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Ribociclib (breast cancer, combination with an aromatase inhibitor) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Ribociclib (Mammakarzinom, Kombination mit einem Aromatasehemmer) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung)* (Version 1.0; Status: 28 May 2020). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module
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)
MMRM	mixed-effects model repeated measures
PFS	progression-free survival
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
VAS	visual analogue scale

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ribociclib in combination with an aromatase inhibitor. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 3 March 2020. The company submitted a first dossier of the drug to be evaluated on 5 September 2017 for the early benefit assessment. In this procedure, the G-BA's decision was limited in time until 1 March 2020.

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

Research question

The aim of the present report is the assessment of the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the appropriate comparator therapy (ACT) in the treatment of postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer as initial endocrine-based therapy.

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

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

Therapeutic indication[a]	**ACT**[b]
Initial endocrine therapy of HR-positive and HER2-negative locally advanced or metastatic breast cancer in postmenopausal women	Anastrozole or letrozole or fulvestrant or, if applicable, tamoxifen if aromatase inhibitors are unsuitable
a. It is assumed for the present therapeutic indication that (if applicable, another) endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent. b. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor	

The company followed the ACT specified by the G-BA.

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

Results

Study pool and study characteristics

The study MONALEESA-2, which compared the combination of ribociclib + letrozole with placebo + letrozole, was included in the benefit assessment of ribociclib. No data were available on the comparison of the combination of ribociclib with other aromatase inhibitors versus the ACT.

The MONALEESA-2 study is already known from the previous benefit assessment of ribociclib in the present therapeutic indication; with the current dossier, the company presented data on a further data cut-off.

Postmenopausal women with locally advanced or metastatic HR-positive and HER2-negative breast cancer were included in the MONALEESA-2 study. On study entry, patients had to have an Eastern Cooperative Oncology Group Performance Status (ECOG PS) < 2 and were not allowed to have received prior systemic anticancer therapy for advanced or metastatic disease. A total of 668 patients were included in the MONALEESA-2 study and randomized to ribociclib + letrozole or placebo + letrozole. Treatment in the therapy arms was largely consistent with the Summaries of Product Characteristics (SPCs) of ribociclib and letrozole.

Treatment with the study medication was conducted until disease progression, unacceptable toxicity, death, or discontinuation due to any other reason. After discontinuation of the study medication, patients in both study arms could start subsequent treatment.

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

Risk of bias and certainty of conclusions of the results

The risk of bias at study level was rated as low for the MONALEESA-2 study. There was a low risk of bias also for the outcome “overall survival”. Due to incomplete observations for potentially informative reasons, there was a high risk of bias for the results of the following outcomes: symptoms, health-related quality of life, serious adverse events (SAEs), severe AEs according to Common Terminology Criteria for Adverse Events (CTCAE) grade 3–4, neutropenia (CTCAE grade 3–4), and further specific AEs. The certainty of results for the outcome “discontinuation due to AEs” was limited despite a low risk of bias.

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

Mortality – overall survival

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

Morbidity – symptoms, recorded with the symptom scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module (EORTC QLQ-BR23)

Dyspnoea

In the total population, there was no statistically significant difference between the treatment groups for the symptom scale "dyspnoea". However, there was an effect modification by the characteristic "age". This resulted in a hint of lesser benefit of ribociclib + letrozole in patients ≥ 65 years of age for the outcome "dyspnoea". For patients < 65 years of age, there was no hint of lesser benefit or of an added benefit of ribociclib + letrozole in comparison with letrozole; lesser benefit or an added benefit is therefore not proven.

All other symptom scales

No statistically significant difference between the treatment groups was shown for any of the other symptom scales (fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation and diarrhoea, side effects of systemic treatment, breast symptoms, and arm symptoms). As a result, there was no hint of an added benefit of ribociclib + letrozole in comparison with letrozole for any of these outcomes; an added benefit is therefore not proven.

Morbidity – health status

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

Health-related quality of life, recorded with the global health status and the functional scales of the EORTC QLQ-C30 and of the EORTC QLQ-BR23

Future perspective

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

All other scales

No statistically significant difference between the treatment arms was shown for any of the other functional scales and for the global health status scale of the EORTC QLQ-C30. In each case, this resulted in no hint of an added benefit of ribociclib + letrozole in comparison with letrozole; an added benefit is therefore not proven.

Side effects – SAEs

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

Side effects – discontinuation due to AEs

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

Side effects – severe AEs (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib + letrozole was shown for the outcome "severe AEs (CTCAE grade 3–4)". Due to the size of the observed effect, there was an indication of greater harm of ribociclib + letrozole in comparison with letrozole for this outcome.

Side effects – specific AEs

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

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

Severe AEs (CTCAE grade 3–4): gastrointestinal disorders, infections and infestations; AEs: eye disorders and skin and subcutaneous tissue disorders

Statistically significant differences to the disadvantage of ribociclib + letrozole were shown for the specific severe AEs (CTCAE grade 3–4) "gastrointestinal disorders" and "infections and infestations", as well as for the specific AEs (regardless of severity grade) "eye disorders" and "skin and subcutaneous tissue disorders". This resulted in a hint of greater harm of ribociclib + letrozole in comparison with letrozole for these outcomes.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug ribociclib in combination with an aromatase inhibitor in comparison with the ACT are assessed as follows:

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of

In the overall consideration, there are both positive and negative effects of ribociclib in comparison with letrozole. There are advantages in the outcome category of mortality (overall survival) and in the functional scale "future perspective" of health-related quality of life, and disadvantages in the outcome category of side effects, and particularly in the category of serious/severe side effects, as well as for the subgroup of patients ≥ 65 years of age in the symptom scale "dyspnoea" of the outcome category of non-serious/non-severe symptoms/late complications.

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

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

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

Therapeutic indication[a]	**ACT**[b]	**Probability and extent of added benefit**
Initial endocrine therapy of HR-positive and HER2-negative advanced or metastatic breast cancer in postmenopausal women	Anastrozole or letrozole or fulvestrant or, if applicable, tamoxifen if aromatase inhibitors are unsuitable	Added benefit not proven[c]

a. It is assumed for the present therapeutic indication that endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
b. Presentation of the respective ACT specified by the G-BA.
c. Only patients with an ECOG PS of 0 or 1 were included in the MONALEESA-2 study. It remains unclear whether the observed results can be transferred to patients with an ECOG PS of ≥ 2. Almost all patients included in the study had stage IV disease (breast cancer with distant metastasis).

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

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

(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].

