Ribociclib
(breast cancer, adjuvant treatment)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Medical and scientific advice

- Volker Heilmann

IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent and the patient organization 'Frauenselbsthilfe Krebs Bundesverband e. V.' for participating in the written exchange and for their support. The respondent and the 'Frauenselbsthilfe Krebs Bundesverband e. V.' were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AJCC	American Joint Committee on Cancer
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GnRH	gonadotropin-releasing hormone
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IDFS	invasive disease-free survival
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug ribociclib (in combination with an aromatase inhibitor). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 17 December 2024.

Research question

The aim of this report is to assess the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the appropriate comparator therapy (ACT) as adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence.

The research questions presented in Table 2 were defined in accordance with the ACT specified by the G-BA.

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

Research question	Therapeutic indication	ACT[a]
As adjuvant treatment of patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence in:		
1	premenopausal women[b, c, d]	▪ tamoxifen (where appropriate in addition to ovarian function suppression), or ▪ abemaciclib in combination with endocrine therapy (only for patients with node-positive breast cancer), or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations)
2	postmenopausal women[c, d, e]	▪ an aromatase inhibitor (anastrozole or letrozole) alone, where appropriate tamoxifen if aromatase inhibitors are unsuitable, or ▪ an aromatase inhibitor (anastrozole or exemestane) in sequence after tamoxifen, or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations)
3	men[b, c, d, f]	▪ tamoxifen, or ▪ abemaciclib in combination with endocrine therapy (only for patients with node-positive breast cancer), or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations)

a. Presented is the respective ACT specified by the G-BA.
b. According to the SPC, in pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with an LH-RH agonist.
c. According to the G-BA, adjuvant chemotherapy – if indicated – is assumed to have been completed.
d. Adjuvant radiotherapy may be performed sequentially or in parallel with endocrine therapy. According to the G-BA, adjuvant radiotherapy is not part of the ACT.
e. As a further treatment option, postmenopausal patients with HR-positive breast cancer should be offered adjuvant bisphosphonate therapy.
f. According to the G-BA, the evidence on treatment options for men with breast cancer is extremely limited. According to the guidelines, the recommendations for the treatment of men with breast cancer are predominantly based on the recommendations for the treatment of women, with aromatase inhibitors only being recommended for men in the presence of contraindications.

ACT: appropriate comparator therapy; BRCA: breast cancer-associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor2; HR: hormone receptor; LH-RH: luteinizing hormone-releasing hormone; SPC: Summary of Product Characteristics

The G-BA's most recent adjustment to the ACT was on 26 November 2024, as shown in Table 2. According to details provided by the company in Module 3 C, the last consultation with the G-BA took place on 25 July 2019. In its dossier, the company referred to the ACT specified at that time.

For research question 1 (premenopausal women), the company named tamoxifen (where appropriate in addition to ovarian function suppression), or an aromatase inhibitor (anastrozole, letrozole or exemestane) in combination with ovarian function suppression as

the ACT. For research question 2 (postmenopausal women), the company named an aromatase inhibitor (anastrozole or letrozole) alone, where appropriate tamoxifen (if aromatase inhibitors are not suitable), or an aromatase inhibitor (anastrozole or exemestane) in sequence after tamoxifen. For research question 3 (men), it named tamoxifen as the ACT. Overall, the company deviated from the G-BA's current ACT in all 3 research questions.

This benefit assessment was conducted in comparison with the ACT specified by the G-BA on 26 November 2024. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used to derive the added benefit. This concurs with the company's inclusion criteria.

Research question 1: Premenopausal women

Evidence presented by the company – NATALEE study

The company identified the RCT NATALEE comparing ribociclib + anastrozole or letrozole versus anastrozole or letrozole in adult patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence. The study included adult patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence whose tumour had been completely resected. To answer research question 1, the company used analyses of the subpopulation of those patients who were classified as premenopausal as per the inclusion criteria of the study.

No data on the comparison of ribociclib with the comparator therapy specified by the G-BA

For premenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence, the G-BA specified tamoxifen (where appropriate in addition to ovarian function suppression) or abemaciclib in combination with endocrine therapy (only for patients with node-positive breast cancer), or olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline breast cancer-associated gene 1/2 mutations) as the ACT. In the subpopulation used by the company, 95.5% of patients in the comparator arm received endocrine therapy alone, consisting of one of the 2 aromatase inhibitors – anastrozole or letrozole – and ovarian function suppression. These drugs do not correspond to the ACT specified by the G-BA for research question 1. The NATALEE study is therefore unsuitable for assessing any added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the G-BA's ACT in premenopausal women.

