcome category**	**Ribociclib + letrozole**		**Placebo + letrozole**		**Ribociclib + letrozole vs. placebo + letrozole**
Outcome **Time point**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI][a]; p-value[b]**
EORTC QLQ-BR23 (symptom scales)[c]					
Side effects of systemic treatment	100	16.6 [9.2; 19.4] 45 (45.0)	105	13.1 [9.2; NA] 41 (39.0)	1.00 [0.65 1.54]; 0.990
Symptoms in chest region	100	24.0 [24.0; NA] 12 (12.0)	105	NA [NA; NA] 18 (17.1)	0.45 [0.21 0.96]; 0.036
Symptoms in arm region	100	NA [16.7; NA] 18 (18.0)	105	22.2 [22.2; NA] 20 (19.0)	0.80 [0.42 1.53]; 0.509
Upset by hair loss				No usable data[d]	
Health status					
EQ-5D VAS				No usable data	
Health-related quality of life					
EORTC QLQ-C30 (general health status and functional scales)[e]					
General health status	100	22.1 [16.6; NA] 31 (31.0)	105	14.8 [12.9; NA] 34 (32.4)	0.73 [0.44 1.22]; 0.222
Physical functioning	100	NA [19.4; NA] 20 (20.0)	105	22.2 [22.2; NA] 23 (21.9)	0.78 [0.42 1.45]; 0.417
Role functioning	100	22.1 [19.4; NA] 29 (29.0)	105	NA [14.8; NA] 30 (28.6)	0.71 [0.42 1.21]; 0.214
Emotional functioning	100	19.3 [16.6; NA] 29 (29.0)	105	16.6 [12.9; NA] 36 (34.3)	0.66 [0.40 1.08]; 0.098
Cognitive functioning	100	22.1 [14.8; NA] 34 (34.0)	105	14.8 [11.3; NA] 38 (36.2)	0.63 [0.39 1.01]; 0.063
Social functioning	100	22.1 [16.6; NA] 31 (31.0)	105	19.4 [16.6; NA] 29 (27.6)	0.78 [0.46 1.32]; 0.349

(continued)

Table 32: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women who have received prior endocrine therapy) (continued)

Study **Outcome category**	**Ribociclib + letrozole**		**Placebo + letrozole**		**Ribociclib + letrozole vs. placebo + letrozole**
Outcome **Time point**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI][a]; p-value[b]**
EORTC QLQ-BR23 (functional scales)[e]					
Body image	100	24.0 [13.0; 27.7] 36 (36.0)	105	16.6 [11.1; NA] 38 (36.2)	0.73 [0.45 1.17]; 0.196
Sexual activity	100	NA [16.9; NA] 20 (20.0)	105	NA [NA; NA] 22 (21.0)	0.81 [0.44 1.48]; 0.487
Enjoyment of sex				No usable data[d]	
Future perspective	100	24.0 [24.0; NA] 16 (16.0)	105	NA [14.8; NA] 25 (23.8)	0.49 [0.25 0.96]; 0.032
Side effects					
AEs (additional information)	100	ND	105	ND	–
SAEs	100	NA [NA; NA] 17 (17.0)	105	NA [NA; NA] 15 (14.3)	1.04 [0.52 2.10]; 0.904
Severe AEs (CTCAE grade ≥ 3)	100	1.0 [0.95; 2.17] 77 (77.0)	105	NA [15.97; NA] 32 (30.5)	3.77 [2.48; 5.72]; < 0.001
Discontinuation due to AEs[f]	100	NA [NA; NA] 5 (5.0)	105	NA [NA; NA] 4 (3.8)	1.01 [0.27 3.84]; 0.983
Blood and lymphatic system disorders (SOC, CTCAE grade 3–4)	100	10.1 [0.99; NA] 53 (53.0)	105	NA [NA; NA] 5 (4.8)	14.04 [5.60; 35.24]; < 0.001
Including: Neutropenia (PT, CTCAE grade 3–4)	100	ND	105	ND	-