2.2 Research question

The aim of the present report is the assessment of the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT in the treatment of postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer as initial endocrine-based therapy.

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

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

Therapeutic indication[a]	**ACT**[b]
Initial endocrine therapy of HR-positive and HER2-negative locally advanced or metastatic breast cancer in postmenopausal women	Anastrozole or letrozole or fulvestrant or, if applicable, tamoxifen if aromatase inhibitors are unsuitable
a. It is assumed for the present therapeutic indication that (if applicable, another) endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent. b. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor	

The company followed the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

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

To check the completeness of the study pool:

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

No additional relevant study was identified from the check.

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

2.3.1 Studies included

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

Table 5: Study pool – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
MONA-LEESA-2	Yes	Yes	No	No[c]	Yes [3-5]	Yes [6-13]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Due to the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

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

The MONALEESA-2 study, which directly compared the combination of ribociclib + letrozole with placebo + letrozole, was included in the benefit assessment of ribociclib in combination with an aromatase inhibitor. This concurs with the company's approach. No data were available on the comparison of the combination of ribociclib with other aromatase inhibitors versus the ACT.

The MONALEESA-2 study is already known from the previous benefit assessment of ribociclib in the present therapeutic indication [12,13]; with the current dossier, the company presented data on a further data cut-off.

2.3.2 Study characteristics

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

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

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MONA-LEESA-2	RCT, double-blind, parallel	Postmenopausal women with locally recurrent or metastatic HR-positive[b] and HER2-negative[c] breast cancer without prior antineoplastic therapy for advanced disease	Ribociclib + letrozole (N = 334) placebo + letrozole (N = 334)[d]	▪ Screening: up to 21 days ▪ Treatment: until disease progression, death, unacceptable toxicity or study discontinuation due to any other reason ▪ Observation: outcome-specific[e], at most until death, withdrawal of consent, loss to follow-up, study discontinuation by sponsor, or final survival time analysis	223 centres in: Argentina, Australia, Austria, Belgium, Brazil, Canada, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Israel, Italy, Lebanon, Netherlands, Norway, Republic of Korea, Russian Federation, Singapore, South Africa, Spain, Sweden, Taiwan, Thailand, Turkey, United Kingdom, USA 12/2013–ongoing Data cut-offs: First interim analysis: after 243 PFS events (29 January 2016) Second interim analysis: after 100 deaths (2 January 2017 or 4 January 2017) Third interim analysis: after 300 deaths (8 May 2019) Pending analysis: ▪ final analysis after 400 deaths	▪ primary: PFS ▪ secondary: overall survival, symptoms, health status, 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. Histological and/or cytological confirmation of positive ER and/or PR status.
c. Defined as a negative in situ hybridization test or an IHC status of 0, 1+ or 2+. If IHC was 2+, a negative FISH, CISH, or SISH test was required.
d. 4 patients in this study arm received no dose of the allocated study medication.
e. Outcome-specific information is provided in Table 8.

AE: adverse event; CISH: chromosome in situ hybridization; ER: oestrogen receptor; FISH: fluorescence in situ hybridization; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IHC: immunohistochemical; N: number of randomized patients; PFS: progression-free survival; PR: progesterone receptor; RCT: randomized controlled trial; SISH: silver-enhanced in situ hybridization; vs.: versus

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

Study	Intervention	Comparison
MONA-LEESA-2	Ribociclib 600 mg/day, orally, day 1–21 in a 28-day cycle + letrozole 2.5 mg/day	Placebo orally, day 1–21 in a 28-day cycle + letrozole 2.5 mg/day
	Dose adjustments: ribociclib/placebo: reduction (to 400 mg/day or 200 mg/day), interruption or discontinuation possible in case of toxicity letrozole: no adjustment allowed	
	Pretreatment: ▪ not allowed: CDK4/6 inhibitors, systemic antineoplastic therapy for advanced or metastatic disease ▪ the following prior therapies had to be completed 1–4 weeks before starting the study treatment: (neo)adjuvant antineoplastic therapy[a], radiotherapy[b], strong CYP3A4/5 inhibitors or inducers, CYP3A4/5 substrates with narrow therapeutic indices, drugs with known risk to prolong the QT interval or induce Torsades de Pointes, herbal agents, systemic corticosteroids[c] **Concomitant treatment:** allowed: ▪ bisphosphonates and denosumab for the treatment of osteoporosis and for the prevention of skeletal-related events in patients with bone metastases (not allowed as chronic concomitant treatment for the prevention of bone metastases) ▪ haematopoietic growth factors (corresponding to ASCO guidelines) ▪ palliative radiotherapy for alleviation of bone pain (except target lesions)[b] ▪ systemic corticosteroids[c, d] not allowed: ▪ strong CYP3A4/5 inhibitors or inducers ▪ CYP3A4/5 substrates with narrow therapeutic indices ▪ drugs with known risk to prolong the QT interval ▪ other study medication and other antineoplastic therapies ▪ herbal agents (except vitamins)	

a. If prior therapy with letrozole or anastrozole was longer than 14 days, the disease-free interval had to be greater than 12 months from the discontinuation of treatment until randomization.
b. Radiation of ≥ 25% of the bone marrow is not allowed.
c. Individual doses of topical application, inhaled use, eye drops and local injections are allowed.
d. Allowed as short-term treatment (< 5 days) with a maximum total daily dose equivalent to the anti-inflammatory potency of 4 mg dexamethasone.

ASCO: American Society of Clinical Oncology; CDK: cyclin-dependent kinase; CYP: cytochrome P450; RCT: randomized controlled trial; vs.: versus

The MONALEESA-2 study was a double-blind RCT directly comparing ribociclib in combination with letrozole versus placebo + letrozole. Postmenopausal women with locally advanced or metastatic HR-positive and HER2-negative breast cancer were included in the study. On study entry, patients had to have an ECOG PS < 2 and were not allowed to have received prior systemic antineoplastic therapy for advanced or metastatic disease. Endocrine-based therapies in the (neo)adjuvant setting were allowed. A total of 668 patients were included

in the MONALEESA-2 study and randomized to the 2 treatment arms. Randomization into the 2 study arms was in a 1:1 ratio, stratified according to the presence of liver and/or lung metastases (yes versus no).

