IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Ribociclib (breast cancer) –

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

Extract

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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-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer 23
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)
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effects model repeated measures
NSAI	nonsteroidal aromatase inhibitor
PFS	progression-free survival
PT	Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
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 5 September 2017.

Research question

The aim of the present report was to assess 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.

Table 2 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of ribociclib

Research question	Therapeutic indication[a]	ACT[b]
1	Initial endocrine therapy of HR-positive and HER2-negative locally advanced or metastatic breast cancer in postmenopausal women	Anastrozole or **letrozole** or, if applicable, tamoxifen if aromatase inhibitors are unsuitable

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. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
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 and chose letrozole as ACT from the options named 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.

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.

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 in a 1:1 ratio to ribociclib + letrozole or placebo + letrozole. Randomization was stratified according to the presence of liver and/or lung metastases (yes versus no). Treatment in the study 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.

Risk of bias

The risk of bias at study level was rated as low for the MONALEESA-2 study. Risk of bias was also low for the outcomes “overall survival” and “discontinuation due to adverse events (AEs)”. The risk of bias was rated as high for the outcomes “symptoms”, “health status”, “health-related quality of life”, “serious AEs (SAEs)”, and “severe AEs”. Despite the high risk of bias, a high certainty of results was derived for severe AEs because of the early occurrence of the events and a very marked effect.

Hence, at most indications, e.g. of an added benefit, could be derived for the outcomes “overall survival”, “discontinuation due to AEs” and “severe AEs”; and at most hints could be derived for the outcomes “symptoms”, health status”, “health-related quality of life” and “SAEs”.

Results

Mortality

- Overall survival

There was no statistically significant difference between the treatment arms for the outcome “overall survival”. Hence there was no hint of an added benefit of ribociclib + letrozole in comparison with letrozole; an added benefit is therefore not proven.

The company presented additional analyses in the dossier to validate progression-free survival (PFS) as surrogate outcome for overall survival. The company’s approach was unsuitable to

show the validity of PFS as surrogate outcome for overall survival, however. In the benefit assessment, PFS was therefore not considered to be a valid surrogate for overall survival.

Morbidity

- Symptoms

Symptoms were recorded with the symptom scales of the questionnaires European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer 23 (EORTC QLQ-BR23). Neither of the symptom scales showed a statistically significant difference between the treatment arms. Hence there was no hint of an added benefit of ribociclib + letrozole in comparison with letrozole; an added benefit is therefore not proven.

- Health status

Health status was measured with the visual analogue scale (VAS) of the European Quality of Life-5 Dimensions (EQ-5D) questionnaire. There was no statistically significant difference between the treatment arms. 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

Health-related quality of life was recorded with the global health status scale and with the functional scales of the questionnaires EORTC QLQ-C30 and EORTC QLQ-BR23. Neither the global health status scale nor the functional scales showed a statistically significant difference between the treatment arms. Hence there was no hint of an added benefit of ribociclib + letrozole in comparison with letrozole; an added benefit is therefore not proven.

Side effects

- Serious adverse events

A statistically significant effect 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 for this outcome.

- Severe adverse events (CTCAE grade 3 or 4)

A statistically significant effect to the disadvantage of ribociclib + letrozole in comparison with placebo + letrozole was shown for severe AEs of Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or 4. This resulted in an indication of greater harm of ribociclib + letrozole in comparison with letrozole for this outcome.

- Discontinuation due to adverse events

Regarding discontinuation due to AEs, data containing both discontinuation of ribociclib or placebo under continued letrozole treatment and discontinuation of the entire study medi-

cation were available for the MONALEESA-2 study. A statistically significant effect to the disadvantage of ribociclib + letrozole in comparison with placebo + letrozole was shown for this outcome. This resulted in an indication of greater harm of ribociclib + letrozole in comparison with letrozole for this outcome.

- Specific adverse events

No specific AEs could be chosen from the available data.

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.

The overall consideration showed no positive effects of ribociclib. In contrast, there were indications of greater harm with the extent "major" for each of the outcomes "severe AEs" and "discontinuation due to AEs", and a hint of greater harm with the extent "considerable" for the outcome "SAEs". In summary, there is an indication of lesser benefit of ribociclib in combination with an aromatase inhibitor as initial endocrine therapy in comparison with the ACT for patients with HR-positive, HER2-negative metastatic breast cancer.

Table 3 presents a summary of probability and extent of the added benefit of ribociclib.

