# Ribociclib
# (breast cancer, adjuvant treatment)

## Addendum to Project A24-124
## (dossier assessment)[1]

**ADDENDUM (DOSSIER ASSESSMENT)**

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# List of abbreviations

| Abbreviation | Meaning |
|---|---|
| ACT | appropriate comparator therapy |
| AE | adverse event |
| AGO | Arbeitsgemeinschaft gynäkologische Onkologie (Gynaecological Oncology Group) |
| AJCC | American Joint Committee on Cancer |
| CDK | cyclin-dependent kinase |
| CI | confidence interval |
| CTCAE | Common Terminology Criteria for Adverse Events |
| EORTC | European Organisation for Research and Treatment of Cancer |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| GnRH | gonadotropin-releasing hormone |
| HER2 | human epidermal growth factor receptor 2 |
| HR | hormone receptor |
| IDFS | invasive-free survival |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MMRM | mixed-effects model with repeated measures |
| PT | Preferred Term |
| QLQ-BR23 | Quality of Life Questionnaire-Breast Cancer 23 |
| QLQ-C30 | Quality of Life Questionnaire-Core 30 |
| SAE | serious adverse event |
| SGB | Sozialgesetzbuch (Social Code Book) |
| SMD | standardized mean difference |
| SOC | System Organ Class |
| VAS | visual analogue scale |

# 1 Background

On 23 April 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-124 (Ribociclib [breast cancer, adjuvant treatment] – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprised the assessment of the NATALEE study 29 April 2024 data cut, taking into account the information in the dossier [2] as well as the documents subsequently submitted by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure [3]. Regardless of the appropriate comparator therapy (ACT), the data for the subpopulation of premenopausal women (research question 1) were also to be analysed.

The responsibility for this 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

**Research question 1: Premenopausal women**

As described in dossier assessment A24-124 [1], the benefit assessment did not use the analyses presented by the company for the subpopulation of premenopausal women with hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence (hereinafter "premenopausal women") from the NATALEE study, which compared adjuvant treatment of ribociclib in combination with anastrozole or letrozole versus anastrozole or letrozole, because the drugs used in the comparator arm did 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.

In compliance with the commission, the results for the subpopulation of premenopausal women from the NATALEE study for the 29 April 2024 data cut-off are presented in Section 2.1.

**Research question 2: Postmenopausal women**

In dossier assessment A24-124 [1], the NATALEE study was assessed as relevant for the benefit assessment for the subpopulation of postmenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence (hereinafter "postmenopausal women"). However, the analyses of the data from the 29 April 2024 data cut-off presented by the company in Module 4 C of its dossier were not used for the benefit assessment, as this data cut-off was not predefined and no information was available to show that it was a data cut-off requested by the regulatory authorities.

In the commenting procedure, the company submitted regulatory documents from the Swiss health agency Swissmedic [4]. These documents show that during the Swiss approval procedure, further data with a longer observation period were requested in addition to the data from the prespecified data cut-off of 21 July 2023. The subsequently submitted results for the 29 April 2024 data cut-off were accepted by Swissmedic. Thus, this data cut-off fulfils the requirements of the module template and is relevant for the benefit assessment. The analyses of the data from this cut-off presented by the company in Module 4 C of its dossier were therefore used for the subpopulation of postmenopausal women (research question 2). The assessment and the derivation of the overall conclusion on the added benefit of ribociclib in research question 2 were conducted using patient-relevant outcomes on the basis of the data presented by the company in the dossier and the comments, and are presented in Section 2.2.

## 2.1 Research question 1: Premenopausal women

### 2.1.1 Study characteristics

A detailed description of the NATALEE study, including information on study design, intervention and data cut-offs conducted to date, can be found in dossier assessment A24-124 [1].

***Subpopulation relevant for research question 1***

Both pre- and postmenopausal women and men were included in the NATALEE study (N = 5101). For the assessment of research question 1, the company presented the subpopulation of premenopausal women. This subpopulation consisted of 2238 patients in total, of which 1115 patients were included in the intervention arm and 1123 patients in the comparator arm.