Treatment in the therapy arms was largely consistent with the SPCs of ribociclib and letrozole [14,15]. For ribociclib, there were deviations from the SPC regarding the handling of toxicities. In case of toxicities that were not explicitly mentioned in the SPC (i.e. other than neutropenia or increased alanine and/or aspartate aminotransferase or QT prolongations), from CTCAE grade 2, administration of ribociclib or placebo in the MONALEESA-2 study was interrupted until improvement to CTCAE grade 1 or lower. The SPC of ribociclib recommends interruption of ribociclib only in case of CTCAE grade 3 or higher. It was unclear how many patients were treated with this deviating approach. It was not assumed, however that this had relevant effects on the applicability of the study results to everyday practice. The MONALEESA-2 study mandated no dose adjustments for letrozole, which concurs with the SPC of letrozole. In the study, letrozole was only allowed to be discontinued together with ribociclib or placebo.

Treatment with the study medication was conducted until disease progression, unacceptable toxicity, death, or discontinuation due to any other reason. After discontinuation of the study medication, patients in both study arms could start subsequent treatment. Treatment switching from the comparator intervention placebo to the experimental intervention ribociclib was not allowed, however. At the time point of the third data cut-off, 234 (70.1%) of the patients in the ribociclib + letrozole arm and 272 (81.4%) of the patients in the placebo + letrozole arm had received subsequent therapy. The most common subsequent antineoplastic therapies can be found in Table 26 in Appendix C of the full dossier assessment.

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

Data cut-offs

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

- First data cut-off (29 January 2016): planned interim analysis after 211 PFS events, first interim analysis for overall survival
- Second data cut-off (2 January 2017 or 4 January 2017): planned second interim analysis for overall survival after 100 deaths or addendum with results on morbidity, quality of life and AEs
- Third data cut-off (8 May 2019): planned third interim analysis for overall survival after 300 deaths

The final analysis of the MONALEESA-2 study is planned for the time point after 400 deaths.

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

Planned duration of follow-up observation

Table 8 shows the planned duration of follow-up observation of the patients for the individual outcomes.

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

Study **Outcome category** **Outcome**	**Planned follow-up observation**
MONALEESA-2	
Mortality	
Overall survival	▪ After discontinuation of treatment until death, withdrawal of consent, loss to follow-up, study discontinuation by sponsor, or final survival time analysis[a]
Morbidity	
Symptoms (EORTC QLQ-C30 and EORTC QLQ-BR23)	▪ Until progression, death, withdrawal of consent, or loss to follow-up
Health status (EQ-5D VAS)	▪ Until progression, death, withdrawal of consent, or loss to follow-up
Health-related quality of life (EORTC QLQ-C30 and EORTC QLQ-BR23)	▪ Until progression, death, withdrawal of consent, or loss to follow-up
Side effects	
All outcomes in the category of side effects	▪ Until up to 30 days after the end of treatment
a. Planned after about 400 deaths.	
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; VAS: visual analogue scale; vs.: versus	

Only overall survival was recorded until the end of study participation.

The observation periods for the outcomes “morbidity”, “health-related quality of life” and “side effects” were systematically shortened because they were only recorded until progression or, for side effects, until the end of treatment (plus 30 days). To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary to record these outcomes over the total period of time, as was the case for overall survival.

Characteristics of the study population

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

Table 9: Characteristics of the study population – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (multipage table)

Study Characteristics Category	**Ribociclib + letrozole N[a] = 334**	**Placebo + letrozole N[a] = 334**
MONALEESA-2		
Age [years], mean (SD)	61 (11)	62 (11)
Region, n (%)		
Asia	35 (10.5)	33 (9.9)
Europe	150 (44.9)	146 (43.7)
Latin America	7 (2.1)	7 (2.1)
North America	108 (32.3)	121 (36.2)
Other	34 (10.2)	27 (8.1)
ECOG PS, n (%)		
0	205 (61.4)	202 (60.5)
1	129 (38.6)	132 (39.5)
Disease stage on study entry, n (%)		
III	1 (0.3)	3 (0.9)
IV	333 (99.7)	331 (99.1)
Disease-free interval, n (%)		
De novo	114 (34.1)	113 (33.8)
Not de novo	220 (65.9)	221 (66.2)
≤ 12 months	4 (1.2)	10 (3.0)
> 12 to ≤ 24 months	14 (4.2)	15 (4.5)
> 24 months	202 (60.5)	195 (58.4)
Unknown	0 (0)	1 (0.3)
Type of most recent treatment, n (%)		
Chemotherapy	7 (2.1)	10 (3.0)
Endocrine therapy	129 (38.6)	134 (40.1)
Radiotherapy	75 (22.5)	64 (19.2)
Surgery (not biopsy)	57 (17.1)	62 (18.6)
Setting of most recent treatment, n (%)		
Adjuvant	136 (40.7)	135 (40.4)
Neoadjuvant	1 (0.3)	2 (0.6)
Palliative	45 (13.5)	45 (13.5)
Prevention	2 (0.6)	5 (1.5)
Other	21 (6.3)	18 (5.4)

Table 9: Characteristics of the study population – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (multipage table)

Study Characteristics Category	**Ribociclib + letrozole N[a] = 334**	**Placebo + letrozole N[a] = 334**
Location of metastases, n (%)		
Breast	8 (2.4)	11 (3.3)
Bone marrow	0 (0)	2 (0.6)
Bones	246 (73.7)	244 (73.1)
Bone only	69 (20.7)	78 (23.4)
Visceral	197 (59.0)	196 (58.7)
Liver	59 (17.7)	73 (21.9)
Lungs	153 (45.8)	150 (44.9)
Other	22 (6.6)	18 (5.4)
Skin	15 (4.5)	10 (3.0)
Lymph nodes	133 (39.8)	123 (36.8)
Other	20 (6.0)	10 (3.0)
None	2 (0.6)	1 (0.3)
Treatment discontinuation[b], n (%)	274 (82.0[c])	299[d] (89.5[c])
Study discontinuation, n (%)	ND	ND

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Discontinuation of the total study medication; data cut-off on 8 May 2019; the ribociclib + letrozole arm contains 5 deaths, the placebo + letrozole arm contains 1 death.
c. Institute's calculation.
d. Without 4 patients who did not start the study medication; main reason for treatment discontinuation was radiological disease progression (intervention: 66%; control: 83%).

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 characteristics of the patients were comparable between both study arms. The mean age of the patients on study entry was about 60 years; they were mostly allocated to the regions of Europe and North America. About 60% of the patients in each study arm had an ECOG PS of 0; the remaining patients had an ECOG PS of 1. More than 99% of the study population had stage IV disease, i.e. distant metastasis, on study entry. Disease history and location of the metastases were comparable beyond the stratification factor "presence of liver and/or lung metastases".

Table 10 shows the median observation period for individual outcomes.