Table 3: Ribociclib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit[b]**
Initial endocrine therapy of HR-positive and HER2-negative advanced or metastatic breast cancer in postmenopausal women	Anastrozole or **letrozole** or, if applicable, tamoxifen if aromatase inhibitors are unsuitable	Indication of lesser benefit

a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b: The relevant study compared ribociclib + letrozole with placebo + letrozole. Patients with stage IV disease (breast cancer with distant metastasis) and an ECOG PS of 0 or 1 were included. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or with other disease stages.
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

[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].

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 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.

Table 4 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of ribociclib

Research question	**Therapeutic indication**[a]	**ACT**[b]
1	Initial endocrine therapy of HR-positive and HER2-negative locally advanced or metastatic breast cancer in postmenopausal women	Anastrozole or **letrozole** or, if applicable, tamoxifen if aromatase inhibitors are unsuitable

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. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
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 and chose letrozole as ACT from the options named 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.

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: 11 July 2017)
- bibliographical literature search on ribociclib (last search on 4 July 2017)
- search in trial registries for studies on ribociclib (last search on 3 July 2017)

To check the completeness of the study pool:

- search in trial registries for studies on ribociclib (last search on 19 September 2017)

The check identified no additional relevant study.

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		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
MONALEESA-2	Yes	Yes	No
a: Study for which the company was sponsor. 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. This corresponded to the company's approach. No data were available on the comparison of the combination of ribociclib with other aromatase inhibitors versus the ACT.

Section 2.6 contains a reference list for the study included.

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]
MONALEESA-2	RCT, double-blind, parallel	Postmenopausal women with locally recurrent or metastatic HR-positive[b] and HER2-negative[c] breast cancer without prior anticancer 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, at most until death, withdrawal of consent, loss to follow-up, study discontinuation by sponsor, or final survival time analysis[e]	223 centres in 29 countries (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: 29 Jan 2016 second interim analysis: 2 Jan 2017 or 4 Jan 2017	Primary: PFS Secondary: overall survival, symptoms, health status, health-related quality of life, AEs

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively include information on the 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 is 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: Planned after about 400 deaths.

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
MONALEESA-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 anticancer therapy for advanced or metastatic disease ▪ the following prior therapies had to be completed 1–4 weeks before starting the study treatment: (neo)adjuvant anticancer 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 anticancer 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 randomized controlled trial (RCT) directly comparing ribociclib in combination with letrozole versus placebo + letrozole. Patients in the letrozole arm additionally received placebo instead of ribociclib to maintain blinding. Postmenopausal women with locally advanced or metastatic HR-positive and HER2-negative

breast cancer were included in the study. The receptor status of the metastases was not recorded. On study entry, patients had to have an ECOG PS < 2 and were not allowed to have received prior systemic anticancer 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 in a 1:1 ratio to the 2 treatment arms. Randomization was stratified according to the presence of liver and/or lung metastases (yes versus no).

Treatment in the study arms was largely consistent with the SPCs of ribociclib and letrozole [3,4]. For ribociclib, there were deviations from the SPC regarding the handling of toxicities. In case of toxicities that were not explicitly mentioned (i.e. no neutropenia or increased alanine and/or aspartate aminotransferase or QT prolongations), from CTCAE grade 2, administration of ribociclib or placebo was discontinued in the MONALEESA-2 study 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.

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.

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. According to the company's information provided in Module 4 A, about 51% of the patients in the ribociclib + letrozole arm and about 64% of the patients in the placebo + letrozole arm were receiving subsequent therapy at the time point of the second data cut-off.

Data cut-offs

Analyses on 2 data cut-offs were available for the MONALEESA-2 study:

- First data cut-off (29 January 2016): planned interim analysis for PFS, first interim analysis for overall survival
- Second data cut-off (2 January 2017): planned second interim analysis for overall survival There was an additional addendum to this data cut-off with data cut-off on 4 January 2017, reporting results on morbidity, quality of life, and side effects.

For the outcome "PFS", there was an additional analysis on 22 June 2016, which the company conducted in consultation with the United States Food and Drug Administration.

Analyses on both planned data cut-offs for all patient-relevant outcomes were available for the present benefit assessment. The data of the last data cut-off were used for the benefit assessment.

Planned duration of follow-up

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**
MONALEESA-2	
Mortality	
Overall survival	Every 12 weeks 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 symptom scales)	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 functional scales	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
a: Planned after about 400 deaths. 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 23; 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 (for side effects plus 30 days after the end of treatment). 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 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

Study Characteristics Category	**Ribociclib + letrozole**	**Placebo + letrozole**
MONALEESA-2	N = 334	N = 334
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	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)

(continued)

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

Study Characteristics Category	**Ribociclib + letrozole**	**Letrozole**
MONALEESA-2	N = 334	N = 334
Setting of most recent treatment		
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)
Location of metastases, n (%)		
Breast	8 (2.4)	11 (3.3)
Bone marrow	0	2 (0.6)
Bone	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)
Lung	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[a], n (%)	203 (60.8)	246 (73.7)
Study discontinuation, n (%)	ND	ND

a: 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 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”.