Results on added benefit

No suitable data are available for the assessment of the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT as adjuvant treatment in premenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence. For these patients, there is no hint of an added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: Postmenopausal women

Study pool and study design

The NATALEE study was considered to be relevant for this research question. However, the data presented by the company are not suitable for deriving conclusions on the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT in postmenopausal women, as the analyses presented by the company in Module 4 C were based on a non-predefined data cut-off. Below, the NATALEE study is first described, and then the unsuitability of the data presented for the benefit assessment is explained.

The NATALEE study is an ongoing, open-label, multicentre RCT comparing ribociclib + anastrozole or letrozole versus anastrozole or letrozole. The study included adult patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence whose tumour had been completely resected. For inclusion in the study, the women's menopausal status had to be known at the time of randomization or initiation of the adjuvant endocrine therapy.

A total of 5101 patients were randomly assigned in a 1:1 ratio to treatment with either ribociclib + anastrozole or letrozole (N = 2549) or anastrozole or letrozole (N = 2552).

Treatment with the study medication was largely in compliance with the respective Summary of Product Characteristics (SPC).

The primary outcome of the NATALEE study was invasive disease-free survival (IDFS). Further secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Analyses of the data from the 29 April 2024 data cut-off unsuitable

According to the module template, the results from the data cut-offs that were either predefined or required by the regulatory authorities should be presented in Module 4 of the dossier. Such data are not available in Module 4 as provided by the company. In Module 4 C of its dossier, the company presented analyses from the last post hoc data cut-off conducted on 29 April 2024. This data cut-off was not predefined and there is no information to show that it was requested by the regulatory authorities. This data cut-off was therefore not used for the benefit assessment. The results from the last prespecified data cut-off of 21 July 2023 are relevant for the benefit assessment. These results were not provided in Module 4 C of the dossier, however, hence the dossier is incomplete. The information on the last predefined data cut-off of 21 July 2023, which is relevant for the assessment, is only available in Module 5.

Overall, the analyses presented by the company in Module 4 C are unsuitable for drawing conclusions on the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT as adjuvant treatment in postmenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence.

Results on added benefit

No suitable data are available for the assessment of the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT as adjuvant treatment in postmenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence. For these patients, there is no hint of an added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT; an added benefit is therefore not proven.

Research question 3: Men

Concurring with the company, a review of the completeness of the study pool did not identify any RCTs that directly compare ribociclib in combination with an aromatase inhibitor versus the ACT for research question 3 (men).

Results on added benefit

No suitable data are available for the assessment of the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT as adjuvant treatment in men with HR-positive, HER2-negative early breast cancer at high risk of recurrence. For these patients, there is no hint of an added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT; an added benefit is therefore not proven.

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

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

[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].

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

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
As adjuvant treatment of patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence in:			
1	premenopausal women[b, c, d]	▪ tamoxifen (where appropriate in addition to ovarian function suppression), or ▪ abemaciclib in combination with endocrine therapy (only for patients with node-positive breast cancer), or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations)	Added benefit not proven
2	postmenopausal women[c, d, e]	▪ an aromatase inhibitor (anastrozole or letrozole) alone, where appropriate tamoxifen if aromatase inhibitors are unsuitable, or ▪ an aromatase inhibitor (anastrozole or exemestane) in sequence after tamoxifen, or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations)	Added benefit not proven
3	men[b, c, d, f]	▪ tamoxifen, or ▪ abemaciclib in combination with endocrine therapy (only for patients with node-positive breast cancer), or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations)	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the SPC, in pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with an LH-RH agonist.
c. According to the G-BA, adjuvant chemotherapy – if indicated – is assumed to have been completed.
d. Adjuvant radiotherapy may be performed sequentially or in parallel with endocrine therapy. According to the G-BA, adjuvant radiotherapy is not part of the ACT.
e. As a further treatment option, postmenopausal patients with HR-positive breast cancer should be offered adjuvant bisphosphonate therapy.
f. According to the G-BA, the evidence on treatment options for men with breast cancer is extremely limited. According to the guidelines, the recommendations for the treatment of men with breast cancer are predominantly based on the recommendations for the treatment of women, with aromatase inhibitors only being recommended for men in the presence of contraindications.

ACT: appropriate comparator therapy; BRCA: breast cancer-associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor2; HR: hormone receptor; LH-RH: luteinizing hormone-releasing hormone; SPC: Summary of Product Characteristics

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT as adjuvant treatment of patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence.

The research questions presented in Table 4 were defined in accordance with the ACT specified by the G-BA.