**Planned duration of follow-up observation**

Table 1 shows the planned duration of follow-up observation of patients for the individual outcomes.

Table 1: Planned duration of follow-up observation – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole

| **Study**<br>**Outcome category**<br>**Outcome** | **Planned follow-up observation** |
|---|---|
| **NATALEE** | |
| Mortality | |
| Overall survival | Until death, withdrawal of consent, loss to follow-up, or end of study[a], whichever was first |
| Morbidity | |
| Recurrence[b] | Until distant recurrence, death, withdrawal of consent, loss to follow-up, or end of study[a], whichever was first |
| Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23) | Until 12 months after confirmation of distant recurrence |
| Health status (EQ-5D VAS) | Until 12 months after confirmation of distant recurrence |
| Health-related quality of life | |
| (EORTC QLQ-C30, EORTC QLQ-BR23) | Until 12 months after confirmation of distant recurrence |
| Side effects | |
| AEs, severe AEs | Up to 36 months after randomization or up to 30 days after discontinuation of study treatment, whichever was first |
| SAEs | Up to 30 days after discontinuation of study treatment[c] |

a. About 60 months after randomization of the last patient.
b. Presented using the recurrence rate and the IDFS, includes local breast cancer recurrence, regional invasive breast cancer recurrence, contralateral invasive breast cancer, distant recurrence, second primary cancer (non-breast cancer), and death from any cause.
c. SAEs related to the treatment were recorded until the end of the study.

AE: adverse event; EORTC: European Organisation for Research and Treatment of Cancer; IDFS: invasive disease-free survival QLQ-BR23: Quality of Life Questionnaire-Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire Core-30; RCT: randomized controlled trial; SAE: serious adverse event; VAS: visual analogue scale

A follow-up observation of up to 12 months was planned for the patient-reported outcomes on symptoms, health status and health-related quality of life. Although the observation periods were therefore shortened and did not cover the entire study period, it can be positively noted that the recording of patient-reported outcomes was continued beyond the recurrence.

The observation periods for the outcomes on side effects were systematically shortened, as the adverse events (AEs) were only recorded up to 36 months after randomization or for the period of study treatment (plus 30 days), and the serious adverse events (SAEs) were only recorded for the period of treatment (plus 30 days). Only SAEs related to the treatment were to be recorded until the end of the study.

To be able to draw a reliable conclusion on the total study period or the time until death of the patients, it would be necessary to record these outcomes over the total period of time, as was the case for overall survival and recurrences.

### Patient characteristics

Table 2 shows the characteristics of the premenopausal patients in the study included.

Table 2: Characterization of the study population and of study/treatment discontinuation – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| Study<br>Characteristic<br>Category | Ribociclib + anastrozole or letrozole<br>N = 1115 | Anastrozole or letrozole<br>N = 1123 |
|---|---|---|
| **NATALEE** | | |
| Age [years], mean (SD) | 44 (6) | 44 (6) |
| Family origin, n (%) | | |
| Asian | 211 (19) | 200 (18) |
| Black or African American | 16 (1) | 22 (2) |
| White | 754 (68) | 757 (67) |
| Other | 73 (7)[a] | 83 (7)[a] |
| No data | 58 (5) | 59 (5) |
| ECOG PS, n (%) | | |
| 0 | 967 (87) | 976 (87) |
| 1 | 146 (13) | 146 (13) |
| No data | 2 (< 1) | 1 (< 1) |
| Disease stage[b], n (%) | | |
| IB | 3 (< 1) | 0 (0) |
| IIA | 171 (15) | 203 (18) |
| IIB | 248 (22) | 229 (20) |
| IIIA | 451 (40) | 416 (37) |
| IIIB | 67 (6) | 61 (5) |
| IIIC | 175 (16) | 214 (19) |
| Hormone receptor status, n (%) | | |
| ER+/PR+ | 972 (87) | 959 (85) |
| ER+/PR- | 137 (12) | 149 (13) |
| ER-/PR+ | 2 (< 1) | 6 (< 1) |
| Missing value | 4 (< 1) | 9 (< 1) |
| Prior radiotherapy, n (%) | 1017 (91) | 1038 (92) |
| Prior chemotherapy, n (%) | 1032 (93) | 1039 (93) |
| Adjuvant | 514 (46) | 511 (46) |
| Neoadjuvant | 548 (49) | 568 (51) |