Table 10: Information on the course of the study – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole

Study **Duration of the study phase** **Outcome category**	**Ribociclib + letrozole** **N = 334**	**Placebo + letrozole** **N = 334[a]**
MONALEESA-2		
Treatment duration	ND	ND
Observation period [months]		
Overall survival	ND	ND
Symptoms and health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	19.4 [ND]	13.3 [ND]
Mean (SD)	ND	ND
Symptoms and health-related quality of life (EORTC QLQ-BR23)		
Median [min; max]	19.4 [ND]	13.3 [ND]
Mean (SD)	ND	ND
Health status (EQ-5D VAS[b])	15.8 [ND]	12.9 [ND]
Side effects		
Median [min; max]	21.2 [ND]	15.1 [ND]
Mean (SD)	ND	ND

a. N = 330 for side effects, this number of patients received at least one dose of the study medication.
b. Unclear discrepancy between observation periods with the same recording.

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; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

There is no information on treatment duration for the new data cut-off from 8 May 2019. The observation periods of the outcomes on symptoms, health-related quality of life, health status and side effects were longer in the ribociclib + letrozole arm than in the placebo + letrozole arm. Since these outcomes were recorded until progression or end of treatment, it can be assumed that the treatment duration was longer in the ribociclib + letrozole arm than in the placebo + letrozole arm. As for treatment duration, there was no information on the observation period of the outcome “overall survival”.

Risk of bias across outcomes (study level)

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

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

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-2	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 RCT MONALEESA-2. This concurs with the company's assessment.

Transferability of the study results to the German health care context

The company described in Module 4 A that the results of the MONALEESA-2 study can be transferred to the German health care context.

It justified this by stating that the majority of the patients in the study were of Caucasian family origin and that the majority of the patients were treated in Europe or North America, i.e. in countries where health care standards are high and largely comparable with those in Germany. It also stated that both age and disease and treatment characteristics reflected the characteristics of the target population in everyday health care. The company additionally argued that the subgroup analyses carried out did not show any relevant effect modifications from the characteristic "family origin" (Asian versus non-Asian) and that the results for the subgroup of patients treated in Europe or North America did not differ notably from the total population.

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

2.4 Results on added benefit

2.4.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - symptoms recorded with the symptom scales of the instruments EORTC QLQ-C30 and EORTC QLQ-BR23
  - health status recorded with the VAS of the EQ-5D questionnaire
- Health-related quality of life
  - recorded with the global health status and the functional scales of the EORTC QLQ-C30 as well as with the functional scales of the EORTC QLQ-BR23
- Side effects
  - SAEs
  - severe AEs (CTCAE grade 3–4)
  - discontinuation due to AEs
  - neutropenia (PT, CTCAE grade 3–4)
  - if applicable, further specific AEs

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

Table 12 shows for which outcomes data were available in the study included.

Table 12: Matrix of outcomes – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole

Study	Outcomes								
	Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)	SAEs	Severe AEs (CTCAE grade 3–4)	Discontinuation due to AEs	Neutropenia (PT, CTCAE grade 3–4)	Further specific AEs[a]
MONALEESA-2	Yes	Yes	No[b]	Yes	Yes	Yes	Yes	Yes	Yes

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

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer-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; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

No usable analyses were available for the outcome "health status" (recorded using EQ-5D VAS). The recording of the health status by means of a VAS is generally regarded as patient-relevant. However, referring to the work of Pickard 2007 [16], the company presented responder analyses for the time to definitive deterioration by ≥ 7 or ≥ 10 points in the dossier. The response criteria chosen by the company are not validated, and their analyses are therefore not usable [17]. A supplementary presentation of the results can be found in Appendix D of the full dossier assessment. The analysis of the mean differences (mixed-effects model repeated measures [MMRM] analysis) predefined for health status is not available.

2.4.2 Risk of bias

Table 13 describes the risk of bias for the results of the relevant outcomes.

Table 13: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole

Study	Study level	Outcomes								
		Overall survival	Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23)	Health status (EQ-5D VAS)	Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23)	SAEs	Severe AEs (CTCAE grade 3–4)	Discontinuation due to AEs	Neutropenia (PT, CTCAE grade 3–4)	Further specific AEs[a]
MONALEESA-2	L	L	H[b, c]	–[c]	H[b, c]	H[b]	H[b]	L[d]	H[b]	H[b]

a. The following events are considered (MedDRA coding): eye disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), blood and lymphatic system disorders (SOC, severe AEs [CTCAE grade 3-4]), gastrointestinal disorders (SOC, severe AEs [CTCAE grade 3–4]), infections and infestations (SOC, severe AE [CTCAE grade 3–4]), and investigations (SOC, severe AEs [CTCAE grade 3–4]).
b. Incomplete observations for potentially informative reasons.
c. No usable data available; for reasons, see Section 2.4.1.
d. Despite the low risk of bias, limited certainty of results is assumed for the outcome "discontinuation due to AEs".

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-BR23: European Organisation for Research and Treatment of Cancer-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; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

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

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

Although the risk of bias for the outcome "discontinuation due to AEs" was low, the certainty of results for this outcome was limited. Premature treatment discontinuation for reasons other than AEs is a competing event for the outcome "discontinuation due to UEs" to be recorded. This means that after discontinuation for other reasons, AEs that would have led to treatment discontinuation may have occurred, but that the criterion "discontinuation" can no longer be applied to them. It cannot be estimated how many AEs this concerns.

This assessment concurs with that of the company.

2.4.3 Results

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

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

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (multipage table)

Study **Outcome category** **Outcome**	**Ribociclib + letrozole**		**Placebo + letrozole**		**Ribociclib + letrozole vs. placebo + letrozole**
	N	**Median time to event in months [95% CI][a]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI][a]** **Patients with event n (%)**	**HR [95% CI][b]; p-value[c]**
MONALEESA-2 (data cut-off 8 May 2019)					
Mortality					
Overall survival	334	NA [52.2; NC] 136 (40.7)	334	51.4 [47.2; 58.4] 167 (50.0)	0.78 [0.62 0.98]; 0.034
Morbidity					
Symptoms					
EORTC QLQ-C30 symptom scales, time to definitive deterioration[d, e]					
Fatigue	334	NA [48.76; NC] 92 (27.5)	334	55.1 [39.52; NC] 91 (27.2)	0.82 [0.61; 1.09]; 0.171
Nausea/vomiting	334	NA 15 (4.5)	334	NA 15 (4.5)	0.84 [0.41; 1.73]; 0.634
Pain	334	NA 57 (17.1)	334	NA 64 (19.2)	0.72 [0.50; 1.03]; 0.068
Dyspnoea	334	NA 24 (7.2)	334	NA 12 (3.6)	1.73 [0.86; 3.48]; 0.120
Insomnia	334	NA 28 (8.4)	334	NA 21 (6.3)	1.04 [0.58; 1.84]; 0.902
Appetite loss	334	NA 17 (5.1)	334	NA 22 (6.6)	0.66 [0.35; 1.26]; 0.204
Constipation	334	NA 13 (3.9)	334	NA 11 (3.3)	0.98 [0.43; 2.20]; 0.955
Diarrhoea	334	NA 5 (1.5)	334	NA 5 (1.5)	0.92 [0.26; 3.16]; 0.889