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

Research question	Therapeutic indication	ACT[a]
As adjuvant treatment of patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence in:		
1	premenopausal women[b, c, d]	▪ tamoxifen (where appropriate in addition to ovarian function suppression), or ▪ abemaciclib in combination with endocrine therapy (only for patients with node-positive breast cancer), or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations)
2	postmenopausal women[c, d, e]	▪ an aromatase inhibitor (anastrozole or letrozole) alone, where appropriate tamoxifen if aromatase inhibitors are unsuitable, or ▪ an aromatase inhibitor (anastrozole or exemestane) in sequence after tamoxifen, or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations)
3	men[b, c, d, f]	▪ tamoxifen, or ▪ abemaciclib in combination with endocrine therapy (only for patients with node-positive breast cancer), or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations)

a. Presented is the respective ACT specified by the G-BA.
b. According to the SPC, in pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with an LH-RH agonist.
c. According to the G-BA, adjuvant chemotherapy – if indicated – is assumed to have been completed.
d. Adjuvant radiotherapy may be performed sequentially or in parallel with endocrine therapy. According to the G-BA, adjuvant radiotherapy is not part of the ACT.
e. As a further treatment option, postmenopausal patients with HR-positive breast cancer should be offered adjuvant bisphosphonate therapy.
f. According to the G-BA, the evidence on treatment options for men with breast cancer is extremely limited. According to the guidelines, the recommendations for the treatment of men with breast cancer are predominantly based on the recommendations for the treatment of women, with aromatase inhibitors only being recommended for men in the presence of contraindications.

ACT: appropriate comparator therapy; BRCA: breast cancer-associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor2; HR: hormone receptor; LH-RH: luteinizing hormone-releasing hormone; SPC: Summary of Product Characteristics

The G-BA's most recent adjustment to the ACT was on 26 November 2024, as shown in Table 4. According to details provided by the company in Module 3 C, the last consultation with the G-BA took place on 25 July 2019 [3]. In its dossier, the company referred to the ACT specified at that time.

For research question 1 (premenopausal women), the company named tamoxifen (where appropriate in addition to ovarian function suppression), or an aromatase inhibitor (anastrozole, letrozole or exemestane) in combination with ovarian function suppression as the ACT. It justified the inclusion of aromatase inhibitors on the one hand with the fact that premenopausal women with medical ovarian suppression are therapeutically equal to postmenopausal women and can therefore be treated with aromatase inhibitors. On the other hand, it argued that aromatase inhibitors in combination with gonadotropin-releasing hormone (GnRH) analogues are more effective in preventing recurrences than tamoxifen and are recommended by current guidelines as equivalent to adjuvant therapy with tamoxifen (where appropriate with ovarian function suppression) [4-6]. For research question 2 (postmenopausal women), the company named an aromatase inhibitor (anastrozole or letrozole) alone, where appropriate tamoxifen (if aromatase inhibitors are not suitable), or an aromatase inhibitor (anastrozole or exemestane) in sequence after tamoxifen. For research question 3 (men), it named tamoxifen as the ACT. Due to the later adjustment of the ACT, these specifications from the company do not correspond to the current ACT specified by the G-BA on 26 November 2024. Overall, the company deviated from the G-BA's current ACT in all 3 research questions.

This benefit assessment was conducted in comparison with the ACT specified by the G-BA on 26 November 2024. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used to derive the added benefit. This concurs with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on ribociclib (status: 27 November 2024)
- Bibliographical literature search on ribociclib (last search on 25 November 2024)
- Search of trial registries/trial results databases for studies on ribociclib (last search on 25 November 2024)
- Search on the G-BA website for ribociclib (last search on 27 November 2024)

To check the completeness of the study pool:

- Search of trial registries for studies on ribociclib (last search on 7 January 2025); for search strategies, see I Appendix A of the full dossier assessment

The company identified the RCT NATALEE comparing ribociclib + anastrozole or letrozole versus anastrozole or letrozole in adult patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence. For the benefit assessment, the company used a subpopulation of the NATALEE study for each of the research questions 1 (premenopausal women) and 2 (postmenopausal women). The NATALEE study is not relevant for research question 1 of this assessment. For research question 2, the NATALEE study was used for this assessment. The company presented no data for research question 3 (men).

The review of the completeness of the study pool did not identify any additional relevant studies.

I 4 Research question 1: Premenopausal women

I 4.1 Evidence presented by the company – NATALEE study

The NATALEE study (see Table 5) is an ongoing, open-label, multicentre RCT comparing ribociclib + anastrozole or letrozole versus anastrozole or letrozole. The study included adult patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence whose tumour had been completely resected. A detailed description of the NATALEE study can be found in Section I 5.1.1. To answer research question 1, the company used analyses of the subpopulation of those patients who were classified as premenopausal as per the inclusion criteria of the study. In the NATALEE study, all patients who did not meet the criteria for postmenopausal status were considered premenopausal (for details of the definition, see Section I 5.1.1).