Table 2: Characterization of the study population and of study/treatment discontinuation – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| Study Characteristic Category | Ribociclib + anastrozole or letrozole N = 1115 | Anastrozole or letrozole N = 1123 |
|---|---|---|
| Prior endocrine therapy, n (%) | 858 (77) | 822 (73) |
| Antioestrogens | 262 (24) | 243 (22) |
| Aromatase inhibitors | 672 (60) | 651 (58) |
| GnRH analogues | 650 (58) | 603 (54) |
| Treatment discontinuation of all components, n (%)[c, d] | 212 (19)[d] | 339 (32)[d] |
| Ribociclib[e] | 328 (30)[d] | 2 (< 1)[d] |
| Anastrozole or letrozole[f] | 282 (25)[d] | 339 (32)[d] |
| Goserelin[g] | 386 (35)[d] | 427 (40)[d] |
| Study discontinuation, n (%)[h] | 167 (15) | 241 (22) |

a. Includes Native Americans, Native Hawaiians/Other Pacific Islanders and Others; Institute's calculation.
b. Staging according to AJCC classification, 8th edition.
c. 9 (< 1%) of the randomized patients in the intervention arm vs. 51 (5%) of the randomized patients in the control arm did not receive any additional treatment. The percentages therefore refer to the patients who received treatment (intervention arm: 1106, control arm: 1072).
d. Institute's calculation.
e. Common reasons for the discontinuation of ribociclib in the intervention arm were the following (percentages refer to patients who discontinued ribociclib; Institute's calculation): AEs (55%), recurrence (15%), patient's decision (14%), end of study participation (11%).
f. Common reasons for the discontinuation of anastrozole or letrozole in the intervention vs. control arm were the following (percentages refer to patients who discontinued anastrozole or letrozole; Institute's calculation): AEs (16% vs. 16%), recurrence (27% vs. 32%), patient's decision (24% vs. 19%), end of study participation (20% vs. 22%). The data additionally include patients who died during treatment with the study medication (intervention arm: 2 vs. control arm: 1).
g. Common reasons for the discontinuation of goserelin in the intervention vs. control arm were the following (percentages refer to patients who discontinued goserelin; Institute's calculation): recurrence (17% vs. 23%), patient's decision (16% vs. 14%), end of study participation (12% vs. 15%), other reasons (38% vs. 33%). The data additionally include patients who died during treatment with the study medication (intervention arm: 2 vs. control arm: 1).
h. A common reason for the study discontinuation in the intervention vs. control arm was the following (percentages refer to randomized patients): end of study participation (10% vs. 15%). The data additionally include patients who died during the course of the study (intervention arm: 3% vs. control arm: 4%).

AE: adverse event; AJCC: American Joint Committee on Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ER: oestrogen receptor; GnRH: gonadotropin-releasing hormone; n: number of patients in the category; N: number of randomized patients; PR: progesterone receptor; RCT: randomized controlled trial; SD: standard deviation

In the NATALEE study, the demographic and clinical characteristics of the premenopausal patients were largely balanced between the intervention and the comparator arm. The mean patient age was 44 years, and most patients were of white family origin (68% versus 67%). The majority of patients had stage II (37% versus 38%) or III (62% versus 61%) disease.

Furthermore, 91% versus 92% of patients had already received radiotherapy, 93% versus 93% chemotherapy, and 77% versus 73% endocrine therapy.

