IQWiG Reports – Commission No. A20-58

Ribociclib (breast cancer, combination with fulvestrant) –

Addendum to Commission A20-22[1]

Addendum

Commission: A20-58
Version: 1.0
Status: 30 July 2020

[1] Translation of addendum A20-58 *Ribociclib (Mammakarzinom, Kombination mit Fulvestrant) – Addendum zum Auftrag A20-22* (Version 1.0; Status: 30 July 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.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Ribociclib (breast cancer, combination with fulvestrant) – Addendum to Commission A20-22

Commissioning agency
Federal Joint Committee

Commission awarded on
6 July 2020

Internal Commission No.
A20-58

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Keywords: Ribociclib, Breast Neoplasms, Benefit Assessment, NCT02422615

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BPI-SF	Brief Pain Inventory-Short Form
CTCAE	Common Terminology Criteria for Adverse Events
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
RCT	randomized controlled trial
SAE	serious adverse event
VAS	visual analogue scale

1 Background

On 6 July 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-22 (Ribociclib – Benefit assessment according to §35a Social Code Book V) [1].

The randomized controlled trial (RCT) MONALEESA-3, which compared the combination of ribociclib + fulvestrant with placebo + fulvestrant, was included for the benefit assessment of ribociclib in combination with fulvestrant in postmenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative locally advanced or metastatic breast cancer.

The G-BA's specification of the appropriate comparator therapy (ACT) resulted in the 2 research questions A1 and B1, for each of which a subpopulation of the MONALEESA-3 study was relevant.

It was noted in dossier assessment A20-22 that there were no relevant analyses for the outcome "health status" (recorded with the European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS]) and for the outcome "pain", operationalized as "worst pain" (recorded with the Brief Pain Inventory-Short Form [BPI-SF]) and that the documentation on the methodological approach for the mixed-effects model repeated measures (MMRM) used was insufficient. The pharmaceutical company (hereinafter referred to as "the company") subsequently submitted the missing analyses with its comments [2]. Following the oral hearing, the company also subsequently submitted further information on the methodological approach and the patient numbers considered in the MMRM analyses [3,4]. In addition, dossier assessment A20-22 noted further missing information (including data on patient characteristics), for which the company also subsequently submitted data with its comments.

The G-BA commissioned IQWiG with the assessment of the following additional data submitted by the company under consideration of the information provided in the dossier [5]:

- Study characteristics for the MONALEESA-3 study:
  - analysis of the time to discontinuation of the study medication including the corresponding Kaplan-Meier curves
  - description of the patient characteristics and subsequent therapies at drug level
- Results for the patient-relevant outcomes of the MONALEESA-3 study included in the assessment:
  - analyses regarding the change from baseline/analysis of the mean differences (MMRM analyses) for the outcome "health status" (EQ-5D VAS)
  - analyses on the change from baseline/MMRM analyses for the BPI-SF Item "worst pain"

- responder analyses of the time to deterioration by ≥ 10% for the BPI-SF for the Item "worst pain" as well as for pain intensity (Items 3–6) and pain interference (Items 9 a-g)
- information on any adverse events (AEs), serious AEs (SAEs) and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade 3–4) leading to treatment discontinuation

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The RCT MONALEESA-3, which compared the combination of ribociclib + fulvestrant with placebo + fulvestrant, was included for the benefit assessment of ribociclib in combination with fulvestrant in postmenopausal women as initial endocrine therapy (research question A1) and in postmenopausal women who have received prior endocrine therapy (research question B1).

Analyses presented

Health status (EQ-5D VAS)

In the present addendum, the MMRM analysis was used for the outcome "health status" (EQ-5D VAS) for the consideration of the change from baseline. The responder analyses presented by the company in the dossier for the time to definitive deterioration were based on unvalidated response criteria and were therefore rated as not usable in dossier assessment A20-22 (see [1] for details).

Pain (BPI-SF)

In the present addendum, the MMRM analysis was used for the outcome "pain" (BPI-SF) for the consideration of the change from baseline (prespecified in the MONALEESA-3 study) for each of the different operationalizations. The pain intensity based on the BPI-SF Items 3–6 represents an equally weighted average of different pains. Of these, the worst pain felt by the patient (Item 3) is of particular importance. It therefore appears meaningful to present the results for this item separately and to use them for the derivation of the added benefit. The results on average pain intensity (BPI-SF Items 3–6) are only presented as supplementary information in the present assessment. The results of the BPI-SF Items 3–6 were not used for the derivation of the added benefit, as otherwise the results of Item 3 would have been considered twice. If there are discrepant results compared with the results of worst pain (Item 3), these are discussed. Pain interference (BPI-SF Items 9 a–g) was also included in the present assessment.