The NATALEE study is unsuitable for the benefit assessment of ribociclib in combination with an aromatase inhibitor in comparison with the ACT in premenopausal women. This is due to the fact that the ACT specified by the G-BA for research question 1 was not implemented in the comparator arm of the NATALEE study. This is explained below.

No data on the comparison of ribociclib with the comparator therapy specified by the G-BA

For premenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence, the G-BA specified tamoxifen (where appropriate in addition to ovarian function suppression) or abemaciclib in combination with endocrine therapy (only for patients with node-positive breast cancer), or olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline breast cancer-associated gene 1/2 mutations) as the ACT. In the subpopulation used by the company, 95.5% of patients in the comparator arm received endocrine therapy alone, consisting of one of the 2 aromatase inhibitors – anastrozole or letrozole – and ovarian function suppression. These drugs do not correspond to the ACT specified by the G-BA for research question 1. Thus, the NATALEE study does not provide a comparison with the ACT and does not answer this research question. The NATALEE study is therefore unsuitable for assessing any added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the G-BA's ACT in premenopausal women.

I 4.2 Results on added benefit

No suitable data are available for the assessment of the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT as adjuvant treatment in premenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence. For these patients, there is no hint of an added benefit of ribociclib in combination

with an aromatase inhibitor in comparison with the ACT; an added benefit is therefore not proven.

I 4.3 Probability and extent of added benefit

Since the company presented no suitable data for the assessment of the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT as adjuvant treatment in premenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence, an added benefit is not proven for these patients.

The assessment described above differs from that by the company, which derived an indication of considerable added benefit for premenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence on the basis of the NATALEE study.

I 5 Research question 2: Postmenopausal women

I 5.1 Studies included

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

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

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
CLEE011O12301C (NATALEE[c])	Yes	Yes	No	Yes [7-10]	Yes [11,12]	Yes [13,14]

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.
CSR: clinical study report; RCT: randomized controlled trial

For research question 2, the study pool of the benefit assessment comprises the RCT NATALEE and is consistent with the company's study pool. To answer research question 2, the company used analyses of the subpopulation of those patients who were classified as postmenopausal as per the inclusion criteria of the study (for the definition, see Section I 5.1.1).

The NATALEE study was considered to be relevant for this research question. However, the data presented by the company are not suitable for deriving conclusions on the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT in postmenopausal women, as the analyses presented by the company in Module 4 C were based on a non-predefined data cut-off. Below, the NATALEE study is first described, and then the unsuitability of the data presented for the benefit assessment is explained.

I 5.1.1 Study characteristics

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

Table 6: Characterization of the included study – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and study period	Primary outcome; secondary outcomes[a]
NATALEE	RCT, open-label, parallel	Adult patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence[b] ▪ after complete surgical resection ▪ ECOG PS 0 or 1	ribociclib + anastrozole or letrozole (N = 2549) anastrozole or letrozole (N = 2552) Relevant subpopulation thereof (postmenopausal women): ribociclib + anastrozole or letrozole (n = 1424) anastrozole or letrozole (n = 1420)	Screening: 28 days Treatment: ▪ ribociclib: 36 months (approx. 39 cycles) ▪ endocrine therapy: 60 months or until evidence of recurrence, intolerable toxicity, withdrawal of consent, lost to follow-up, end of study or death Observation: outcome-specific, at most until death, withdrawal of consent, lost to follow-up or end of study	393 study centres in Argentina, Australia, Austria, Belgium, Brazil, Canada, China, France, Germany, Hungary, Ireland, Italy, Poland, Romania, Russia, South Korea, Spain, Taiwan, United Kingdom, United States 12/2018–ongoing Data cut-offs: ▪ 3 September 2021 (1st interim analysis, planned to take place after 200 IDSF events) ▪ 15 August 2022 (2nd interim analysis, planned to take place after 350 IDSF events) ▪ 11 January 2023 (3rd interim analysis, planned to take place after 425 IDSF events) ▪ 21 July 2023 (final IDFS analysis, planned to take place after 500 IDFS events) ▪ 29 April 2024[c] (post hoc)	Primary: IDFS Secondary: overall survival, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes comprise exclusively data based on the information provided by the company in Module 4.
b. Stage IIA, IIB and III according to the AJCC classification, 8th edition. Patients with stage IIA also had to fulfil the following criteria: N1 or N0 with grade 3 or N0 with grade 2 and additionally Ki67 ≥ 20%, or a high-risk categorization as per the biomarker-based tests Oncotype DX, Prosigna/PAM50, MammaPrint or EndoPredict.
c. Data cut-off presented by the company in Module 4 C. According to the company, all patients in the intervention arm had completed treatment with ribociclib by this time.