(continued)

Table 32: Results (mortality, morbidity, health-related quality of life, side effects, time to event) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women who have received prior endocrine therapy) (continued)

a: Cox proportional hazards model stratified by the presence of liver and/or lung metastases, prior chemotherapy in the advanced setting and endocrine combination partner (tamoxifen and goserelin vs. NSAI and goserelin), based on an extension of the Cox regression model with the corresponding subgroup variable and the interaction term treatment*subgroup variable.
b: Two-sided log-rank test stratified by the presence of liver and/or lung metastases, prior chemotherapy in the advanced setting and endocrine combination partner (tamoxifen and goserelin vs. NSAI and goserelin).
c: An increase in score by ≥ 10 points compared with baseline was considered a clinically relevant deterioration if this also applied to all subsequent values.
d: Unclear proportion of patients with missing values at baseline and in the course of the study; drastically decreasing proportion of patients in the analysis until the first documentation time (cycle 3).
e: A decrease in score by ≥ 10 points compared with baseline was considered a clinically relevant deterioration if this also applied to all subsequent values.
f: Defined as AEs that led to discontinuation of treatment with ribociclib or placebo; termination of letrozole treatment alone was not allowed in the framework of the study.
AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module; 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; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; ND: no data; NSAI: nonsteroidal aromatase inhibitor; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Based on the available data, indications, e.g. of an added benefit, can be determined for the outcomes “overall survival” and “discontinuation due to AEs”. There was a high risk of bias of the results for the further outcomes; for the specific outcomes, however, the certainty of conclusions of the results was not always downgraded (see description of the results below and Section 2.9.4.2 of the full dossier assessment).

Mortality

Overall survival

There was no statistically significant difference between the treatment groups for the outcome “overall survival”. This resulted in no hint of an added benefit of ribociclib + letrozole in comparison with letrozole. An added benefit for this outcome is therefore not proven.

This concurs with the assessment of the company, which used the total population for this, however.

Morbidity

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

Symptom outcomes were recorded with the symptom scales of the disease-specific instruments EORTC QLQ-C30 and EORTC QLQ-BR23. In each case, the proportion of patients with definitive deterioration by ≥ 10 points was considered.

Fatigue, pain, symptoms in the chest region

Statistically significant differences, each in favour of ribociclib + letrozole, were shown between the treatment groups for the outcomes "fatigue" and "pain". This resulted in a hint of an added benefit of ribociclib + letrozole in comparison with letrozole for each of both outcomes.

There was also a statistically significant difference in favour of ribociclib for the outcome "symptoms in the chest region". This effect was no more than marginal, however (see Section 2.7.4.1). This resulted in no hint of an added benefit of ribociclib + letrozole in comparison with letrozole for this outcome.

Nausea/vomiting, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, side effects of systemic treatment, symptoms in the arm region, upset by hair loss

No statistically significant difference between the treatment groups was shown for each of the following outcomes: nausea/vomiting, dyspnoea, insomnia, appetite loss, constipation, diarrhoea, side effects of systemic treatment, and symptoms in the arm region. There were no usable data for the outcome "upset by hair loss". In each case, this resulted in no hint of an added benefit of ribociclib + letrozole in comparison with letrozole. An added benefit for these outcomes is therefore not proven.

The company derived an overall added benefit of ribociclib + placebo for symptom outcomes, but on the basis of the total population and without addressing the certainty of conclusions.

Health status (EQ-5D VAS)

There were no usable data for the VAS of the EQ-5D questionnaire for the relevant subpopulation.

Health-related quality of life

EORTC QLQ-C30 and EORTC QLQ-BR23 (functional scales)

A statistically significant difference between the treatment groups was only shown for one outcome in the functional scales of the EORTC questionnaires.

Future perspective

A statistically significant difference in favour of ribociclib + letrozole was shown for the outcome "future perspective". This resulted in a hint of an added benefit of ribociclib + letrozole in comparison with letrozole.