Course of the study

Table 10 shows the mean/median treatment duration of the patients and the mean/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**	**Placebo + letrozole**
MONALEESA-2	N = 334	N = 334[a]
Treatment duration[b] [months]		
Median [min; max]	20.2 [0; 24]	14.1 [0; 32]
Mean (SD)	17.2 (10.0)	15.1 (9.4)
Observation period [months]		
Overall survival		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Symptoms and health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	19.3 [−0.7[c]; 33.6]	13.1 [−0.4[c]; 32.4]
Mean (SD)	16.2 (9.6)	14.1 (9.1)
Symptoms and health-related quality of life (EORTC QLQ-BR23)		
Median [min; max]	19.3 [−0.2[c]; 33.6]	13.2 [−0.2[c]; 32.4]
Mean (SD)	16.2 (9.6)	14.1 (9.0)
Health status (EQ-5D)		
Median [min; max]	14.7 [−0.7[c]; 33.1]	12.9 [−0.5[c]; 32.4]
Mean (SD)	14.2 (10.0)	12.9 (9.2)
Side effects		
Median [min; max]	21.2 [0.8; 34.4]	15.1 [1.4; 33.2]
Mean (SD)	17.8 (9.6)	15.8 (9.1)

a: N = 330 for side effects and treatment duration.
b: In relation to the study medication (ribociclib + letrozole or placebo + letrozole).
c: Apparently, there were patients without valid recordings on or after randomization for whom a time point before randomization was erroneously included in the observation period instead.
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 23; 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; vs.: versus

The median treatment duration was notably longer in the ribociclib + letrozole arm than in the placebo + letrozole arm (20 versus 14 months). Hence, the observation periods for the

outcomes “symptoms”, “health status”, “health-related quality of life” and “side effects” were also longer in the ribociclib + letrozole arm.

The outcome “overall survival” was recorded irrespective of the treatment duration. However, there was no information on the observation period for this outcome.

Risk of bias at study level

Table 11 shows the risk of bias at study level.

Table 11: Risk of bias at 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
			Patient	Treating staff			
MONALEESA-2	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low. This concurs with the company’s assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - overall survival
- Morbidity
  - symptoms measured with the symptom scales of the instruments EORTC QLQ-C30 and EORTC QLQ-BR23
  - health status measured with the VAS of the EQ-5D questionnaire
- Health-related quality of life
  - measured with the functional scales of the EORTC QLQ-C30 and of the EORTC QLQ-BR23

- Side effects
  - SAEs
  - severe AEs (CTCAE grade 3 or 4)
  - treatment discontinuations due to AEs
  - 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 2.7.2.4.3 of the full dossier assessment).

Presenting extensive data in its dossier, the company additionally tried to validate the outcome "PFS" as surrogate for the outcome "overall survival". However, it cannot be derived from these data that PFS constitutes a valid surrogate for overall survival (see Section 2.7.2.9.4 of the full dossier assessment).

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 or 4)	Discontinuation due to AEs
MONALEESA-2	Yes	Yes	Yes	Yes	Yes	Yes	Yes

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 23; EQ-5D: European Quality of Life-5 Dimensions; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.4.2 Risk of bias

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

Table 13: Risk of bias at study and outcome level – 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 or 4)	Discontinuation due to AEs
MONALEESA-2	L	L	H[a]	H[b]	H[a]	H[a]	H[a]	L

a: Different observation periods between the treatment arms with possible informative censoring; see Section 2.7.2.4.2 of the full dossier assessment.
b: Decreasing response to questionnaires over the course of the study, with increasing difference between the treatment arms.
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 23; EQ-5D: European Quality of Life-5 Dimensions; H: high; L: low; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

The risk of bias for the outcome “overall survival” was rated as low. This concurs with the company’s assessment.

There was a high risk of bias for the outcomes “symptoms”, “health-related quality of life”, “SAEs” and “severe AEs” due to the difference in observation periods and possible informative censoring. There were additional aspects, which are described in Section 2.7.2.4.2 of the full dossier assessment. The company also rated the risk of bias as high for these outcomes.

Analyses of the mean differences were used for the outcome “health status”. There was a high risk of bias due to the decreasing response to questionnaires over the course of the study, with increasing difference between the treatment arms (see Section 2.7.2.4.2 of the full dossier assessment). This deviates from the assessment of the company insofar as the company used the result of a different analysis (event time analysis) for this outcome, but also assumed a high risk of bias for this.