MMRM analyses – documentation of the company on the methodological approach

The company stated in its documents subsequently submitted that its analyses for the MMRM model only included data from the period in which at least 50 patients per arm were still under treatment. In principle, analyses that take into account all data recorded are preferable. Such analyses were available for the BPI-SF and were therefore used for this instrument in the present addendum. No analyses including all data recorded were available for health status (EQ-5D VAS), so that the analysis was used that only included data in the MMRM model from the period in which at least 50 patients per arm were still under treatment. However, the restriction of the period considered means that no results were available for the outcome "health status" (EQ-5D VAS) for subpopulation B1, as the comparator arm of this subpopulation only included 39 patients. This had no consequence for the present assessment insofar as the results from subpopulation A1 (see Table 2) and the total population (see Table 12) allow at least the conclusion to be drawn that there were no significant effects to the disadvantage of the intervention for the outcome "health status" in subpopulation B1.

Further results

The responder analyses (time to deterioration by ≥ 10%, see Appendix C), prespecified also for the BPI-SF in the MONALEESA-3 study and subsequently submitted with the comments, were not used because the company did not provide any evidence that this is a validated response criterion. Overall, both analyses prespecified for the BPI-SF in the MONALEESA-3 study were now available completely. As described above, the present addendum used the analysis with the MMRM model for the BPI-SF.

In accordance with the 2 research questions A1 and B1, the assessment in the present addendum was carried out for the subpopulations A1 and B1 of the MONALEESA-3 study (information for the total population is presented in Appendix D).

Risk of bias

The assessment of the risk of bias across outcomes is in line with the assessment in dossier assessment A20-22 for the subpopulations A1 and B1. In each case, there was a high risk of bias for the results presented for the EQ-5D VAS and the BPI-SF, as more than 10% of the patients were missing in the analyses and, in addition, drop-outs in the further course of the study were caused by potentially informative reasons.

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

2.1.1 Study characteristics

Characteristics of the study population

Table 1 shows the characteristics of the patients in subpopulation A1 of the MONALEESA-3 study.

Table 1: Characteristics of the study population – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine therapy for the advanced stage) (multipage table)

Study **Characteristics** **Category**	**Ribociclib + fulvestrant** **N[a] = 374**	**Placebo + fulvestrant** **N[a] = 198**
MONALEESA-3		
Age [years], mean (SD)	63 (10)	63 (11)
Region, n (%)		
Asia	34 (9.1)	14 (7.1)
Europe/Australia[b]	258 (69.0)	143 (72.2)
Latin America	5 (1.3)	3 (1.5)
North America	59 (15.8)	31 (15.7)
Other	18 (4.8)	7 (3.5)
ECOG PS, n (%)		
0	232 (62.0)	137 (69.2)
1	141 (37.7)	61 (30.8)
Missing	1 (0.3)	0 (0)
Disease stage on study entry, n (%)		
II	1 (0.3)	0 (0)
III	3 (0.8)	2 (1.0)
IV	370 (98.9)	196 (99.0)
Disease-free interval, n (%)		
De novo	94 (25.1)	42 (21.2)
Not de novo	280 (74.9)	156 (78.8)
≤ 12 months	9 (2.4)	4 (2.0)
> 12 months	271 (72.5)	152 (76.8)
Type of most recent treatment, n (%)		
Chemotherapy	12 (3.2)	13 (6.6)
Endocrine therapy	133 (35.6)	76 (38.4)
Radiotherapy	106 (28.3)	59 (29.8)
Surgery (not biopsy)	60 (16.0)	35 (17.7)
Other	0 (0)	1 (0.5)
Setting of most recent treatment, n (%)		
Adjuvant	197 (52.7)	111 (56.1)
Neoadjuvant	3 (0.8)	2 (1.0)
Therapeutic	6 (1.6)	7 (3.5)
Palliative	41 (11.0)	20 (10.1)
Not applicable	60 (16.0)	35 (17.7)

Table 1: Characteristics of the study population – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine therapy for the advanced stage) (multipage table)

Study **Characteristics** **Category**	**Ribociclib + fulvestrant** **N[a] = 374**	**Placebo + fulvestrant** **N[a] = 198**
Location of metastases, n (%)		
Soft tissue	16 (4.3)	11 (5.6)
Breast	2 (0.5)	1 (0.5)
Bone	277 (74.1)	144 (72.7)
Bone only	86 (23.0)	41 (20.7)
Visceral	218 (58.3)	122 (61.6)
Lungs	114 (30.5)	61 (30.8)
Liver	91 (24.3)	49 (24.7)
Lung or liver	177 (47.3)	100 (50.5)
CNS	6 (1.6)	2 (1.0)
Other	72 (19.3)	44 (22.2)
Skin	18 (4.8)	5 (2.5)
Lymph nodes	159 (42.5)	94 (47.5)
None	5 (1.3)	0 (0)
Treatment discontinuation[c], n (%)	276 (73.8[d])	169 (85.4[d])
Study discontinuation, n (%)	ND	ND

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

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

The patient characteristics are comparable between the treatment groups.