Further functional scales

No statistically significant differences between the treatment groups were shown for each of the following outcomes: general health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning, body image, and sexual activity. There were no usable data for the outcome "enjoyment of sex". In each case, this resulted in no hint

of an added benefit of ribociclib + letrozole in comparison with letrozole. An added benefit for these outcomes is therefore not proven.

This deviates from the approach of the company, which derived an added benefit of ribociclib on the basis of the total population of the study using the EORTC QLQ-C30 functional scales.

Side effects

Serious adverse events

There was no statistically significant difference between the treatment groups for the outcome "SAEs". This resulted in no hint of greater or lesser harm of ribociclib + letrozole in comparison with letrozole. An added benefit for this outcome is therefore not proven.

This concurs with the assessment of the company, which used the total population for this, however.

Severe adverse events (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib + letrozole was shown for the outcome "severe AEs". Due to the size of the effect, there was an indication of greater harm of ribociclib + letrozole in comparison with letrozole despite the high risk of bias.

This concurs with the assessment of the company, which used the total population for this, however, and made no statement on the certainty of conclusions.

Discontinuation due to adverse events

There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". This resulted in no hint of an added benefit of ribociclib + letrozole in comparison with letrozole. An added benefit for this outcome is therefore not proven.

This concurs with the assessment of the company, which used the total population for this, however.

Blood and lymphatic system disorders (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib + letrozole was shown for the outcome "severe blood and lymphatic system disorders". Due to the size of the effect, there was an indication of greater harm of ribociclib + letrozole in comparison with letrozole despite the high risk of bias.

This concurs with the assessment of the company, which used the total population for this, however, and made no statement on the certainty of conclusions.

The company also saw greater harm from ribociclib for the side effect outcomes, but did not downgrade the added benefit because of this. This approach was not followed, see Section 2.7.4.2.

Further specific adverse events

There were no complete usable data for further specific AEs. Due to the differences in observation periods in the study arms, AEs can only be interpreted if event time analyses are available (see Section 2.7.3.2). The company provided these event time analyses only for the AEs chosen by the company itself.

2.7.3.4 Subgroups and other effect modifiers

The assessment of the added benefit was conducted on the basis of a subpopulation of the MONALEESA-7 study. In its dossier, the company presented the results for the relevant subpopulation only in the framework of subgroup analyses because it itself assessed the added benefit on the basis of the total population. There were no data on subgroups of the considered subpopulation for research question B2.

2.7.4 Probability and extent of added benefit

The derivation of probability and extent of the added benefit per subpopulation is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

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

2.7.4.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level was estimated from the results presented in Section 2.7.3.3 (see Table 33).

Determination of the outcome category for the outcomes on “symptoms”

It could not be inferred from the dossier for all outcomes considered in the present benefit assessment whether they were non-serious/non-severe or serious/severe. The classification of these outcomes is justified below.

The symptom scales of the questionnaires EORTC QLQ-C30 and EORTC QLQ-BR23 were considered as non-serious/non-severe outcomes as it was not clear from the dossier whether the symptoms of the patients in the relevant subpopulation were in a range that would be considered serious/severe. In addition, there was no information on absolute threshold values of the EORTC scales that mark a transition on a scale from non-severe to severe manifestation of a symptom or late complication.

Table 33: Extent of added benefit at outcome level: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women who have received prior endocrine therapy)