AE: adverse event; AJCC: American Joint Committee on Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; IDFS: invasive disease-free survival; Ki67: Kiel antigen no. 67; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial

Table 7: Characterization of the intervention – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (multipage table)

Study	Intervention	Comparison
NATALEE	ribociclib 400 mg/day, orally, Days 1–21 of a 28-day cycle + letrozole 2.5 mg/day, orally, or anastrozole 1 mg/day, orally[a] in premenopausal women and in men combined with: goserelin 3.6 mg SC on Day 1 ± 3 of a 28-day cycle[b]	letrozole 2.5 mg/day, orally, or anastrozole 1 mg/day, orally[a] in premenopausal women and in men combined with: goserelin 3.6 mg SC on Day 1 ± 3 of a 28-day cycle[b]
	Dose adjustment: ▪ ribociclib: ▫ one dose reduction to 200 mg/day in case of intolerable toxicity; re-escalation was not permitted; if a 2nd dose reduction was required: discontinuation of treatment ▫ interruptions ≤ 28 days in case of toxicity ▪ endocrine therapy: ▫ interruption ≤ 28 days allowed[c]	
	Pretreatment <u>Allowed</u> ▪ completed adjuvant and/or neoadjuvant chemotherapy ▪ completed adjuvant radiotherapy ▪ neoadjuvant and/or adjuvant endocrine therapy within 12 months prior to randomization[d] <u>Disallowed</u> ▪ CDK4/6 inhibitors ▪ tamoxifen, raloxifene or aromatase inhibitors for the prevention of breast cancer and/or treatment of osteoporosis within the last 2 years prior to randomization ▪ anthracyclines (doxorubicin ≥ 450 mg/m², epirubicin ≥ 900 mg/m²) ▪ other antineoplastic therapy, with the exception of adjuvant endocrine therapy ▪ major surgery, chemotherapy or radiotherapy within 14 days prior to randomization ▪ investigational products within 30 days or 5 half-lives (whichever was longer) prior to randomization **Concomitant treatment** <u>Allowed</u> ▪ bisphosphonates/denosumab for the treatment of osteoporosis or as adjuvant therapy for the prevention of bone metastases ▪ supportive therapy <u>Disallowed</u> ▪ systemic corticosteroids ≤ 2 weeks before study start and during the study treatment[e] ▪ tamoxifen or toremifene ▪ hormonal contraception or hormone replacement therapy	

Table 7: Characterization of the intervention – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (multipage table)

Study	Intervention	Comparison
a. In the study, switching from letrozole to anastrozole or vice versa was only allowed due to intolerable toxicity, patient's request, or any other medically important event. b. In the case of monthly pretreatment with goserelin or another GnRH agonist: continuation of the treatment schedule permitted irrespective of the treatment cycles in the study; in the case of pretreatment with 3-month depot goserelin: switch to the one-month formulation. c. In case of interruption > 4 weeks due to toxicity, risk/benefit balance of continuing the study to be considered in consultation with the clinical monitor. d. Ovarian suppression or short-term endocrine therapy for fertility preservation is not considered neoadjuvant/adjuvant endocrine therapy. In case of adjuvant endocrine therapy with tamoxifen or toremifene, a washout period of 5 half-lives (i.e. 35 days) prior to randomization was required. During that period patients could take aromatase inhibitors. e. Short-term use (< 5 days) of systemic corticosteroids and topical applications, inhaled sprays, eye drops or local injections were permitted. CDK: cyclin-dependent kinase; GnRH: gonadotropin-releasing hormone; RCT: randomized controlled trial; SC: subcutaneous		

The NATALEE study is an ongoing, open-label, multicentre RCT comparing ribociclib + anastrozole or letrozole versus anastrozole or letrozole. The study included adult patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence whose tumour had been completely resected. High risk of recurrence was defined in the study as stage IIA, IIB or III (classification according to the American Joint Committee on Cancer [AJCC] 8th edition). Patients with stage IIA who were node-negative also had to have a histological grade 3 or grade 2 with Ki67 ≥ 20%, or a high-risk categorization as per the biomarker-based tests Oncotype DX, Prosigna/PAM50, MammaPrint or EndoPredict. In this therapeutic indication, there are no uniform criteria for defining high risk of recurrence. However, it is assumed that the patients included in the study had a high risk of recurrence.

Patients included in the study could already have started neoadjuvant/adjuvant endocrine therapy before the start of the study. However, randomization had to take place within 12 months of the start of endocrine therapy. Neoadjuvant/adjuvant chemotherapy and adjuvant radiotherapy had to be completed before screening.