Information on the course of the study

There was no information on treatment duration in dossier assessment A20-22 (data cut-off from 3 June 2019). The data subsequently submitted by the company on the analysis of the time to discontinuation of the study medication allow an estimation of the treatment duration for the total population (see Appendix A). The company did not provide any information on the 2 subpopulations A1 and B1.

Information on subsequent therapies

A presentation of any subsequent antineoplastic therapy by type of therapy for subpopulation A1 can be found in dossier assessment A20-22. A detailed list of the drugs administered in subpopulation A1 is presented in Appendix B.

2.1.2 Results (outcome level)

Table 2 summarizes the results of the comparison of ribociclib + fulvestrant with placebo + fulvestrant in postmenopausal patients with HR-positive, HER2-negative metastatic breast cancer for the outcomes “health status” (EQ-5D VAS) and “pain” (BPI-SF). Dossier assessment A20-22 considered the subgroup characteristic of age (< 65 years, ≥ 65 years), but results on subgroups for the outcomes “health status” (EQ-5D VAS) and “pain” (BPI-SF) are not available for this addendum.

Table 2: Results (morbidity, continuous) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine therapy for the advanced stage)

Study **Outcome category** **Outcome**	**Ribociclib + fulvestrant**			**Placebo + fulvestrant**			**Ribociclib + fulvestrant vs. placebo + fulvestrant**
	N[a]	**Values at baseline mean (SD)**	**Mean change in the course of the study mean [95% CI]**	**N[a]**	**Values at baseline mean (SD)**	**Mean change in the course of the study mean [95% CI]**	**MD [95% CI][b, c]; p-value**
MONALEESA-3 (data cut-off 3 June 2019)							
Morbidity							
Health status							
EQ-5D VAS	330	ND	ND	174	ND	ND	−1.44 [−4.15; 1.28]; 0.299
Pain (BPI-SF)							
Worst pain (Item 3)	329	3.3 (2.9)	ND	172	2.7 (2.8)	ND	−0.16 [−0.53, 0.22]; 0.405
Pain interference (Items 9 a–g)	329	2.2 (2.4)	ND	172	1.8 (2.4)	ND	0.01 [−0.30; 0.33]; 0.936
Supplementary information:							
Pain intensity (Items 3–6)	*329*	*2.5 (2.2)*	*ND*	*172*	*2.1 (2.1)*	*ND*	*−0.09 [−0.39; 0.20]; 0.526*

a. Number of patients considered in the analysis to calculate the effect estimation; the values for pain (BPI-SF) at baseline are based on 348 patients in the intervention arm and 183 patients in the control arm.
b. EQ-5D VAS: linear mixed-effects model repeated measures (MMRM) with change from baseline as a dependent variable, adjusted for values at baseline, stratified for the presence of liver and/or lung metastases. The resulting effect can be interpreted as a kind of average over the study period until the last time point at which at least 50 patients in each arm were still under treatment. A positive effect estimation indicates an advantage for ribociclib.
c. BPI SF: linear mixed-effects model repeated measures (MMRM) with change from baseline as a dependent variable, adjusted for values at baseline, stratified for the presence of liver and/or lung metastases. The resulting effect can be interpreted as a kind of average over the total study period. Higher values indicate a worse condition or a worse sense of wellbeing of the patient; a negative effect estimation indicates an advantage for ribociclib.

BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; MMRM: mixed-effects model repeated measures; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs: versus

Health status (EQ-5D VAS)

No statistically significant difference between the treatment arms was shown for the outcome "health status" recorded with the EQ-5D VAS. This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

Pain (BPI-SF)

Worst pain (BPI-SF Item 3)

No statistically significant difference between the treatment arms was shown for the outcome "pain", analysed using "worst pain" (BPI-SF Item 3). This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

Pain interference (BPI-SF Items 9 a–g)

No statistically significant difference between the treatment arms was shown for the outcome "pain interference" (BPI-SF Items 9 a–g). This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

2.1.3 Outcome category for the outcome "discontinuation due to AEs"

For the outcome "discontinuation due to AEs" in subpopulation A1, the data subsequently submitted by the company showed that, at the data cut-off from 3 June 2019, 53% (n = 31) of the AEs leading to discontinuation of the study medication in the ribociclib + fulvestrant arm, and 69% (n = 9) in the placebo + fulvestrant arm, were severe AEs (CTCAE grade 3–4). As was the case already in dossier assessment A20-22, the outcome "discontinuation due to AEs" was therefore allocated to the outcome category of serious/severe side effects.