The risk of bias was rated as low for the outcome “discontinuation due to AEs” for the analyses based on the relative risk (see Section 2.7.2.4.2 of the full dossier assessment). This assessment deviates from that of the company, which used the result of a different analysis (event time analysis) for this outcome and also assumed a high risk of bias for this.

2.4.3 Results

The results on the comparison of ribociclib + letrozole with placebo + letrozole in postmenopausal patients with HR-positive, HER2-negative metastatic breast cancer are summarized in Table 14 and Table 15. Where necessary, the data from the company’s dossier were supplemented with the Institute’s calculations.

The Kaplan-Meier curves on the event time analyses are presented in Appendix B of the full dossier assessment.

Table 14: Results (mortality, symptoms, health-related quality of life, side effects – time to event) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole

Study Outcome category Outcome	Ribociclib + letrozole N	Ribociclib + letrozole Median time to event in months [95% CI] Patients with event n (%)	Placebo + letrozole N	Placebo + letrozole Median time to event in months [95% CI] Patients with event n (%)	Ribociclib + letrozole vs. placebo + letrozole HR [95% CI]; p-value
MONALEESA-2[a]					
Mortality					
Overall survival	334	NA 50 (15.0)	334	33.0 [33.0; NC] 66 (19.8)	0.75 [0.52; 1.08]; 0.118[b]
Morbidity – symptoms – time to deterioration[c, d]					
EORTC QLQ-C30 symptom scales					
Fatigue	334	33.6 [NC; NC] 86 (25.7)	334	NA [27.6; NC] 83 (24.9)	0.91 [0.67; 1.24]; 0.564
Nausea/vomiting	334	NA 14 (4.2)	334	NA 15 (4.5)	0.83 [0.40; 1.72]; 0.609
Pain	334	33.6 [30.4; 33.6] 55 (16.5)	334	30.6 [28.0; NC] 60 (18.0)	0.79 [0.55; 1.15]; 0.216
Dyspnoea	334	NA 22 (6.6)	334	NA 10 (3.0)	2.08 [0.99; 4.41]; 0.0503
Insomnia	334	NA 30 (9.0)	334	NA 21 (6.3)	1.21 [0.69; 2.12]; 0.506
Appetite loss	334	NA 18 (5.4)	334	NA 19 (5.7)	0.89 [0.47; 1.70]; 0.719
Constipation	334	NA 12 (3.6)	334	NA 12 (3.6)	0.85 [0.38; 1.90]; 0.686
Diarrhoea	334	NA 6 (1.8)	334	NA 5 (1.5)	1.05 [0.32; 3.45]; 0.938
EORTC QLQ-BR23 symptom scales					
Side effects of systemic treatment	334	22.0 [14.7; 24.7] 159 (47.6)	334	22.1 [19.2; 27.6] 131 (39.2)	1.19 [0.94; 1.50]; 0.159
Breast symptoms	334	NA [30.3; NC] 33 (9.9)	334	NA 26 (7.8)	1.09 [0.65; 1.83]; 0.732
Arm symptoms	334	NA 32 (9.6)	334	NA [30.4; NC] 40 (12.0)	0.68 [0.43; 1.08]; 0.104
Upset by hair loss	334	NA 9 (2.7)	334	NA 2 (0.6)	3.69 [0.79; 17.21]; 0.074

(continued)

Table 14: Results (mortality, symptoms, health-related quality of life, side effects – time to event) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (continued)

Study Outcome category Outcome	Ribociclib + letrozole N	Ribociclib + letrozole Median time to event in months [95% CI] Patients with event n (%)	Placebo + letrozole N	Placebo + letrozole Median time to event in months [95% CI] Patients with event n (%)	Ribociclib + letrozole vs. placebo + letrozole HR [95% CI]; p-value
MONALEESA-2[a]					
Health-related quality of life – time to deterioration[d, e]					
EORTC QLQ-C30 global health status and functional scales					
Global health status	334	27.7 [25.4; 32.0] 105 (31.4)	334	27.6 [24.9; NC] 103 (30.8)	0.91 [0.69; 1.19]; 0.481
Physical functioning	334	30.3 [25.4; 33.6] 91 (27.2)	334	NA 76 (22.8)	1.04 [0.77; 1.41]; 0.805
Role functioning	334	32.0 [27.6; 33.6] 94 (28.1)	334	NA [25.8; NC] 88 (26.3)	0.93 [0.69; 1.25]; 0.629
Emotional functioning	334	28.8 [27.7; 33.6] 90 (26.9)	334	NA [25.0; NC] 91 (27.2)	0.83 [0.62; 1.12]; 0.227
Cognitive functioning	334	27.7 [24.8; NC] 108 (32.3)	334	27.6 [24.8; 30.4] 112 (33.5)	0.89 [0.68; 1.16]; 0.376
Social functioning	334	28.8 [25.2; 33.6] 88 (26.3)	334	NA [27.6; NC] 75 (22.5)	1.00 [0.73; 1.36]; 0.979
EORTC QLQ-BR23 functional scales					
Body image	334	30.4 [27.6; NC] 100 (29.9)	334	32.4 [27.6; 32.4] 76 (22.8)	1.31 [0.97; 1.77]; 0.081
Sexual functioning	334	NA 47 (14.1)	334	NA 56 (16.8)	0.73 [0.49; 1.07]; 0.104
Sexual pleasure	334	NA 9 (2.7)	334	NA 6 (1.8)	1.46 [0.52; 4.11]; 0.476
Perspective on the future	334	NA 54 (16.2)	334	NA 61 (18.3)	0.79 [0.55; 1.14]; 0.208