Outcome category **Outcome**	**Ribociclib + letrozole vs. placebo + letrozole** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	NA vs. 28.2 HR:0.89 [0.47; 1.71]; p = 0.730	Lesser benefit/added benefit not proven
Morbidity		
EORTC QLQ-C30 (symptom scales)		
Fatigue	27.7 vs. 16.6 HR: 0.41 [0.24; 0.71] p = 0.001 probability: “hint”	Outcome category non-serious/non-severe symptoms/late complications $CI_u < 0.80$ added benefit, extent: “considerable”
Nausea/vomiting	NA vs. NA HR: 1.13 [0.30; 4.25] p = 0.862	Lesser benefit/added benefit not proven
Pain	NA vs. NA HR: 0.44 [0.22; 0.88] p = 0.017 probability: “hint”	Outcome category non-serious/non-severe symptoms/late complications $0.80 \leq CI_u < 0.90$ Added benefit, extent: “minor”
Dyspnoea	NA vs. NA HR: 2.12 [0.54; 8.28] p = 0.267	Lesser benefit/added benefit not proven
Insomnia	24.9 vs. 22.2 HR: 2.34 [0.74; 7.40] p = 0.136	Lesser benefit/added benefit not proven
Appetite loss	NA vs. NA HR: 1.17 [0.40; 3.41] p = 0.769	Lesser benefit/added benefit not proven
Constipation	NA vs. NA HR: 1.50 [0.45; 5.04] p = 0.509	Lesser benefit/added benefit not proven
Diarrhoea	NA vs. NA HR: 0.97 [0.06; 15.52] p = 0.981	Lesser benefit/added benefit not proven

(continued)

Table 33: Extent of added benefit at outcome level: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women who have received prior endocrine therapy) (continued)

Outcome category **Outcome**	**Ribociclib + letrozole vs. placebo + letrozole** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
EORTC QLQ-BR23 (symptom scales)		
Side effects of systemic treatment	16.6 vs. 13.1 HR: 1.00 [0.65; 1.54] p = 0.990	Lesser benefit/added benefit not proven
Symptoms in chest region	24.0 vs. NA HR: 0.45 [0.21; 0.96] p = 0.036	Outcome category non-serious/non-severe symptoms/late complications $0.90 \leq CI_u < 1.00$ Lesser benefit/added benefit not proven[c]
Symptoms in arm region	NA vs. 22.2 HR: 0.80 [0.42; 1.53] p = 0.509	Lesser benefit/added benefit not proven
Upset by hair loss	No usable data available	
Health status		
EQ-5D VAS	No usable data available	
Health-related quality of life		
EORTC QLQ-C30 (functional scales)		
General health status	22.1 vs. 14.8 HR: 0.73 [0.44; 1.22] p = 0.222	Lesser benefit/added benefit not proven
Physical functioning	NA vs. 22.2 HR: 0.78 [0.42; 1.45] p = 0.417	Lesser benefit/added benefit not proven
Role functioning	22.1 vs. NA HR: 0.71 [0.42; 1.21] p = 0.214	Lesser benefit/added benefit not proven
Emotional functioning	19.3 vs. 16.6 HR: 0.66 [0.40; 1.08] p = 0.098	Lesser benefit/added benefit not proven
Cognitive functioning	22.1 vs. 14.8 HR: 0.63 [0.39; 1.01] p = 0.063	Lesser benefit/added benefit not proven
Social functioning	22.1 vs. 19.4 HR: 0.78 [0.46; 1.32] p = 0.349	Lesser benefit/added benefit not proven

(continued)

Table 33: Extent of added benefit at outcome level: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women who have received prior endocrine therapy) (continued)

Outcome category **Outcome**	**Ribociclib + letrozole vs. placebo + letrozole** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
EORTC QLQ-BR23 (functional scales)		
Body image	24.0 vs. 16.6 HR: 0.73 [0.45; 1.17] p = 0.196	Lesser benefit/added benefit not proven
Sexual activity	NA vs. NA HR: 0.81 [0.44; 1.48] p = 0.487	Lesser benefit/added benefit not proven
Enjoyment of sex	No usable data available	
Future perspective	24.0 vs. NA HR: 0.49 [0.25; 0.96] p = 0.032 probability: "hint"	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Added benefit, extent: "minor"
Side effects		
SAEs	NA vs. NA HR: 1.04 [0.52; 2.10] p = 0.904	Greater/lesser harm not proven
Severe AEs (CTCAE grade 3–4)	1.0 vs. NA HR: 3.77 [2.48; 5.72] HR: 0.27 [0.17; 0.40][d] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent: "major"
Discontinuation due to AEs	NA vs. NA HR: 1.01 [0.27; 3.84] p = 0.983	Greater/lesser harm not proven
Blood and lymphatic system disorders (SOC, CTCAE grade 3–4)	10.1 vs. NA HR: 14.04 [5.60; 35.24] HR: 0.07 [0.03; 0.18][d] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$ and risk ≥ 5% greater harm, extent: "major"