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

2.2.1 Study characteristics

Characteristics of the study population

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

Table 3: Characteristics of the study population – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy for the advanced stage) (multipage table)

Study **Characteristics** **Category**	**Ribociclib + fulvestrant** **N[a] = 100**	**Placebo + fulvestrant** **N[a] = 39**
MONALEESA-3		
Age [years], mean (SD)	66 (9)	62 (11)
Region, n (%)		
Asia	6 (6.0)	2 (5.1)
Europe/Australia	81 (81.0)	26 (66.7)
Latin America	1 (1.0)	0 (0)
North America	9 (9.0)	11 (28.2)
Other	3 (3.0)	0 (0)
ECOG PS, n (%)		
0	71 (71.0)	19 (48.7)
1	29 (29.0)	20 (51.3)
Disease stage on study entry, n (%)		
II	1 (1.0)	0 (0)
IV	99 (99.0)	39 (100.0)
Disease-free interval, n (%)		
De novo	2 (2.0)	0 (0)
Not de novo	98 (98.0)	39 (100.0)
≤ 12 months	13 (13.0)	5 (12.8)
> 12 months	85 (85.0)	34 (87.2)
Type of most recent treatment, n (%)		
Chemotherapy	1 (1.0)	0 (0)
Endocrine therapy	66 (66.0)	22 (56.4)
Targeted therapy	2 (2.0)	2 (5.1)
Radiotherapy	25 (25.0)	14 (35.9)
Surgery (not biopsy)	6 (6.0)	2 (5.1)
Other	4 (4.0)	0 (0)
Setting of most recent treatment, n (%)		
Adjuvant	1 (1.0)	0 (0)
Therapeutic	71 (71.0)	26 (66.7)
Palliative	22 (22.0)	11 (28.2)
Not applicable	6 (6.0)	2 (5.1)

Table 3: Characteristics of the study population – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy for the advanced stage) (multipage table)

Study **Characteristics** **Category**	**Ribociclib + fulvestrant** **N[a] = 100**	**Placebo + fulvestrant** **N[a] = 39**
Location of metastases, n (%)		
Soft tissue	7 (7.0)	2 (5.1)
Breast	1 (1.0)	0 (0)
Bone	86 (86.0)	34 (87.2)
Bone only	13 (13.0)	9 (23.1)
Visceral	70 (70.0)	23 (59.0)
Lungs	29 (29.0)	11 (28.2)
Liver	41 (41.0)	13 (33.3)
Lung or liver	60 (60.0)	20 (51.3)
Other	28 (28.0)	8 (20.5)
Skin	2 (2.0)	3 (7.7)
Lymph nodes	41 (41.0)	20 (51.3)
Treatment discontinuation[b], n (%)	80 (80.0[c])	37 (94.9[c])
Study discontinuation, n (%)	ND	ND

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

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 patient characteristics are comparable between the treatment groups.

Information on the course of the study

There was no information on treatment duration in dossier assessment A20-22 (data cut-off from 3 June 2019). The data subsequently submitted by the company on the analysis of the time to discontinuation of the study medication allow an estimation of the treatment duration for the total population (see Appendix A). The company did not provide any information on the 2 subpopulations A1 and B1.

Information on subsequent therapies

A presentation of any subsequent antineoplastic therapy by type of therapy for subpopulation B1 can be found in dossier assessment A20-22. A detailed list of the drugs administered in subpopulation B1 is presented in Appendix B.

2.2.2 Results at outcome level

Table 4 summarizes the results of the comparison of ribociclib + fulvestrant with placebo + fulvestrant in postmenopausal patients with HR-positive, HER2-negative metastatic breast cancer for health status (EQ-5D VAS) and pain (BPI-SF). Dossier assessment A20-22 considered the subgroup characteristic of age (< 65 years, ≥ 65 years), but results on subgroups for the outcomes "health status" (EQ-5D VAS) and "pain" (BPI-SF) are not available for this addendum.

Table 4: Results (morbidity, continuous) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy for the advanced stage)

Study **Outcome category** **Outcome**	**Ribociclib + fulvestrant**			**Placebo + fulvestrant**			**Ribociclib + fulvestrant vs. placebo + fulvestrant**
	N[a]	**Values at baseline mean (SD)**	**Mean change in the course of the study mean [95% CI]**	**N[a]**	**Values at baseline mean (SD)**	**Mean change in the course of the study mean [95% CI]**	**MD [95% CI][b]; p-value**
MONALEESA-3 (data cut-off 3 June 2019)							
Morbidity							
Health status							
EQ-5D VAS	No data available[c]						
Pain (BPI-SF)							
Worst pain (Item 3)	82	2.2 (2.4)	ND	30	3.8 (2.7)	ND	−0.77 [−1.62; 0.09]; 0.080
Pain interference (Items 9 a–g)	82	1.4 (2.0)	ND	30	2.5 (2.1)	ND	−0.58 [−1.24; 0.08]; 0.086
Supplementary information:							
Pain intensity (Items 3–6)	*82*	*1.8 (1.8)*	*ND*	*30*	*3.1 (2.0)*	*ND*	*−0.35 [−1.04; 0.33]; 0.310*

a. Number of patients considered in the analysis to calculate the effect estimation; the values at baseline are based on 89 patients in the intervention arm and 35 patients in the control arm.
b. BPI SF: linear mixed-effects model repeated measures with change from baseline as a dependent variable, adjusted for values at baseline, stratified for the presence of liver and/or lung metastases. The resulting effect can be interpreted as a kind of average over the total study period. Higher values indicate a worse condition or a worse sense of wellbeing of the patient; a negative effect estimation indicates an advantage for ribociclib.
c. The company stated that the analysis only included data from the time points at which at least 50 patients per arm were still under treatment. For subpopulation B1, this prerequisite cannot be fulfilled per se due to the size of the population in the comparator arm (n = 39).

BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus

Health status (EQ-5D VAS)

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

Pain (BPI-SF)

Worst pain (BPI-SF Item 3)

No statistically significant difference between the treatment arms was shown for the outcome "pain", analysed using "worst pain" (BPI-SF Item 3). This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

Pain interference (BPI-SF Items 9 a–g)

No statistically significant difference between the treatment arms was shown for the outcome "pain interference" (BPI-SF Items 9 a–g). This resulted in no hint of an added benefit of ribociclib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven.

2.2.3 Outcome category for the outcome "discontinuation due to AEs"

For the outcome "discontinuation due to AEs" in subpopulation B1, the data subsequently submitted by the company showed that, at the data cut-off from 3 June 2019, 71% (n = 17) of the AEs leading to discontinuation of the study medication in the ribociclib + fulvestrant arm, and 50% (n = 1) in the placebo + fulvestrant arm, were severe AEs (CTCAE grade 3–4). As was the case already in dossier assessment A20-22, the outcome "discontinuation due to AEs" was therefore allocated to the outcome category of serious/severe side effects.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of ribociclib in combination with fulvestrant from dossier assessment A20-22.

The following Table 5 shows the result of the benefit assessment of ribociclib in combination with fulvestrant under consideration of dossier assessment A20-22 and the present addendum.

Table 5: Ribociclib in combination with fulvestrant – probability and extent of added benefit

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

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

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

The G-BA decides on the added benefit.

3 References

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Appendix A – Information on the course of the study

Table 6: Information on the course of the study – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (total population)

Study **Duration of the study phase** **Outcome category**	**Ribociclib + fulvestrant** **N = 484**	**Placebo + fulvestrant** **N = 242**
MONALEESA-3 (data cut-off from 3 June 2019)		
Treatment duration [months]		
Median [95% CI]	15.8 [13.1; 19.0]	11.9 [9.8; 14.8]
Mean (SD)	ND	ND
CI: confidence interval; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus		

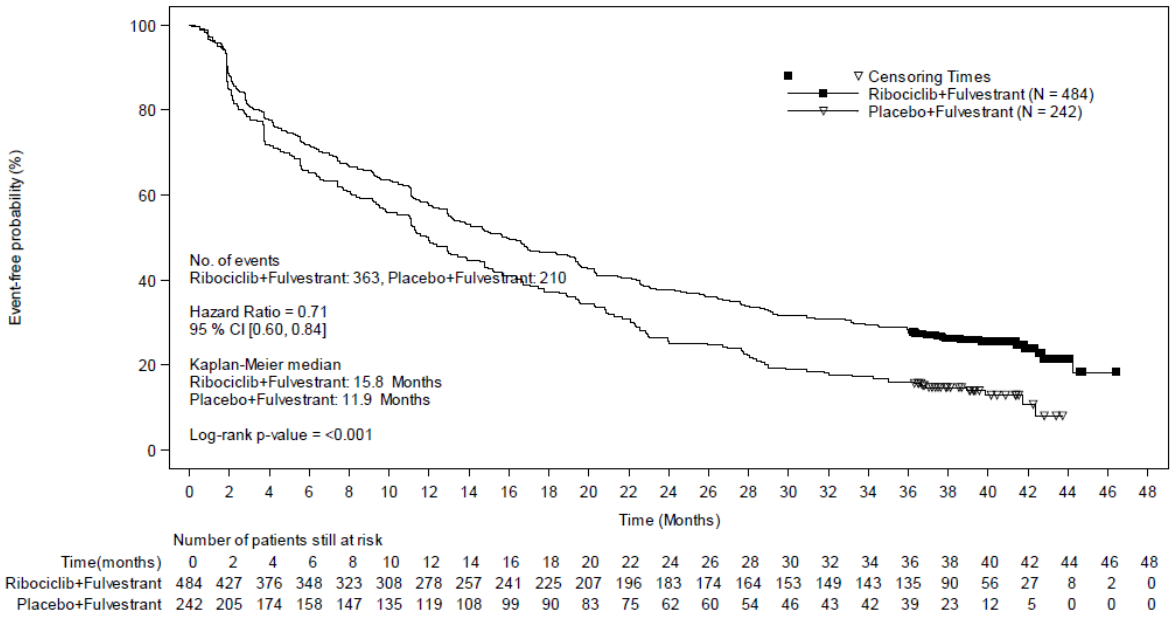

Figure 1: Kaplan-Meier curves for the time to discontinuation of the study medication in MONALEESA-3 (total population)