The proportion of patients who discontinued all treatment components was slightly lower in the intervention arm than in the comparator arm (19% vs. 32%). In the intervention arm, 30% of patients discontinued treatment with ribociclib, primarily due to the occurrence of AEs. The most common reason for discontinuation of anastrozole or letrozole in both study arms was the occurrence of recurrences. Study discontinuations occurred mainly due to an end of study participation and were slightly less frequent in the intervention arm than in the comparator arm (15% versus 22%).

**Information on the course of the study**

Table 3 shows the premenopausal patients' median and mean treatment durations and the median and mean observation periods for individual outcomes.

Table 3: Information on the course of the study – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| **Study**<br>**Duration of the study phase**<br>**Drug or outcome category/outcome** | **Ribociclib + anastrozole or letrozole**<br>**N = 1115[a]** | **Anastrozole or letrozole**<br>**N = 1123[a]** |
|---|---|---|
| **NATALEE (29 April 2024 data cut-off)** | | |
| Treatment duration [months] | | |
| Ribociclib | N = 1106 | N = 2 |
| Median [Q1; Q3] | 35.7 [24.4; 35.7] | 2.0 [0.1; 4.0] |
| Mean (SD) | 28.3 (12.8) | 2.0 (2.8) |
| Anastrozole or letrozole | N = 1106 | N = 1072 |
| Median [Q1; Q3] | 45.0 [37.5; 50.6] | 44.6 [31.6; 50.4] |
| Mean (SD) | 40.5 (14.9) | 38.1 (16.6) |
| Goserelin | N = 1088 | N = 1051 |
| Median [Q1; Q3] | 43.4 [29.6; 49.7] | 40.5 [20.4; 49.7] |
| Mean (SD) | 37.2 (16.5) | 35.1 (17.6) |
| Observation period [months] | | |
| Overall survival[b] | N = 1115 | N = 1123 |
| Median [Q1; Q3] | 44.4 [38.1; 49.8] | 44.2 [36.9; 49.7] |
| Mean (SD) | 41.9 (13.1) | 39.7 (15.5) |
| Recurrence | N = 1115 | N = 1123 |
| Median [Q1; Q3] | 44.2 [35.7; 49.7] | 44.2 [33.1; 49.7] |
| Mean (SD) | 39.2 (14.2) | 36.5 (16.4) |

Table 3: Information on the course of the study – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| **Study**<br>**Duration of the study phase**<br>**Drug or outcome category/outcome** | **Ribociclib + anastrozole or letrozole**<br>**N = 1115[a]** | **Anastrozole or letrozole**<br>**N = 1123[a]** |
|---|---|---|
| Symptoms (EORTC QLQ-C30)[c] | N = 1060 | N = 1005 |
| Median [Q1; Q3] | 44.4 [33.8; 49.9] | 44.4 [33.5; 49.8] |
| Mean (SD) | 40.3 (12.3) | 39.6 (12.9) |
| Symptoms (EORTC QLQ-BR23)[c] | N = 1060 | N = 1003 |
| Median [Q1; Q3] | 44.4 [33.8; 49.9] | 44.4 [33.5; 49.8] |
| Mean (SD) | 40.3 (12.3) | 39.6 (12.9) |
| Health status (EQ-5D VAS) | N = 1051 | N = 999 |
| Median [Q1; Q3] | 44.4 [33.8; 49.8] | 44.4 [33.5; 49.8] |
| Mean (SD) | 40.3 (12.6) | 39.6 (12.9) |
| Health-related quality of life (EORTC QLQ-C30)[c] | N = 1060 | N = 1003 |
| Median [Q1; Q3] | 44.4 [33.8; 49.9] | 44.4 [33.5; 49.8] |
| Mean (SD) | 40.3 (12.3) | 39.6 (12.8) |
| Health-related quality of life (EORTC QLQ-BR23)[c] | N = 1060 | N = 1000 |
| Median [Q1; Q3] | 44.4 [33.8; 49.9] | 44.4 [33.5; 49.8] |
| Mean (SD) | 40.3 (12.3) | 39.6 (12.8) |
| Side effects | N = 1108[d] | N = 1070[d] |
| Median [Q1; Q3] | 45.0 [37.7; 50.7] | 44.6 [32.5; 50.4] |
| Mean (SD) | 40.7 (14.7) | 38.4 (16.3) |