(continued)

Table 33: Extent of added benefit at outcome level: ribociclib + letrozole vs. placebo + letrozole (pre- and perimenopausal women who have received prior endocrine therapy) (continued)

a: Probability provided if there is a statistically significant and relevant effect.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: The extent of the effect in this non-serious/non-severe outcome was no more than marginal.
d: Institute's calculation, reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module; 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; NA: not achieved; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.7.4.2 Overall conclusion on added benefit

Relevant data were available for the combination of ribociclib + aromatase inhibitor for research question B2. However, these were not applicable to the total population comprised by the research question, but only to pre- and perimenopausal patients with (neo)adjuvant tamoxifen pretreatment and with recurrence during or within 12 months after completion of (neo)adjuvant treatment.

Table 34 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 34: Positive and negative effects from the assessment of ribociclib + letrozole in comparison with letrozole (pre- and perimenopausal women with recurrence ≤ 12 months after completion of [neo]adjuvant treatment)

Positive effects	**Negative effects**
Hint of an added benefit – extent: "considerable" (morbidity: fatigue)	Serious/severe side effects Overall rate of severe AEs (CTCAE grade 3–4): indication of greater harm – extent: "major" ▪ Including in particular: SOC blood and lymphatic system disorders
Hint of an added benefit – extent: "minor" (morbidity: pain)	
Hint of an added benefit – extent: "minor" (health-related quality of life: future perspective)	
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; SOC: System Organ Class	

The consideration of the results showed both positive and negative effects of ribociclib in comparison with the ACT.

Hints of an added benefit of ribociclib were shown for the symptoms "fatigue" and "pain" and for 1 of a total of 10 aspects of health-related quality of life (future perspective). The extents were minor to considerable. This was accompanied by an indication of greater harm of major

extent in severe AEs, including in particular blood and lymphatic system disorders. It can be assumed that, as in the total population of the study, events of severe neutropenia were the determining events (see Table 50 of the full dossier assessment).

There were only hints for all effects in favour of ribociclib. In addition, there was no consistent picture of an advantage across several outcomes for health-related quality of life, but only for 1 of a total of 10 outcomes. This does not allow the derivation of an added benefit for health-related quality of life as a whole. Two positive effects on symptom outcomes remain, which, however, are not sufficient in their certainty of conclusions and extent to compensate for the observed disadvantage from severe side effects.

In summary, there is an indication of lesser benefit of ribociclib + letrozole versus letrozole for pre- and perimenopausal patients with HR-positive, HER2-negative, locally advanced or metastatic breast cancer who have received prior endocrine therapy. This conclusion only refers to part of research question B2, i. e. pre- and perimenopausal patients with (neo)adjuvant tamoxifen pretreatment and with recurrence during or within 12 months after completion of (neo)adjuvant treatment.

This deviates from the assessment of the company, which – based on the total population of the MONALEESA-7 study – derived considerable added benefit of ribociclib with high certainty of conclusions.

2.7.5 List of included studies

MONALEESA-7

Novartis. A phase III randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer: study CLEE011E2301 (MONALEESA-7); clinical study report [unpublished]. 2018.

Novartis. A phase III randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer: study CLEE011E2301 (MONALEESA-7); Zusatzanalysen [unpublished]. 2018.

Novartis Healthcare. A phase III randomized, double-blind, placebo controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI)and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer [online]. In: Clinical Trials Registry - India. 09.01.2019 [Accessed: 08.02.2019]. URL: http://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?trialid=10826.