For inclusion in the study, the women's menopausal status had to be known at the time of randomization or initiation of the adjuvant endocrine therapy. Patients were considered postmenopausal if one of the following criteria applied:

- bilateral oophorectomy
- age ≥ 60 years

- age < 60 years and amenorrhoea for 12 or more months (in the absence of chemotherapy, tamoxifen, toremifene or ovarian suppression) and follicle-stimulating hormone (FSH) and plasma oestradiol within the normal postmenopausal ranges
- if taking tamoxifen or toremifene and age < 60 years, then FSH and plasma oestradiol levels within normal postmenopausal ranges

A total of 5101 patients were randomly assigned in a 1:1 ratio to treatment with either ribociclib + anastrozole or letrozole (N = 2549) or anastrozole or letrozole (N = 2552). Randomization was stratified according to menopausal status (premenopausal women and men versus postmenopausal women), tumour stage (II versus III), prior neoadjuvant/adjuvant chemotherapy (yes versus no), and geographical region (North America/Western Europe/Oceania versus rest of the world).

In accordance with their randomization, patients in the intervention arm received on-label ribociclib 200 mg orally twice daily on Days 1 to 21 of each 28-day treatment cycle [15]. In addition, patients in both treatment arms received endocrine therapy consisting of once-daily oral administration of 2.5 mg letrozole or 1 mg anastrozole. Premenopausal women and men received additional treatment with the GnRH analogue goserelin. Treatment with the study medication was largely in compliance with the respective SPC [15-18]. Supportive therapy with bisphosphonates or denosumab was permitted in the NATALEE study. This corresponds to the guideline recommendations [19,20].

In the study, treatment with ribociclib was continued for up to 36 months (approx. 39 cycles) or until recurrence, unacceptable toxicity, withdrawal of consent or death. Endocrine therapy was administered in both study arms up to a maximum of 60 months after randomization or until one of the above-mentioned events occurred. Patient switching from the comparator arm to treatment with ribociclib was not generally provided for in the NATALEE study. The study materials do not contain any information on restrictions regarding subsequent therapies.

The primary outcome of the NATALEE study was IDFS. Further secondary outcomes were recorded in the categories of mortality, morbidity, health-related quality of life, and side effects.

Data cut-offs

The following 5 data cut-offs are currently available for the NATALEE study:

- 1st data cut-off dated 3 September 2021: futility analysis, planned to take place after about 200 events in the outcome of IDFS

- 2nd data cut-off dated 15 August 2022: 2nd interim analysis on the outcome of IDFS, planned to take place after about 350 events
- 3rd data cut-off dated 11 January 2023: 3rd interim analysis on the outcome of IDFS, planned to take place after about 425 events
- 4th data cut-off dated 21 July 2023: final data cut-off on the outcome of IDFS, planned to take place after about 500 events
- 5th data cut-off dated 29 April 2024: post hoc data cut-off conducted by the company; according to the company's information in Module 4 C, all patients in the intervention arm had discontinued treatment with ribociclib by this time

Analyses of the data from the 29 April 2024 data cut-off unsuitable

According to the module template, the results from the data cut-offs that were either predefined or required by the regulatory authorities should be presented in Module 4 of the dossier. Such data are not available in Module 4 as provided by the company. In Module 4 C of its dossier, the company presented analyses from the last post hoc data cut-off conducted on 29 April 2024. This data cut-off was not predefined and there is no information to show that it was requested by the regulatory authorities. This data cut-off was therefore not used for the benefit assessment. The results from the last prespecified data cut-off of 21 July 2023 are relevant for the benefit assessment. These results were not provided in Module 4 C of the dossier, however, hence the dossier is incomplete. The information on the last predefined data cut-off of 21 July 2023, which is relevant for the assessment, is only available in Module 5.

The company's data cut-off on 29 April 2024 was potentially result-driven. This can be illustrated by comparing the results from this data cut-off with the results from the last predefined data cut-off on 21 July 2023. Table 8 shows the results for outcomes with statistically significant and clinically relevant differences between the treatment arms for both data cut-offs. Based on the data cut-off from 29 April 2024, an advantage relevant to the conclusion was shown in favour of the intervention for the outcome of recurrence in relation to the proportion of patients with recurrence. This advantage was not shown for the last predefined data cut-off from 21 July 2023, however.

Table 8: Comparison of the results for the data cut-offs from 29 April 2024 and 21 July 2023, subpopulation of postmenopausal women[a]