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (multipage table)

Study **Outcome category** **Outcome**	**Ribociclib + letrozole** **N**	**Ribociclib + letrozole** **Median time to event in months [95% CI][a]** **Patients with event n (%)**	**Placebo + letrozole** **N**	**Placebo + letrozole** **Median time to event in months [95% CI][a]** **Patients with event n (%)**	**Ribociclib + letrozole vs. placebo + letrozole** **HR [95% CI][b]; p-value[c]**
EORTC QLQ-BR23 symptom scales, time to definitive deterioration[d, e]					
Side effects of systemic therapy	334	32.0 [19.35; 41.66] 155 (46.4)	334	31.3 [19.42; 40.21] 129 (38.6)	1.14 [0.90; 1.44]; 0.292
Breast symptoms	334	NA 35 (10.5)	334	NA [55.20; NC] 27 (8.1)	1.07 [0.64; 1.77]; 0.804
Arm symptoms	334	58.0 [NC] 34 (10.2)	334	NA [52.47; NC] 38 (11.4)	0.70 [0.44; 1.12]; 0.139
Upset by hair loss				No usable data[f]	
Health status					
EQ-5D VAS				No usable data	
Health-related quality of life					
EORTC QLQ-C30 global health status and functional scales, time to definitive deterioration[e, g]					
Global health status	334	47.9 [39.33; 52.47] 112 (33.5)	334	46.9 [33.12; 55.49] 106 (31.7)	0.89 [0.68; 1.16]; 0.400
Physical functioning	334	52.7 [44.09; NC] 98 (29.3)	334	55.1 [41.43; NC] 81 (24.3)	1.00 [0.75; 1.35]; 0.986
Role functioning	334	52.5 [46.92; NC] 102 (30.5)	334	40.1 [30.46; NC] 98 (29.3)	0.84 [0.63; 1.11]; 0.218
Emotional functioning	334	52.7 [49.71; NC] 92 (27.5)	334	48.4 [39.13; NC] 95 (28.4)	0.76 [0.57; 1.02]; 0.069
Cognitive functioning	334	50.6 [38.67; 52.50] 116 (34.7)	334	41.5 [33.02; 49.71] 113 (33.8)	0.85 [0.66; 1.11]; 0.227
Social functioning	334	NA [50.04; NC] 88 (26.3)	334	56.1 [39.56; NC] 78 (23.4)	0.93 [0.68; 1.26]; 0.641
EORTC QLQ-BR23 functional scales, time to definitive deterioration[e, g]					
Body image	334	58.2 [50.73; 58.22] 99 (29.6)	334	NA [49.68; NC] 74 (22.2)	1.23 [0.91; 1.67]; 0.179
Sexual functioning	334	NA 43 (12.9)	334	NA [55.20; NC] 54 (16.2)	0.68 [0.46; 1.02]; 0.059
Sexual enjoyment				No usable data[f]	
Future perspective	334	NA 55 (16.5)	334	NA [41.43; NC] 69 (20.7)	0.63 [0.44; 0.90]; 0.011

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (multipage table)

Study Outcome category Outcome	Ribociclib + letrozole N	Ribociclib + letrozole Median time to event in months [95% CI][a] Patients with event n (%)	Placebo + letrozole N	Placebo + letrozole Median time to event in months [95% CI][a] Patients with event n (%)	Ribociclib + letrozole vs. placebo + letrozole HR [95% CI][b]; p-value[c]
Side effects					
AEs (supplementary information)	334	0.20 [0.13; 0.26] 331 (99.1)	330	0.38 [0.26; 0.46] 322 (97.6)	-
SAEs	334	NA [48.69; NC] 100 (29.9)	330	NA [52.47; NC] 61 (18.5)	1.52 [1.11; 2.10]; 0.009
Severe AEs (CTCAE grade 3–4)	334	0.95 [NC] 295 (88.3)	330	27.63 [19.35; 37.55] 139 (42.1)	3.99 [3.25; 4.90]; < 0.001
Discontinuation due to AEs[h]	334	NA 66 (19.8)	330	NA 15 (4.5)	4.08 [2.33; 7.16]; < 0.001
Blood and lymphatic system disorders (SOC, CTCAE grade 3–4)	334	3.14 [6.37; 20.73] 187 (56.0)	330	NA 11 (3.3)	23.58 [12.83; 43.34]; < 0.001
including: neutropenia (PT, CTCAE grade 3–4)	334	15.67 [7.82; 26.02] 173 (51.8)	330	NA 3 (0.9)	77.22 [24.65; 241.83]; < 0.001
Gastrointestinal disorders (SOC, CTCAE grade 3–4)	334	NA 49 (14.7)	330	NA 14 (4.2)	3.35 [1.85; 6.07]; < 0.001
Infections and infestations (SOC, CTCAE grade 3–4)	334	NA 29 (8.7)	330	NA 12 (3.6)	2.13 [1.08; 4.18]; 0.024
Investigations (SOC, CTCAE grade 3–4)	334	53.95 [27.53; NC] 136 (40.7)	330	NA 28 (8.5)	5.54 [3.69; 8.33]; < 0.001
Eye disorders (SOC, AEs)	334	NA [40.84; NC] 105 (31.4)	330	NA 45 (13.6)	2.30 [1.62; 3.27]; < 0.001
Skin and subcutaneous tissue disorders (SOC, AEs)	334	4.67 [3.71; 6.47] 217 (65.0)	330	42.64 [17.25; NC] 130 (39.4)	2.15 [1.73; 2.67]; < 0.001

Table 14: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (multipage table)

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

a. Median time to event and corresponding 95% CI were estimated using the Kaplan-Meier method.
b. Effect and CI: Cox proportional hazards model, stratified by the presence of liver and/or lung metastases according to IRT.
c. p-value: log-rank test stratified by the presence of liver and/or lung metastases according to IRT.
d. An increase by at least 10 points on the respective score was considered to be a clinically relevant deterioration if this also applied to all subsequent values or if the deterioration occurred at the patient's last documentation time.
e. Deaths were not recorded as deterioration.
f. Due to the absence of hair loss or sexual activity at the start of the study, an unknown proportion, but up to 80% of the patients, are censored at month 0. The approach of the company does not ensure that the burden of patients who develop hair loss or become sexually active in the course of the treatment is recorded.
g. A decrease by at least 10 points on the respective score was considered to be a clinically relevant deterioration if this also applied to all subsequent values or if the deterioration occurred at the patient's last documentation time.
h. Discontinuation of therapy with ribociclib or placebo or of the combination of ribociclib and letrozole or placebo and letrozole; discontinuation 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; IRT: interactive response technology; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; NC: not calculable; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

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

Mortality

Overall survival

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

This concurs with the company's assessment.