Novartis Pharma Services. A phase III randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer [online]. In: EU Clinical Trials Register. [Accessed: 08.02.2019]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2014-001931-36.

Novartis Pharmaceuticals. Study of efficacy and safety in premenopausal women with hormone receptor positive, HER2-negative advanced breast cancer (MONALEESA-7): study details [online]. In: ClinicalTrials.gov. 10.08.2018 [Accessed: 08.02.2019]. URL: https://ClinicalTrials.gov/show/NCT02278120.

Tripathy D, Im SA, Colleoni M, Franke F, Bardia A, Harbeck N et al. Ribociclib plus endocrine therapy for premenopausal women with hormone-receptor-positive, advanced breast cancer (MONALEESA-7): a randomised phase 3 trial. Lancet Oncol 2018; 19(7): 904-915.

2.8 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of ribociclib in comparison with the ACT is summarized in Table 35.

Table 35: Ribociclib – 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	▪ *Combination with fulvestrant:* added benefit not proven
A2: pre- and perimenopausal women, initial endocrine therapy	Tamoxifen in combination with suppression of the ovarian function	▪ *Combination with fulvestrant:* added benefit not proven ▪ *Combination with aromatase inhibitor:* added benefit not proven
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[d] 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	▪ *Combination with fulvestrant:* added benefit not proven[c] ▪ *Combination with aromatase inhibitor:* added benefit not proven
B2: pre- and perimenopausal women who have received prior endocrine therapy	Endocrine therapy specified by the physician under consideration of the respective approval[e] Tamoxifen, letrozole, exemestane, megestrol acetate and medroxyprogesterone acetate are approved in the present therapeutic indication.	▪ *Combination with fulvestrant:* added benefit not proven ▪ *Combination with aromatase inhibitor:* ▫ indication of lesser benefit[f, g]

(continued)

Table 35: Ribociclib – probability and extent of added benefit (continued)

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 the overall assessment, the results of the MONALEESA-3 study led neither to an advantage nor to a disadvantage of ribociclib + fulvestrant versus placebo + fulvestrant.
d: 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 comparison.
e: It is assumed that ovarian suppression with a GnRH analogue is continued in the therapeutic indication B2. The available evidence for megestrol acetate and medroxyprogesterone acetate in the therapeutic indication B2 is considered inadequate for a concrete recommendation. In addition, the progestogens are explicitly approved only for the palliative treatment of breast cancer.
f: Only patients with an ECOG PS of 0 or 1 were included in the MONALEESA-7 study. It remains unclear whether the observed effects can be transferred to patients with an ECOG PS of ≥ 2.
g: This conclusion only refers to part of research question B2, i. e. pre- and perimenopausal patients with (neo)adjuvant tamoxifen pretreatment and with recurrence during or within 12 months after completion of (neo)adjuvant treatment.

ACT: appropriate comparator therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; GnRH: gonadotropin-releasing hormone

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.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58.

3. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Ribociclib (Mammakarzinom): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A17-45 [online]. 13.12.2017 [Accessed: 04.01.2018]. (IQWiG-Berichte; Volume 567). URL: https://www.iqwig.de/download/A17-45_Ribociclib_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

4. AstraZeneca. Faslodex 250 mg Injektionslösung: Fachinformation [online]. 09.2018 [Accessed: 14.02.2019]. URL: https://www.fachinfo.de.

5. Novartis Pharma. Kisqali 200 mg Filmtabletten: Fachinformation [online]. 12.2018 [Accessed: 13.02.2019]. URL: https://www.fachinfo.de.

6. European Medicines Agency. Kisqali: European public assessment report; variation EMEA/H/C/004213/II/0004 [online]. 15.11.2018 [Accessed: 22.02.2019]. URL: https://www.ema.europa.eu/documents/variation-report/kisqali-h-c-4213-ii-0004-epar-assessment-report-variation_en.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-06-ribociclib-breast-cancer-benefit-assessment-according-to-35a-social-code-book-v.11476.html.