Outcome	Results for data cut-off on 29 April 2024	Results for data cut-off on 21 July 2023
	RR [95% CI]; p-value[b]	RR [95% CI]; p-value[b]
Morbidity		
Recurrence[c]		
Recurrence rate	0.81 [0.67; 0.98]; 0.027	0.84 [0.69; 1.04]; 0.113
Invasive disease-free survival	HR: 0.75 [0.61; 0.92]; 0.005[d]	HR: 0.79 [0.64; 0.99]; 0.042[d]
Side effects		
SAEs	1.37 [1.13; 1.65]; 0.001	1.38 [1.14; 1.67]; < 0.001
Severe AEs[e]	3.05 [2.73; 3.41]; < 0.001	3.11 [2.77; 3.49]; < 0.001
Discontinuation due to AEs	4.83 [3.77; 6.20]; < 0.001	4.67 [3.64; 5.98]; < 0.001
Neutropenia (PT, severe AEs[e])	90.38 [33.84; 241.39]; < 0.001	90.14 [33.75; 240.75]; < 0.001

a. Only the results for outcomes with statistically significant and relevant differences between the treatment groups are shown.
b. Effect and CI: Cochran-Mantel-Haenszel method, p-value: 2-sided Cochran-Mantel-Haenszel chi-square test, each stratified by anatomical stage according to AJCC staging, prior neo-/adjuvant chemotherapy, and region.
c. Composite outcome, includes the events of local breast cancer recurrence, regional invasive breast cancer recurrence, contralateral invasive breast cancer, distant recurrence, second primary cancer (no breast cancer), and death from any cause.
d. Effect and CI: Cox proportional hazards model, p-value: log-rank test, each stratified by anatomical stage according to AJCC staging, prior neo-/adjuvant chemotherapy, and region.
e. Operationalized as CTCAE grade ≥ 3.

AE: adverse event; AJCC: American Joint Committee on Cancer; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Overall, the analyses presented by the company in Module 4 C are unsuitable for drawing conclusions on the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT as adjuvant treatment in postmenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence.

I 5.2 Results on added benefit

No suitable data are available for the assessment of the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT as adjuvant treatment in postmenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence. For these patients, there is no hint of an added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT; an added benefit is therefore not proven.

I 5.3 Probability and extent of added benefit

Since the company presented no suitable data for the assessment of the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT as adjuvant treatment in postmenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence, an added benefit is not proven for these patients.

The assessment described above differs from that by the company, which derived an indication of a minor added benefit for postmenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence on the basis of the NATALEE study.

I 6 Research question 3: Men

Concurring with the company, a review of the completeness of the study pool did not identify any RCTs that directly compare ribociclib in combination with an aromatase inhibitor versus the ACT for research question 3 (men).

I 6.1 Results on added benefit

No suitable data are available for the assessment of the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT as adjuvant treatment in men with HR-positive, HER2-negative early breast cancer at high risk of recurrence. For these patients, there is no hint of an added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT; an added benefit is therefore not proven.

I 6.2 Probability and extent of added benefit

Since the company presented no data for the assessment of the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT as adjuvant treatment in men with HR-positive, HER2-negative early breast cancer at high risk of recurrence, an added benefit is not proven for these patients.

The assessment described above concurs with that by the company.

I 7 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of ribociclib in combination with an aromatase inhibitor in comparison with the ACT is summarized in Table 9.

Table 9: Ribociclib in combination with an aromatase inhibitor – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
As adjuvant treatment of patients with HR-positive, HER2-negative early breast cancer at high risk of recurrence in:			
1	premenopausal women[b, c, d]	▪ tamoxifen (where appropriate in addition to ovarian function suppression), or ▪ abemaciclib in combination with endocrine therapy (only for patients with node-positive breast cancer), or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations)	Added benefit not proven
2	postmenopausal women[c, d, e]	▪ An aromatase inhibitor (anastrozole or letrozole) alone, where appropriate tamoxifen if aromatase inhibitors are unsuitable, or ▪ an aromatase inhibitor (anastrozole or exemestane) in sequence after tamoxifen, or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations)	Added benefit not proven
3	men[b, c, d, f]	▪ tamoxifen, or ▪ abemaciclib in combination with endocrine therapy (only for patients with node-positive breast cancer), or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations)	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the SPC, in pre- or perimenopausal women, or in men, the aromatase inhibitor should be combined with an LH-RH agonist.
c. According to the G-BA, adjuvant chemotherapy – if indicated – is assumed to have been completed.
d. Adjuvant radiotherapy may be performed sequentially or in parallel with endocrine therapy. According to the G-BA, adjuvant radiotherapy is not part of the ACT.
e. As a further treatment option, postmenopausal patients with HR-positive breast cancer should be offered adjuvant bisphosphonate therapy.
f. According to the G-BA, the evidence on treatment options for men with breast cancer is extremely limited. According to the guidelines, the recommendations for the treatment of men with breast cancer are predominantly based on the recommendations for the treatment of women, with aromatase inhibitors only being recommended for men in the presence of contraindications.

ACT: appropriate comparator therapy; BRCA: breast cancer-associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor2; HR: hormone receptor; LH-RH: luteinizing hormone-releasing hormone; SPC: Summary of Product Characteristics

The G-BA decides on the added benefit.

I 8 References for English extract

Please see full dossier assessment for full reference list.