a. Number of patients in the ITT population, any deviating numbers are indicated in the relevant place.
b. Inverse Kaplan-Meier method.
c. Partially deviating information between the subscales.
d. Number of randomized patients who received at least one dose of the study medication.

EORTC: European Organisation for Research and Treatment of Cancer; ITT: intention to treat; N: number of analysed patients; Q1: 1st quartile; Q3: 3rd quartile; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

In the subpopulation of premenopausal women, both the median treatment duration and the median observation period were approximately the same for all outcomes in both treatment arms. The study documents show that at the time of the given data cut-off, all premenopausal patients in the intervention arm had either completed the 3-year treatment with ribociclib according to the study protocol or had discontinued this treatment prematurely.

### Subsequent therapies

Table 4 shows which subsequent therapies premenopausal patients received after discontinuing one component or the entire study medication. Data are only available for all treatments regardless of the line of treatment.

Table 4: Information on subsequent therapies (≥ 2 patients in one treatment arm) – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| Study<br>Drug class[a] | Patients with subsequent therapy n (%)[b] | |
|---|---|---|
| | Ribociclib + anastrozole or letrozole<br>N = 1115 | Anastrozole or letrozole<br>N = 1123 |
| **NATALEE (29 April 2024 data cut-off)** | | |
| Total | 157 (14.1) | 220 (19.6) |
| Anthracyclines and related substances | 2 (1.3) | 4 (1.8) |
| Antioestrogens | 68 (43.3) | 110 (50) |
| Aromatase inhibitors | 73 (46.5) | 94 (42.7) |
| Bisphosphonates | 4 (2.5) | 4 (1.8) |
| CDK inhibitors | 25 (15.9) | 78 (35.5) |
| Folic acid analogues | 0 (0) | 2 (0.9) |
| GnRH analogues | 46 (29.3) | 65 (29.5) |
| HER2 inhibitors | 5 (3.2) | 9 (4.1) |
| mTOR kinase inhibitors | 4 (2.5) | 1 (0.5) |
| Nitrogen mustard analogues | 4 (2.5) | 2 (0.9) |
| Other antineoplastic agents | 5 (3.2) | 16 (7.2) |
| Other drugs affecting bone structure and mineralization | 5 (3.2) | 7 (3.2) |
| Other monoclonal antibodies and antibody drug conjugates | 7 (4.5) | 9 (4.1) |
| Other protein kinase inhibitors | 3 (1.9) | 2 (0.9) |
| PD-1/PD-L1 inhibitors | 6 (3.8) | 9 (4.1) |
| pi3k inhibitors | 3 (1.9) | 1 (0.5) |
| Platinum compounds | 16 (10.2) | 23 (10.5) |
| PARP inhibitors | 4 (2.5) | 3 (1.4) |
| Pyrimidine analogues | 24 (15.3) | 42 (19.1) |
| Taxanes | 17 (10.8) | 26 (11.8) |
| Unspecified herbal and traditional drugs | 0 (0) | 2 (0.9) |
| VEGF/VEGFR inhibitors | 2 (1.3) | 6 (2.7) |
| Vinca alkaloids and analogues | 4 (2.5) | 6 (2.7) |
| Radiotherapy | 10 (6.4) | 18 (8.2) |
| Surgical therapy | 18 (11.5) | 23 (10.5) |

Table 4: Information on subsequent therapies (≥ 2 patients in one treatment arm) – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| **Study**<br>**Drug class**[a] | **Patients with subsequent therapy n (%)**[b] | |
|---|---|---|
| | **Ribociclib + anastrozole or letrozole**<br>**N = 1115** | **Anastrozole or letrozole**<br>**N = 1123** |

a. Drug classes according to the Anatomical Therapeutic Chemical Classification.
b. The percentages at the level of the drug classes were calculated by the Institute and refer to patients with subsequent therapy (intervention arm vs. control arm: n = 157 vs. n = 220).