Appendix B – Subsequent therapies

Table 7: Information on any subsequent antineoplastic therapies (≥ 5% of the patients with treatment discontinuation in ≥ 1 treatment arm) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine therapy for the advanced stage) (multipage table)

Study **Drug class**[a] **Drug**	**Patients with subsequent therapy n (%**[b]**)**	
	Ribociclib + fulvestrant **N = 374**	**Placebo + fulvestrant** **N = 198**
MONALEESA-3 (data cut-off 3 June 2019)	**Number of patients who discontinued treatment**	
	M = 276	**M = 169**
Total	226 (81.9)	146 (86.4)
Aromatase inhibitors	128 (46.4)	89 (52.7)
Exemestane	76 (27.5)	57 (33.7)
Letrozole	63 (22.8)	48 (28.4)
Pyrimidine analogues	92 (33.3)	60 (35.5)
Capecitabine	85 (30.8)	53 (31.4)
Protein kinase inhibitors	87 (31.5)	79 (46.7)
Everolimus	67 (24.3)	51 (30.2)
Palbociclib	24 (8.7)	34 (20.1)
Taxanes	75 (27.2)	55 (32.5)
Paclitaxel	56 (20.3)	42 (24.9)
Docetaxel	12 (4.3)	12 (7.1)
Selective immunosuppressants	67 (24.3)	51 (30.2)
Everolimus	67 (24.3)	51 (30.2)
Antioestrogens	57 (20.7)	36 (21.3)
Fulvestrant	38 (13.8)	24 (14.2)
Tamoxifen	18 (6.5)	13 (7.7)
Anthracyclines and related substances	29 (10.5)	28 (16.6)
Epirubicin	15 (5.4)	11 (6.5)
Other antineoplastic agents	28 (10.1)	17 (10.1)
Eribulin	22 (8.0)	12 (7.1)
Vinca alkaloids and analogues	24 (8.7)	9 (5.3)
Vinorelbine	16 (5.8)	5 (3.0)
Monoclonal antibodies	19 (6.9)	18 (10.7)
Bevacizumab	15 (5.4)	14 (8.3)
Nitrogen mustard analogues	18 (6.5)	13 (7.7)
Cyclophosphamide	18 (6.5)	13 (7.7)
Platinum-containing compounds	17 (6.2)	12 (7.1)
Carboplatin	15 (5.4)	8 (4.7)
Antineovascular agents	15 (5.4)	14 (8.3)
Bevacizumab	15 (5.4)	14 (8.3)

Table 7: Information on any subsequent antineoplastic therapies (≥ 5% of the patients with treatment discontinuation in ≥ 1 treatment arm) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine therapy for the advanced stage) (multipage table)

Study **Drug class[a]** **Drug**	**Patients with subsequent therapy n (%[b])**	
	Ribociclib + fulvestrant **N = 374**	**Placebo + fulvestrant** **N = 198**

a. Pharmacological drug class according to ATC classification (coded according to WHO-DD version 17.3); multiple assignment of a drug to different ATC classes is possible; in case of multiple occurrence within an ATC class, the patient was counted only once in the drug class line.
b. Institute's calculation. Proportion of patients with subsequent therapy of a category of patients with premature treatment discontinuation.

ATC: anatomical therapeutic chemical; M: number of patients with treatment discontinuation; n: number of patients with subsequent therapy (percentages refer to the number of patients who discontinued treatment); N: number of analysed patients; RCT: randomized controlled trial; vs.: versus; WHO-DD: World Health Organization Drug Dictionary

Table 8: Information on any subsequent antineoplastic therapies (≥ 5% of the patients with treatment discontinuation in ≥ 1 treatment arm) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy for the advanced stage) (multipage table)

Study **Drug class[a]** **Drug**	**Patients with subsequent therapy n (%[b])**	
	Ribociclib + fulvestrant **N = 100**	**Placebo + fulvestrant** **N = 39**
MONALEESA-3 (data cut-off 3 June 2019)	**Number of patients who discontinued treatment**	
	M = 80	**M = 39**
Total	64 (80.0)	28 (75.7)
Pyrimidine analogues	28 (35.0)	15 (40.5)
Capecitabine	25 (31.3)	15 (40.5)
Aromatase inhibitors	25 (31.3)	16 (43.2)
Exemestane	17 (21.3)	12 (32.4)
Letrozole	7 (8.8)	4 (10.8)
Taxanes	20 (25.0)	15 (40.5)
Paclitaxel	13 (16.3)	11 (29.7)
Paclitaxel albumin	4 (5.0)	4 (10.8)
Antioestrogens	19 (23.8)	8 (21.6)
Fulvestrant	14 (17.5)	7 (18.9)
Tamoxifen	6 (7.5)	1 (2.7)
Protein kinase inhibitors	18 (22.5)	15 (40.5)
Everolimus	12 (15.0)	9 (24.3)
Palbociclib	6 (7.5)	8 (21.6)
Selective immunosuppressants	12 (15.0)	9 (24.3)
Everolimus	12 (15.0)	9 (24.3)
Vinca alkaloids and analogues	11 (13.8)	3 (8.1)
Vinorelbine tartrate	7 (8.8)	2 (5.4)
Vinorelbine	4 (5.0)	1 (2.7)
Anthracyclines and related substances	10 (12.5)	8 (21.6)
Doxorubicin	6 (7.5)	3 (8.1)
PEGylated doxorubicin	2 (2.5)	2 (5.4)
Epirubicin	2 (2.5)	3 (8.1)
Other antineoplastic agents	7 (8.8)	0 (0)
Eribulin	5 (6.3)	0 (0)
Monoclonal antibodies	4 (5.0)	3 (8.1)
Nitrogen mustard analogues	4 (5.0)	3 (8.1)
Cyclophosphamide	4 (5.0)	3 (8.1)
Investigational preparation	1 (1.3)	3 (8.1)
Investigational preparation	1 (1.3)	3 (8.1)