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

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 02.09.2024]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Gemeinsamer Bundesausschuss. Niederschrift zum Beratungsgespräch gemäß § 8 Abs.1 AM-NutzenV, Beratungsanforderung 2019-B-075 Ribociclib [unpublished]. 2019.

4. Arbeitsgemeinschaft Gynäkologische Onkologie. Diagnostik und Therapie früher und fortgeschrittener Mammakarzinome; Adjuvante endokrin-basierte Therapie bei prä- und postmenopausalen Patientinnen [online]. 2024 [Accessed: 13.02.2025]. URL: https://www.ago-online.de/fileadmin/ago-online/downloads/_leitlinien/kommission_mamma/2024/Einzeldateien/AGO_2024D_10_Adjuvante_Endokrine_Therapie.pdf.

5. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) - Breast Cancer - Version 5. 2024.

6. Loibl S, Andre F, Bachelot T et al. Early breast cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. Ann Oncol 2024; 35(2): 159-182. https://doi.org/10.1016/j.annonc.2023.11.016.

7. Novartis. CLEE011O12301C (NATALEE) - A phase III, multicenter, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, early breast cancer (New Adjuvant TriAl with ribociclib [LEE011]: NATALEE) - Clinical Study Report Primary endpoint/third interim analysis (Version 1.0). 2023.

8. Novartis. CLEE011O12301C (NATALEE) - A phase III, multicenter, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, early breast cancer: efficacy analysis and safety update. Final iDFS Analysis (21-Jul-2023 data cut-off). 2023.

9. Novartis. CLEE011O12301C (NATALEE) - A phase III, multicenter, randomized, open-label trial to evaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, early breast cancer - End of Ribociclib Analysis Report. 2024.

10. Novartis Pharma. Ribociclib EBC CLEE011O12301C (NATALEE) - AMNOG initial full dossier submission. Subpopulation: post-menopausal female patients. Cut-off date: 21st Jul 2023. 2023.

11. ClinicalTrials.gov. A Trial to Evaluate Efficacy and Safety of Ribociclib With Endocrine Therapy as Adjuvant Treatment in Patients With HR+/HER2- Early Breast Cancer (NATALEE) [online]. 2018 [Accessed: 27.11.2024]. URL: https://clinicaltrials.gov/study/NCT03701334.

12. EU Clinical Trials Register. A phase III, multicenter, randomized, open-label trial toevaluate efficacy and safety of ribociclib with endocrine therapy as an adjuvant treatment in patients with hormone receptor-positive, HER2-negative, early breast cancer (New Adjuvant TriAl with Ribociclib [LEE011]: NATALEE) [online]. 2018 [Accessed: 27.11.2024]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=2018-002998-21.

13. Slamon D, Lipatov O, Nowecki Z et al. Ribociclib plus Endocrine Therapy in Early Breast Cancer. N Engl J Med 2024; 390(12): 1080-1091. https://doi.org/10.1056/NEJMoa2305488.

14. Hortobagyi GN, Lacko A, Sohn J et al. A phase III trial of adjuvant ribociclib plus endocrine therapy versus endocrine therapy alone in patients with HR-positive/HER2-negative early breast cancer: final invasive disease-free survival results from the NATALEE trial. Ann Oncol 2024. https://doi.org/10.1016/j.annonc.2024.10.015.

15. Novartis Pharma. Kisqali 200 mg Filmtabletten [online]. 11.2024 [Accessed: 13.02.2025]. URL: https://www.fachinfo.de.

16. Pfleger. Anablock 1 mg Filmtabletten [online]. 07.2021 [Accessed: 13.02.2025]. URL: https://www.fachinfo.de.

17. Pfleger. Letroblock 2,5 mg Filmtabletten [online]. 11.2020 [Accessed: 13.02.2025]. URL: https://www.fachinfo.de.

18. AstraZeneca. Zoladex 3,6 mg [online]. 03.2024. URL: https://www.fachinfo.de.

19. Leitlinienprogramm Onkologie. Interdisziplinäre S3-Leitlinie für die Früherkennung, Diagnostik, Therapie und Nachsorge des Mammakarzinoms; Langversion 4.4 - Juni 2021 [online]. 2021 [Accessed: 13.02.2025]. URL: https://register.awmf.org/assets/guidelines/032-045OLl_S3_Mammakarzinom_2021-07.pdf.

20. Bernhard Wörmann, Stefan Aebi, Marija Balic et al. Mammakarzinom der Frau [online]. 2018 [Accessed: 13.02.2025]. URL: https://www.onkopedia.com/de/onkopedia/guidelines/mammakarzinom-der-frau/@@guideline/html/index.html.

The full report (German version) is published under https://www.iqwig.de/en/projects/a24-124.html.