Morbidity

Symptoms, recorded with the symptom scales of the EORTC QLQ-C30 and of the EORTC QLQ-BR23

In the MONALEESA-2 study, symptom outcomes were recorded using the symptom scales of the EORTC QLQ-C30 and of the EORTC QLQ-BR23. The time to definitive deterioration by ≥ 10 points was considered in each case.

Dyspnoea

In the total population, there was no statistically significant difference between the treatment groups for the symptom scale "dyspnoea" of the EORTC QLQ-C30. However, there was an effect modification by the characteristic "age". This resulted in a hint of lesser benefit of ribociclib + letrozole in patients ≥ 65 years of age for the outcome "dyspnoea". For patients < 65 years of age, there was no hint of lesser benefit or of an added benefit of ribociclib + letrozole in comparison with letrozole; lesser benefit or an added benefit is therefore not proven.

This assessment deviates from that of the company, which overall derived no added benefit for symptom outcomes recorded using the EORTC QLQ-C30.

Upset by hair loss

There were no usable analyses for the EORTC QLQ-BR23 symptom scale "upset by hair loss". Hence, there was no hint of an added benefit of ribociclib + letrozole in comparison with letrozole; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company arrived at the same result on the basis of the analyses it used.

All other symptom scales

No statistically significant difference between the treatment groups was shown for any of the other symptom scales (fatigue, nausea and vomiting, pain, insomnia, appetite loss, constipation and diarrhoea of the EORTC QLQ-C30, as well as the 3 EORTC QLQ-BR23 scales of side effects of systemic treatment, breast symptoms, and arm symptoms). As a result, there was no hint of an added benefit of ribociclib + letrozole in comparison with letrozole for any of these outcomes; an added benefit is therefore not proven.

This concurs with the company's assessment.

Health status (EQ-5D VAS)

There were no usable analyses for the outcome "health status" recorded with the EQ-5D VAS (see Section 2.4.1). Hence, there was no hint of an added benefit of ribociclib + letrozole in comparison with letrozole; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company also derived no added benefit for this outcome on the basis of the analyses it used.

Health-related quality of life

Global health status and functional scales recorded using the EORTC QLQ-C30 and EORTC QLQ-BR23

Health-related quality of life was recorded with the global health status and the functional scales of the EORTC QLQ-C30, as well as with the functional scales of the EORTC QLQ-BR23. The time to definitive deterioration by ≥ 10 points was considered in each case.

Future perspective

A statistically significant difference in favour of ribociclib + letrozole was shown for the EORTC QLQ-BR23 functional scale "future perspective". This resulted in a hint of an added benefit of ribociclib + letrozole in comparison with letrozole.

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

Sexual enjoyment

There were no usable analyses for the EORTC QLQ-BR23 functional scale "sexual enjoyment". Hence, there was no hint of an added benefit of ribociclib + letrozole in comparison with letrozole; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company arrived at the same result on the basis of the analyses it used.

All other scales

There was no statistically significant difference between the treatment groups for any of the other scales (the global health status and the 5 functional scales of the EORTC QLQ-C30, as well as the EORTC QLQ-BR23 functional scales "body image" and "sexual functioning"). As a result, there was no hint of an added benefit of ribociclib + letrozole in comparison with letrozole for any of these outcomes; an added benefit is therefore not proven.

This concurs with the company's assessment.

Side effects

SAEs

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

This concurs with the company's assessment.

Discontinuation due to AEs

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

This concurs with the company's assessment.

Severe AEs (CTCAE grade 3–4)

A statistically significant difference to the disadvantage of ribociclib + letrozole in comparison with placebo + letrozole was shown for the outcome "severe AEs (CTCAE grade 3–4)". Due to the size of the observed effect and the early occurrence of the events in the course of the study (see Figure 23 of the full dossier assessment), there was an indication of greater harm of ribociclib + letrozole in comparison with letrozole for this outcome despite the high risk of bias.

This concurs with the assessment of the company insofar as the company also derived greater harm, but with low certainty of conclusions.

Specific AEs

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

A statistically significant difference to the disadvantage of ribociclib + letrozole in comparison with placebo + letrozole was shown for the specific severe AEs (CTCAE grade 3–4) "blood and lymphatic system disorders" (including: "neutropenia") and "investigations". Due to the size of the observed effects in each case, and the early occurrence of the events in the course of the study (see Figure 25, Figure 26 and Figure 29 of the full dossier assessment), there was an indication of greater harm of ribociclib + letrozole in comparison with letrozole for each of these outcomes despite the high risk of bias.

Severe AEs (CTCAE grade 3–4): gastrointestinal disorders, infections and infestations; AEs: eye disorders and skin and subcutaneous tissue disorders

Statistically significant differences to the disadvantage of ribociclib + letrozole in comparison with placebo + letrozole were shown for the specific severe AEs (CTCAE grade 3–4) "gastrointestinal disorders" and "infections and infestations", as well as for the specific AEs (regardless of severity grade) "eye disorders" and "skin and subcutaneous tissue disorders". This resulted in a hint of greater harm of ribociclib + letrozole in comparison with letrozole for these outcomes.

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

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristic was considered in the present benefit assessment:

- age (< 65 years, ≥ 65 years)

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

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

The company did not use the results on the subgroup analyses for any of the outcomes for the derivation of an added benefit.