(continued)

Table 14: Results (mortality, symptoms, health-related quality of life, side effects – time to event) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole (continued)

Study Outcome category Outcome	Ribociclib + letrozole N	Ribociclib + letrozole Median time to event in months [95% CI] Patients with event n (%)	Placebo + letrozole N	Placebo + letrozole Median time to event in months [95% CI] Patients with event n (%)	Ribociclib + letrozole vs. placebo + letrozole HR [95% CI]; p-value
MONALEESA-2[a]					
Side effects					
AEs (supplementary information)	334	0.2 [0.1; 0.3] 331 (99.1)	330	0.4 [0.3; 0.5] 322 (97.6)	
SAEs	334	NA 85 (25.4)	330	NA 51 (15.5)	1.65 [1.17; 2.34]; 0.004
Severe AEs (CTCAE grade 3 or 4)	334	1.0 [NC; NC] 288 (86.2)	330	NA [19.6; NC] 123 (37.3)	4.21 [3.40; 5.21]; < 0.001
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
Discontinuation due to AEs[f]	334	56 (16.8)	330	13 (3.9)	4.26 [2.37; 7.63]; < 0.001[g]

a: Data cut-off: 2 January 2017 for overall survival; 4 January 2017 for symptoms, health-related quality of life, and side effects.
b: Institute's calculation (2-sided test).
c: 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.
d: Deaths were not recorded as deterioration.
e: 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.
f: Discontinuation of ribociclib/placebo or the respective combination with letrozole.
g: Institute's calculation of RR, 95% CI (asymptotic) and p-value (unconditional exact test; CSZ method according to [5]).

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; 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; 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; RR: relative risk; SAE: serious adverse event; vs.: versus

Table 15: Results (health status, continuous) – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole

Study Outcome category Outcome	Ribociclib + letrozole			Placebo + letrozole			Ribociclib + letrozole vs. placebo + letrozole
	N[a]	Values at start of study mean (SD)	Change at end of treatment mean[b] (SD)	N[a]	Values at start of study mean (SD)	Change at end of treatment mean[b] (SD)	LSMD [95% CI][c]; p-value
MONALEESA-2[d]							
Morbidity – health status							
EQ-5D VAS	ND	71.7 (17.96)	−1.6 (18.47)	ND	69.4 (19.74)	0.6 (22.06)	−1.46 [−3.54; 0.63]; 0.170[e]

a: Number of patients considered in the analysis for the calculation of the effect estimate.
b: A negative value indicates deterioration.
c: LSMD and 95% CI from mixed model with repeated measures.
d: Data cut-off 4 January 2017
e: Institute's calculation using the 95% CI.
CI: confidence interval; EQ-5D European Quality of Life-5 Dimensions; LSMD: least-square mean difference; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Based on the available data of the MONALEESA-2 study, at most indications, e.g. of an added benefit, can be determined for all outcomes.

Mortality

Overall survival

There was no statistically significant difference between the treatment arms for the outcome "overall survival". Hence there was no hint of an added benefit of ribociclib + letrozole in comparison with letrozole; an added benefit is therefore not proven.

This assessment deviates from that of the company. The company described that there was no statistically significant difference between the treatment arms in the total study population, but derived an added benefit for the subgroup of patients without liver and/or lung metastases.

Morbidity

Symptoms

Symptoms were recorded with the symptom scales of the questionnaires EORTC QLQ-C30 and EORTC QLQ-BR23. Neither of the symptom scales showed a statistically significant difference between the treatment arms. 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 company's assessment.