Table 8: Information on any subsequent antineoplastic therapies (≥ 5% of the patients with treatment discontinuation in ≥ 1 treatment arm) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy for the advanced stage) (multipage table)

Study **Drug class**[a] **Drug**	**Patients with subsequent therapy n (%**[b]**)**	
	Ribociclib + fulvestrant **N = 100**	**Placebo + fulvestrant** **N = 39**

a. Pharmacological drug class according to ATC classification (coded according to WHO-DD version 17.3); multiple assignment of a drug to different ATC classes is possible; in case of multiple occurrence within an ATC class, the patient was counted only once in the drug class line.
b. Institute's calculation.

ATC: anatomical therapeutic chemical; M: number of patients with treatment discontinuation; n: number of patients with subsequent therapy (percentages refer to the number of patients who discontinued treatment); N: number of analysed patients; RCT: randomized controlled trial; vs.: versus; WHO-DD: World Health Organization Drug Dictionary

Appendix C – BPI-SF – responder analyses of time to deterioration by ≥ 10%

Table 9: Results (morbidity, time to event) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, initial endocrine therapy for the advanced stage)

Study **Outcome category**	**Ribociclib + fulvestrant**		**Placebo + fulvestrant**		**Ribociclib + fulvestrant vs. placebo + fulvestrant**
Outcome	**N[a]**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N[a]**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[b]**
MONALEESA-3 (data cut-off 3 June 2019)					
Morbidity (symptoms)					
Pain (BPI-SF, time to definitive deterioration[c])					
Worst pain (Item 3)	374	NA [38.6; NC] 85 (22.7)	198	NA [36.1; NC] 40 (20.2)	0.98 [0.67; 1.43]; 0.936
Pain interference (Items 9a–g)	374	41.4 [35.9; NC] 98 (26.2)	198	42.3 [NC] 47 (23.7)	0.94 [0.66; 1.34]; 0.744
Supplementary information:					
Pain intensity (Items 3–6)	*374*	*42.7 [36.1; NC]* *95 (25.4)*	*198*	*35.9 [33.1; NC]* *55 (27.8)*	*0.79 [0.57; 1.11]; 0.172*

a. Information provided by the company. However, according to the information on continuous analyses using MMRM, a maximum of 329 patients in the intervention arm and 172 in the control arm could contribute information to the analysis.
b: Cox model and log-rank test stratified by the presence of liver and/or lung metastases.
c. An increase of the respective score by at least 10% was considered to be a clinically relevant definitive deterioration if this also applied to all subsequent values or if the deterioration occurred at the patient's last documentation time.

BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; HR: hazard ratio; MMRM: mixed-effects model repeated measures; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; vs.: versus

Table 10: Results (morbidity, time to event) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women who have received prior endocrine therapy for the advanced stage)

Study **Outcome category**	**Ribociclib + fulvestrant**		**Placebo + fulvestrant**		**Ribociclib + fulvestrant vs. placebo + fulvestrant**
Outcome	**N[a]**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N[a]**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[b]**
MONALEESA-3 (data cut-off 3 June 2019)					
Morbidity (symptoms)					
Pain (BPI-SF, time to definitive deterioration[c])					
Worst pain (Item 3)	100	NA [33.3; NC] 17 (17.0)	39	16.7 [11.1; NC] 13 (33.3)	0.37 [0.18; 0.77]; 0.006
Pain interference (Items 9a–g)	100	*38.6 [32.5; NC]* *24 (24.0)*	39	22.9 [14.9; NC] 11 (28.2)	0.61 [0.29; 1.27]; 0.184
Supplementary information:					
Pain intensity (Items 3–6)	*100*	*36.1 [32.5; NC]* *25 (25.0)*	*39*	*22.9 [13.1; NC]* *11 (28.2)*	*0.61 [0.29; 1.27]; 0.192*

a. Information provided by the company. However, according to the information on continuous analyses using MMRM, a maximum of 82 patients in the intervention arm and 30 in the control arm could contribute information to the analysis.
b: Cox model and log-rank test stratified by the presence of liver and/or lung metastases.
c. An increase of the respective score by at least 10% was considered to be a clinically relevant definitive deterioration if this also applied to all subsequent values or if the deterioration occurred at the patient's last documentation time.

BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; HR: hazard ratio; MMRM: mixed-effects model repeated measures; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; vs.: versus

Appendix D – Results on morbidity for the total population

Table 11: Results (morbidity, time to event) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (total population)

Study Outcome category	Ribociclib + fulvestrant		Placebo + fulvestrant		Ribociclib + fulvestrant vs. placebo + fulvestrant
Outcome	**N[a]**	**Median time to event in months [95% CI] Patients with event n (%)**	**N[a]**	**Median time to event in months [95% CI] Patients with event n (%)**	**HR [95% CI]; p-value[b]**
MONALEESA-3 (data cut-off 3 June 2019)					
Morbidity (symptoms)					
Pain (BPI-SF, time to definitive deterioration[c])					
Worst pain (Item 3)	484	NA 105 (21.7)	242	NA [34.9; NC] 55 (22.7)	0.81 [0.58; 1.12]; 0.204
Pain interference (Items 9a–g)	484	39.6 [35.9; NC] 125 (25.8)	242	42.3 [35.9; 42.3] 59 (24.4)	0.88 [0.65; 1.20]; 0.427
Supplementary information:					
Pain intensity (Items 3–6)	*484*	*42.7 [36.1; NC] 123 (25.4)*	*242*	*35.9 [27.6; NC] 68 (28.1)*	*0.76 [0.56; 1.02]; 0.071*

a. Information provided by the company. However, according to the information on continuous analyses using MMRM, a maximum of 419 patients in the intervention arm and 206 in the control arm could contribute information to the analysis.
b: Cox model and log-rank test stratified by the presence of liver and/or lung metastases as well as prior endocrine therapy.
c. An increase of the respective score by at least 10% was considered to be a clinically relevant definitive deterioration if this also applied to all subsequent values or if the deterioration occurred at the patient's last documentation time.

BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; HR: hazard ratio; MMRM: mixed-effects model repeated measures; n: number of patients with event; N: number of analysed patients; NA: not achieved; NC: not calculable; RCT: randomized controlled trial; vs.: versus

Table 12: Results (morbidity – continuous) – RCT, direct comparison: ribociclib + fulvestrant vs. placebo + fulvestrant (total population)

Study **Outcome category** **Outcome**	**Ribociclib + fulvestrant**			**Placebo + fulvestrant**			**Ribociclib + fulvestrant vs. placebo + fulvestrant**
	N[a]	**Values at baseline mean (SD)**	**Mean change in the course of the study mean [95% CI]**	**N[a]**	**Values at baseline mean (SD)**	**Mean change in the course of the study mean [95% CI]**	**MD [95% CI][b, c]; p-value**
MONALEESA-3 (data cut-off 3 June 2019)							
Morbidity							
Health status							
EQ-5D VAS	422	ND	ND	209	ND	ND	−0.55 [−2.91; 1.81]; 0.648
Pain (BPI-SF)							
Worst pain (Item 3)	419	3.1 (2.83)	ND	206	2.9 (2.80)	ND	−0.31 [−0.64; 0.02]; 0.070
Pain interference (Items 9 a–g)	419	2.0 (2.33)	ND	206	1.9 (2.32)	ND	−0.11 [−0.39; 0.17]; 0.442
Supplementary information:							
Pain intensity (Items 3–6)	*419*	*2.4 (2.13)*	*ND*	*206*	*2.3 (2.16)*	*ND*	*−0.18 [−0.44; 0.08]; 0.180*

a. Number of patients considered in the analysis to calculate the effect estimation; the values at baseline are based on 445 patients in the intervention arm and 222 patients in the control arm.

b. EQ-5D VAS: linear mixed-effects model repeated measures with change from baseline as a dependent variable, adjusted for values at baseline, stratified for the presence of liver and/or lung metastases as well as prior endocrine therapy. The resulting effect can be interpreted as a kind of average over the study period until the last time point at which at least 50 patients in each arm were still under treatment. A positive effect estimation indicates an advantage for ribociclib.

b. BPI-SF: linear mixed-effects model repeated measures with change from baseline as a dependent variable, adjusted for values at baseline, stratified for the presence of liver and/or lung metastases as well as prior endocrine therapy. The resulting effect can be interpreted as a kind of average over the total study period. Higher values indicate a worse condition or a worse sense of wellbeing of the patient; a negative effect estimation indicates an advantage for ribociclib.

BPI-SF: Brief Pain Inventory-Short Form; CI: confidence interval; EQ-5D: European Quality of Life-5 Dimensions; MD: mean difference; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale; vs.: versus