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

Table 15: Subgroups (morbidity) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole

Study Outcome	Ribociclib + letrozole		Placebo + letrozole		Ribociclib + letrozole vs. placebo + letrozole	
Characteristic Subgroup	N	Median time to event in months [95% CI][a] Patients with event n (%)	N	Median time to event in months [95% CI][a] Patients with event n (%)	HR [95% CI][b]	p-value[c]
MONALEESA-2 (data cut-off 8 May 2019)						
EORTC QLQ-C30 symptom scales, time to deterioration[d, e]						
Dyspnoea						
Age						
< 65 years	184	NA 9 (4.9)	189	NA 9 (4.8)	0.85 [0.34; 2.17]	0.719
≥ 65 years	150	NA 15 (10.0)	145	NA 3 (2.1)	4.64 [1.34; 16.06]	0.008
Total					Interaction:	0.030[f]

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

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

Morbidity

EORTC QLQ-C30 (symptom scales)

Dyspnoea

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

This assessment deviates from that of the company, which overall derived no added benefit for symptom outcomes recorded using the EORTC QLQ-C30.

2.5 Probability and extent of added benefit

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

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

2.5.1 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 (see Table 16).

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

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

Dyspnoea (EORTC QLQ-C30 [symptom scales])

The dossier contained no information on the assignment of the severity category for the outcome "dyspnoea" of the EORTC QLQ-C30 (symptom scales). Therefore, the outcome "dyspnoea" was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

The company did not assign dyspnoea to an outcome category.

Discontinuation due to AEs

For the outcome "discontinuation due to AEs", the first assessment [12] showed that, at the data cut-off from 2 January 2017, 70% (n = 39) of the AEs leading to discontinuation of the study medication in the ribociclib + letrozole arm, and 62% (n = 8) in the placebo + letrozole arm, were CTCAE grade 3–4 AEs. There is no information on the proportion of SAEs or severe AEs (CTCAE grade 3–4) from the events that occurred in the outcome "discontinuation due to AEs" for the new data cut-off from 8 May 2019. However, since even with an unchanged number of severe AEs (CTCAE grade 3–4) in both treatment arms compared with the previous data cut-off, more than half of all events that had occurred at the current data cut-off were severe (ribociclib + letrozole: at least 59%; placebo + letrozole: at least 53%), this outcome was assigned to the outcome category of serious/severe side effects.

The company did not assign the outcome "discontinuation due to AEs" to an outcome category.

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

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

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

Table 16: Extent of added benefit at outcome level – RCT, direct comparison: ribociclib + letrozole vs. letrozole (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ribociclib + letrozole vs. letrozole** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
Overall survival	NA vs. 51.4 HR: 0.78 [0.62; 0.98] p = 0.034 probability: "indication"	Outcome category: mortality $0.95 \leq CI_u < 1.00$ added benefit, extent: "minor"
Morbidity		
Symptoms		
EORTC QLQ-C30 symptom scales, time to definitive deterioration		
Fatigue	NA vs. 55.1 HR: 0.82 [0.61; 1.09] p = 0.171	Lesser benefit/added benefit not proven
Nausea/vomiting	NA vs. NA HR: 0.84 [0.41; 1.73] p = 0.634	Lesser benefit/added benefit not proven
Pain	NA vs. NA HR: 0.72 [0.50; 1.03] p = 0.068	Lesser benefit/added benefit not proven
Dyspnoea Age < 65 years	NA vs. NA HR: 0.85 [0.34; 2.17] p = 0.719	Lesser benefit/added benefit not proven
≥ 65 years	NA vs. NA HR: 4.64 [1.34; 16.06] HR: 0.22 [0.06; 0.75][c] p = 0.008 probability: "hint"	Outcome category: non-serious/non-severe symptoms/late complications $CI_u \leq 0.80$ lesser benefit, extent: "considerable"
Insomnia	NA vs. NA HR: 1.04 [0.58; 1.84] p = 0.902	Lesser benefit/added benefit not proven
Appetite loss	NA vs. NA HR: 0.66 [0.35; 1.26] p = 0.204	Lesser benefit/added benefit not proven
Constipation	NA vs. NA HR: 0.98 [0.43; 2.20] p = 0.955	Lesser benefit/added benefit not proven
Diarrhoea	NA vs. NA HR: 0.92 [0.26; 3.16] p = 0.889	Lesser benefit/added benefit not proven

Table 16: Extent of added benefit at outcome level – RCT, direct comparison: ribociclib + letrozole vs. letrozole (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ribociclib + letrozole vs. letrozole** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
EORTC QLQ-BR23 symptom scales, time to definitive deterioration		
Side effects of systemic therapy	32.0 vs. 31.3 HR: 1.14 [0.90; 1.44] p = 0.292	Lesser benefit/added benefit not proven
Breast symptoms	NA vs. NA HR: 1.07 [0.64; 1.77] p = 0.804	Lesser benefit/added benefit not proven
Arm symptoms	58.0 vs. NA HR: 0.70 [0.44; 1.12] p = 0.139	Lesser benefit/added benefit not proven
Upset by hair loss	No usable data	
Health status		
EQ-5D VAS	No usable data	
Health-related quality of life		
EORTC QLQ-C30 global health status and functional scales, time to definitive deterioration		
Global health status	47.9 vs. 46.9 HR: 0.89 [0.68; 1.16] p = 0.400	Lesser benefit/added benefit not proven
Physical functioning	52.7 vs. 55.1 HR: 1.00 [0.75; 1.35] p = 0.986	Lesser benefit/added benefit not proven
Role functioning	52.5 vs. 40.1 HR: 0.84 [0.63; 1.11] p = 0.218	Lesser benefit/added benefit not proven
Emotional functioning	52.7 vs. 48.4 HR: 0.76 [0.57; 1.02] p = 0.069	Lesser benefit/added benefit not proven
Cognitive functioning	50.6 vs. 41.5 HR: 0.85 [0.66; 1.11] p = 0.227	Lesser benefit/added benefit not proven
Social functioning	NA vs. 56.1 HR: 0.93 [0.68; 1.26] p = 0.641	Lesser benefit/added benefit not proven

Table 16: Extent of added benefit at outcome level – RCT, direct comparison: ribociclib + letrozole vs. letrozole (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ribociclib + letrozole vs. letrozole** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
EORTC QLQ-BR23 functional scales, time to definitive deterioration		
Body image	58.2 vs. NA HR: 1.23 [0.91; 1.67] p = 0.179	Lesser benefit/added benefit not proven
Sexual functioning	NA vs. NA HR: 0.68 [0.46; 1.02] p = 0.059	Lesser benefit/added benefit not proven
Sexual enjoyment	No usable data	
Future perspective	NA vs. NA HR: 0.63 [0.44; 0.90] p = 0.011 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: 1.52 [1.11; 2.10] HR: 0.66 [0.48; 0.90][c] p = 0.009 probability: "hint"	Outcome category: serious/severe side effects $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Severe AEs (CTCAE grade 3–4)	0.95 vs. 27.63 HR: 3.99 [3.25; 4.90] HR: 0.25 [0.20; 0.31][c] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Discontinuation due to AEs[d]	NA vs. NA HR: 4.08 [2.33; 7.16] HR: 0.25 [0.14; 0.43][c] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Blood and lymphatic system disorders (SOC, CTCAE grade 3–4)	3.14 vs. NA HR: 23.58 [12.83; 43.34] HR: 0.04 [0.02; 0.08][c] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
including: neutropenia (PT, CTCAE grade 3–4)	15.67 vs. NA HR: 77.22 [24.65; 241.83] HR: 0.01 [0.00; 0.04][c] p < 0.001 probability: "indication"	