Health status

Health status was recorded with the EQ-5D VAS. In the present benefit assessment, the mean change of the values at the end of the study compared with the start of the study was considered (mixed-effects model repeated measures [MMRM] analysis) (see Section 2.7.2.4.3 of the full dossier assessment). There was no statistically significant difference between the treatment arms. 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, which also derived no added benefit for this outcome on the basis of event time analyses.

Health-related quality of life

Health-related quality of life was recorded with the global health status scale and with the functional scales of the questionnaires EORTC QLQ-C30 and EORTC QLQ-BR23. Neither the global health status scale nor the functional scales showed a statistically significant difference between the treatment arms. 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 company's assessment.

Side effects

Serious adverse events

A statistically significant effect to the disadvantage of ribociclib + letrozole in comparison with placebo + letrozole was shown for the outcome "SAEs". Due to the high risk of bias, this resulted in a hint of greater harm of ribociclib + letrozole in comparison with letrozole for this outcome.

This partly concurred with the assessment of the company, which derived greater harm, which, from the company's point of view, did not result in downgrading of the added benefit, however.

Severe adverse events (CTCAE grade 3 or 4)

A statistically significant effect to the disadvantage of ribociclib + letrozole in comparison with placebo + letrozole was shown for severe AEs of CTCAE grade 3 or 4. Despite the high risk of bias at outcome level, high certainty of results was assumed for this outcome due to the marked effect and the fact that the events occurred at early time points in the observation period (see Figure 25 and Section 2.7.2.4.2 of the full dossier assessment). This resulted in an indication of greater harm of ribociclib + letrozole in comparison with letrozole for this outcome.

This deviates from the assessment of the company, which derived greater harm with low certainty of results, which did not result in downgrading of the added benefit.

Discontinuation due to adverse events

Regarding discontinuation due to AEs, data containing both discontinuation of ribociclib or placebo under continued letrozole treatment and discontinuation of the entire study medication were available for the MONALEESA-2 study. A statistically significant effect to the disadvantage of ribociclib + letrozole in comparison with placebo + letrozole was shown for this outcome. This resulted in an indication of greater harm of ribociclib + letrozole in comparison with letrozole for this outcome.

This deviates from the assessment of the company, which derived greater harm with low certainty of results, which did not result in downgrading of the added benefit.

Specific adverse events

Not enough usable data were available for the benefit assessment to choose specific AEs. The company provided no complete presentation of the event time analyses required for this for the patient-relevant outcomes "SAEs" and "severe AEs (CTCAE grade 3 or 4)" at System Organ Class (SOC) and Preferred Term (PT) level of the Medical Dictionary for Regulatory Activities (MedDRA) (see Section 2.7.2.4.3 of the full dossier assessment).

Irrespective of the fact that no choice of specific AEs was possible, differences in frequency per study arm were found for individual AEs at SOC and PT level. These differences were so large that they were not caused by differences in observation periods alone. Among the severe AEs, neutropenia and leukopenia were particularly notable, supporting the marked effect shown in the overall rate of severe AEs. The corresponding SOCs and PTs are shown in Table 16 as additional information. Further tables of the most common AEs, SAEs, severe AEs and discontinuation due to AEs at SOC and PT level are shown in Appendix A of the full dossier assessment.

Table 16: Supplementary presentation: patient-relevant AEs with large differences in frequency per study arm – RCT, direct comparison: ribociclib + letrozole vs. placebo + letrozole

Study	Patients with event n (%)	
SOC[a] PT[a]	Ribociclib + letrozole N = 334	Placebo + letrozole N = 330
MONALEESA-2[b]		
Severe AEs with CTCAE grade 3 or 4	288 (86.2)	123 (37.3)
Blood and lymphatic system disorders	178 (53.3)	9 (2.7)
Neutropenia	168 (50.3)	3 (0.9)
Leukopenia	30 (9.0)	1 (0.3)
Investigations	127 (38.0)	27 (8.2)
Neutrophil count decreased	56 (16.8)	1 (0.3)
White blood cell count decreased	43 (12.9)	2 (0.6)

a: MedDRA version 19.0.
b: Data cut-off 4 January 2017.
AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

This assessment deviates from that of the company. The company derived greater harm with low certainty of results, which did not result in downgrading of the added benefit, for each of the SOCs "blood and lymphatic system disorders (CTCAE grade 3 or 4)", "infections and infestations" and "investigations (CTCAE grade 3 or 4)". The company derived lesser harm with high certainty of results for the SOC "musculoskeletal and connective tissue disorders".

2.4.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered in the benefit assessment:

- age (< 65 years, ≥ 65 years)
- region (Europe, North America, Asia, Latin America, other)
- hormonal therapy in the (neo)adjuvant setting (nonsteroidal aromatase inhibitors [NSAIs] and others, tamoxifen, none)
- presence of liver and/or lung metastases (yes, no)

The company presented no subgroup analyses for any of the patient-relevant outcomes for the subgroup characteristic "hormonal therapy in the (neo)adjuvant setting".