Table 16: Extent of added benefit at outcome level – RCT, direct comparison: ribociclib + letrozole vs. letrozole (multipage table)

Outcome category **Outcome** **Effect modifier** **Subgroup**	**Ribociclib + letrozole vs. letrozole** **Median time to event (months)** **Effect estimation [95% CI]; p-value** **Probability**[a]	**Derivation of extent**[b]
Gastrointestinal disorders (SOC, CTCAE grade 3–4)	NA vs. NA HR: 3.35 [1.85; 6.07] HR: 0.30 [0.16; 0.54][c] p < 0.001 probability: "hint"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Infections and infestations (SOC, CTCAE grade 3–4)	NA vs. NA HR: 2.13 [1.08; 4.18] HR: 0.47 [0.24; 0.93][c] p = 0.024 probability: "hint"	Outcome category: serious/severe symptoms/late complications $0.90 \leq CI_u < 1.00$ greater harm, extent: "minor"
Investigations (SOC, CTCAE grade 3–4)	53.95 vs. NA HR: 5.54 [3.69; 8.33] HR: 0.18 [0.12; 0.27][c] p < 0.001 probability: "indication"	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5% greater harm, extent: "major"
Eye disorders (SOC, AEs)	NA vs. NA HR: 2.30 [1.62; 3.27] HR: 0.43 [0.30; 0.62][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"
Skin and subcutaneous tissue disorders (SOC, AEs)	4.67 vs. 42.64 HR: 2.15 [1.73; 2.67] HR: 0.47 [0.37; 0.58][c] p < 0.001 probability: "hint"	Outcome category: non-serious/non-severe side effects $CI_u < 0.80$ greater harm, extent: "considerable"

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.
d. Discontinuation of therapy with ribociclib or placebo or of the combination of ribociclib and letrozole or placebo and letrozole; discontinuation of letrozole treatment alone was not allowed in the framework of the study.

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; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

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

Table 17: Positive and negative effects from the assessment of ribociclib in combination with letrozole in comparison with letrozole

Positive effects	**Negative effects**
Mortality ▪ overall survival: indication of an added benefit – extent: "minor"	–
Health-related quality of life ▪ future perspective: hint of an added benefit – extent "minor"	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: "minor" ▪ discontinuation due to AEs: hint of greater harm – extent "major" ▪ severe AEs (CTCAE grade 3–4): indication of greater harm – extent: "major" ▫ specific AEs (CTCAE grade 3–4): - blood and lymphatic system disorders (including: neutropenia) and investigations: in each case indication of greater harm – extent: "major" - infections and infestations: hint of greater harm – extent: "minor" - gastrointestinal disorders: hint of greater harm – extent: "major"
–	Non-serious/non-severe side effects ▪ specific AEs: ▫ eye disorders and skin and subcutaneous tissue disorders: in each case hint of greater harm – extent: "considerable"
–	Non-serious/non-severe symptoms/late complications ▪ dyspnoea: ▫ age (≥ 65 years): hint of lesser benefit – extent: "considerable"
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; SAE: serious adverse event	

In the overall consideration, there are both positive and negative effects of ribociclib in comparison with letrozole. There are advantages in the outcome category of mortality (overall survival) and in the functional scale "future perspective" of health-related quality of life, and disadvantages in the outcome category of side effects, and particularly in the category of serious/severe side effects, as well as for the subgroup of patients ≥ 65 years of age in the symptom scale "dyspnoea" of the outcome category of non-serious/non-severe symptoms/late complications.

There is an indication of a minor added benefit for the outcome "overall survival". In addition, there is a hint of a minor added benefit in the functional scale "future perspective" in the outcome category of health-related quality of life.

Due to the size and the certainty of conclusions, the effects in severe CTCAE grade 3–4 AEs determined the derivation of harm. These events were mainly blood and lymphatic system

disorders, particularly severe neutropenia. Greater harm was not only shown in severe neutropenia, however, but also in severe infections (hint of greater harm of minor extent). In addition, the greater harm was shown in all 3 superordinate AE outcomes, i.e. besides the overall rates of severe AEs (CTCAE grade 3–4), also in the overall rates of SAEs and of discontinuations due to AEs. These negative effects are also not called into question by the present results on symptoms and health-related quality of life, as the different operationalizations (at least one event versus definitive deterioration), among other aspects, do not allow such a conclusion.

In the overall assessment, there is therefore an indication 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 in combination with an aromatase inhibitor as initial endocrine therapy in comparison with the ACT for postmenopausal patients with HR-positive, HER2-negative locally advanced or metastatic breast cancer; an added benefit is therefore not proven.

The result of the assessment of the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT is summarized in Table 18.

Table 18: Ribociclib in combination with an aromatase inhibitor – probability and extent of added benefit

Therapeutic indication[a]	**ACT**[b]	**Probability and extent of added benefit**
Initial endocrine therapy of HR-positive and HER2-negative advanced or metastatic breast cancer in postmenopausal women	Anastrozole or letrozole or fulvestrant or, if applicable, tamoxifen if aromatase inhibitors are unsuitable	Added benefit not proven[c]

a. It is assumed for the present therapeutic indication that endocrine therapy is indicated for the patients and that there is no indication for chemotherapy or (secondary) resection or radiotherapy with curative intent.
b. Presentation of the respective ACT specified by the G-BA.
c. Only patients with an ECOG PS of 0 or 1 were included in the MONALEESA-2 study. It remains unclear whether the observed results can be transferred to patients with an ECOG PS of ≥ 2. Almost all patients included in the study had stage IV disease (breast cancer with distant metastasis).

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

The assessment described above deviates from the assessment of the company, which derived considerable added benefit with high certainty of conclusions for postmenopausal women with HR-positive, HER2-negative locally advanced or metastatic breast cancer.

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

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Please see full dossier assessment for full reference list.

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

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