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. Since none of the outcomes included fulfilled these criteria, the subgroup analyses were not considered.

2.5 Probability and extent of added benefit

The derivation of probability and extent of the added benefit 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 approach for deriving an overall conclusion on 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 added benefit at outcome level

The data presented in Section 2.4 resulted in a hint of lesser benefit of ribociclib for the outcome "SAEs", and in an indication of lesser benefit for each of the outcomes "discontinuation due to AEs" and "severe AEs".

The assessment of the outcome category of "discontinuation due to AEs" depends on the severity of the underlying events. It could be inferred from the study documents that 70% of the AEs leading to discontinuation of the study medication in the ribociclib + letrozole arm, and 62% in the letrozole arm, were CTCAE grade 3 or 4 AEs. Correspondingly, the results of the outcome "discontinuation due to AEs" were allocated to the outcome category of serious/severe side effects.

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

Table 17: Extent of added benefit at outcome level: ribociclib + letrozole vs. letrozole

Outcome category **Outcome**	**Ribociclib + letrozole vs. letrozole** **Median time to event or mean change from start of study until end of treatment or proportion of events** **Effect [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
Overall survival	Median: NA vs. 33.0 months HR: 0.75 [0.52; 1.08]; p = 0.118	Lesser benefit/added benefit not proven
Morbidity		
Symptoms		
EORTC QLQ-C30 symptom scales		
Fatigue	Median: 33.6 vs. NA months HR: 0.91 [0.67; 1.24]; p = 0.564	Lesser benefit/added benefit not proven
Nausea/vomiting	Median: NA vs. NA HR: 0.83 [0.40; 1.72]; p = 0.609	Lesser benefit/added benefit not proven
Pain	Median: 33.6 vs. 30.6 months HR: 0.79 [0.55; 1.15]; p = 0.216	Lesser benefit/added benefit not proven
Dyspnoea	Median: NA vs. NA HR: 2.08 [0.99; 4.41]; p = 0.0503	Lesser benefit/added benefit not proven
Insomnia	Median: NA vs. NA HR: 1.21 [0.69; 2.12]; p = 0.506	Lesser benefit/added benefit not proven
Appetite loss	Median: NA vs. NA HR: 0.89 [0.47; 1.70]; p = 0.719	Lesser benefit/added benefit not proven
Constipation	Median: NA vs. NA HR: 0.85 [0.38; 1.90]; p = 0.686	Lesser benefit/added benefit not proven
Diarrhoea	Median: NA vs. NA HR: 1.05 [0.32; 3.45]; p = 0.938	Lesser benefit/added benefit not proven
EORTC QLQ-BR23 symptom scales		
Side effects of systemic treatment	Median: 22.0 vs. 22.1 months HR: 1.19 [0.94; 1.50]; p = 0.159	Lesser benefit/added benefit not proven
Breast symptoms	Median: NA vs. NA HR: 1.09 [0.65; 1.83]; p = 0.732	Lesser benefit/added benefit not proven
Arm symptoms	Median: NA vs. NA HR: 0.68 [0.43; 1.08]; p = 0.104	Lesser benefit/added benefit not proven
Upset by hair loss	Median: NA vs. NA HR: 3.69 [0.79; 17.21]; p = 0.074	Lesser benefit/added benefit not proven

(continued)

Table 17: Extent of added benefit at outcome level: ribociclib + letrozole vs. letrozole (continued)

Outcome category **Outcome**	**Ribociclib + letrozole vs. letrozole** **Median time to event or mean change from start of study until end of treatment or proportion of events** **Effect [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Health status		
EQ-5D VAS	Mean change: −1.6 vs. 0.6 LSMD: −1.46 [−3.54; 0.63]; p = 0.170	Lesser benefit/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 global health status and functional scales		
Global health status	Median: 27.7 vs. 27.6 months HR: 0.91 [0.69; 1.19]; p = 0.481	Lesser benefit/added benefit not proven
Physical functioning	Median: 30.3 vs. NA months HR: 1.04 [0.77; 1.41]; p = 0.805	Lesser benefit/added benefit not proven
Role functioning	Median: 32.0 vs. NA months HR: 0.93 [0.69; 1.25]; p = 0.629	Lesser benefit/added benefit not proven
Emotional functioning	Median: 28.8 vs. NA months HR: 0.83 [0.62; 1.12]; p = 0.227	Lesser benefit/added benefit not proven
Cognitive functioning	Median: 27.7 vs. 27.6 months HR: 0.89 [0.68; 1.16]; p = 0.376	Lesser benefit/added benefit not proven
Social functioning	Median: 28.8 vs. NA months HR: 1.00 [0.73; 1.36]; p = 0.979	Lesser benefit/added benefit not proven
EORTC QLQ-BR23 functional scales		
Body image	Median: 30.4 vs. 32.4 months HR: 1.31 [0.97; 1.77]; p = 0.081	Lesser benefit/added benefit not proven
Sexual functioning	Median: NA vs. NA HR: 0.73 [0.49; 1.07]; p = 0.104	Lesser benefit/added benefit not proven
Sexual pleasure	Median: NA vs. NA HR: 1.46 [0.52; 4.11]; p = 0.476	Lesser benefit/added benefit not proven
Perspective on the future	Median: NA vs. NA HR: 0.79 [0.55; 1.14]; p = 0.208	Lesser benefit/added benefit not proven

(continued)

Table 17: Extent of added benefit at outcome level: ribociclib + letrozole vs. letrozole (continued)

Outcome category **Outcome**	**Ribociclib + letrozole vs. letrozole** **Median time to event or mean change from start of study until end of treatment or proportion of events** **Effect [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Side effects		
SAEs	Median: NA vs. NA HR: 1.65 [1.17; 2.34] HR: 0.61 [0.43; 0.85][c]; p = 0.004 probability: "hint"	Outcome category: Serious/severe side effects $0.75 < CI_u < 0.90$ greater harm, extent: "considerable"
Severe AEs (CTCAE grade 3 or 4)	Median: 1.0 vs. NA months HR: 4.21 [3.40; 5.21] HR: 0.24 [0.19; 0.29][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]	Proportion of events: 16.8% vs. 3.9% RR: 4.26 [2.37; 7.63] RR: 0.23 [0.13; 0.42][c]; p < 0.001 probability: "indication"	Outcome category: Serious/severe side effects $CI_u < 0.75$; risk ≥ 5% greater harm, extent: "major"

a: Probability provided if a statistically significant and relevant effect is present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the 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 ribociclib/placebo or the respective combination with letrozole.

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 23; EQ-5D: European Quality of Life-5 Dimensions; HR: hazard ratio; LSMD: least-square mean difference; NA: not achieved; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; VAS: visual analogue scale; vs.: versus

2.5.2 Overall conclusion on added benefit

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

Table 18: Positive and negative effects from the assessment of ribociclib + letrozole in comparison with letrozole

Positive effects	**Negative effects**
–	Serious/severe side effects: ▪ SAEs: hint of greater harm – extent: "considerable" ▪ Severe AEs (CTCAE grade 3 or 4): indication of greater harm – extent: "major" ▪ Discontinuation of the study medication due to AEs: indication of greater harm – extent: "major"
AE: adverse event; CTCAE: Common Terminology Criteria of Adverse Events; SAE: serious adverse event	

The overall consideration showed no positive effects of ribociclib. In contrast, there were indications of greater harm with the extent "major" for each of the outcomes "severe AEs" and "discontinuation due to AEs", and a hint of greater harm with the extent "considerable" for the outcome "SAEs".

In summary, there is an indication of lesser benefit of ribociclib in combination with an aromatase inhibitor as initial endocrine therapy in comparison with the ACT for patients with HR-positive, HER2-negative metastatic breast cancer.

The result of the assessment of the added benefit of ribociclib in comparison with the ACT is summarized in Table 19.

Table 19: Ribociclib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**[b]
Initial endocrine therapy of HR-positive and HER2-negative advanced or metastatic breast cancer in postmenopausal women	Anastrozole or **letrozole** or, if applicable, tamoxifen if aromatase inhibitors are unsuitable	Indication of lesser benefit
a: Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b: The relevant study compared ribociclib + letrozole with placebo + letrozole. Patients with stage IV disease (breast cancer with distant metastasis) and an ECOG PS of 0 or 1 were included. It remains unclear whether the observed effects can be transferred to patients with ECOG PS ≥ 2 or with other disease stages. 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.

2.6 List of included studies

MONALEESA-2

Hortobagyi GN, Stemmer SM, Burris HA, Yap YS, Sonke GS, Paluch-Shimon S et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. N Engl J Med 2016; 375(18): 1738-1748.

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Novartis Pharmaceuticals. A randomized double-blind, placebo-controlled study of LEE011 in combination with letrozole for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease: study CLEE011A2301; amended protocol; version 05 (clean) [unpublished]. 2016.

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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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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a17-45-ribociclib-breast-cancer-benefit-assessment-according-to-35a-social-code-book-v.7965.html.