CDK: cyclin-dependent kinase; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2; mTOR: mammalian target of rapamycin; n: number of patients with subsequent therapy; N: number of randomized patients; PARP: poly(adenosine diphosphate-ribose) polymerase; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; Pi3K: phosphatidylinositol-3-kinase; RCT: randomized controlled trial; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor

In the NATALEE study, subsequent antineoplastic therapies were permitted without restrictions in both study arms. The proportion of premenopausal patients who received at least one subsequent therapy was approx. 14% in the intervention arm and 20% in the comparator arm, and was thus notably higher than the proportion of patients with recurrence (approx. 9% and 12%, see also Table 8). This is assumed to be due to the fact that, for example, switching a component of endocrine therapy after discontinuation due to AEs was also included in this analysis. The most common subsequent therapies in both study arms were antioestrogens, aromatase inhibitors and gonadotropin-releasing hormone (GnRH) analogues, and in the comparator arm also cyclin-dependent kinase (CDK) inhibitors. Patients were also treated with chemotherapy.

According to the S3 Guideline on Early Detection, Diagnostics, Therapy and Follow-up of Breast Cancer [5], surgery and, if necessary, radiotherapy or systemic treatment (endocrine therapy or chemotherapy) are indicated if local recurrence occurs. Depending on their previous therapy, premenopausal women with distant recurrences are recommended to have endocrine-based therapy with a CDK4/6 inhibitor with ovarian function suppression and in combination with an aromatase inhibitor or fulvestrant, if they had not already had these therapies [5]. The company's dossier shows that the recurrences that occurred in both study arms were mainly distant recurrences (in approx. 69% vs. 77% of patients with recurrence). Overall, the subsequent therapies appeared to be largely consistent with the recommendations of the S3 guideline and were therefore considered adequate.

### Risk of bias across outcomes (study level)

Table 5 shows the risk of bias across outcomes (risk of bias at study level).

Table 5: Risk of bias across outcomes (study level) – RCT, direct comparison: ribociclib + anastrozole or letrozole versus anastrozole or letrozole

| Study | Adequate random sequence generation | Allocation concealment | Blinding | | Reporting independent of the results | No additional aspects | Risk of bias at study level |
|---|---|---|---|---|---|---|---|
| | | | Patients | Treating staff | | | |
| NATALEE | Yes | Yes | No | No | Yes | No[a] | High |

a. Continuously high proportion of censoring for potentially informative reasons in the course of the study (see Kaplan-Meier curves for overall survival and recurrences in Appendix A). It is assumed that the censoring was largely due to study discontinuations. The exact reasons for most study discontinuations are not described, however (see Table 2 and Table 11).

RCT: randomized controlled trial

The risk of bias across outcomes was rated as high for the NATALEE study. The Kaplan-Meier curves for all-cause mortality show that censoring already occurred early and then continuously over the entire course, and also to a relevant extent. For example, at Month 36, 16% versus 21% of premenopausal patients were no longer at risk (see Figure 1), meaning that they were censored or deceased. In postmenopausal women, this figure was 20% vs. 25% at Month 36 (see Figure 3). The proportion of deaths was very low, however (see Table 8 and Table 16). Up to this point, administrative censoring due to data cut-offs, for example, also played a subordinate role at most. A similar picture regarding censoring can also be seen for the outcome of recurrence (see Figure 2 and Figure 4). The reasons for the early and, in some cases, differential censoring between the study arms are largely unclear. It is assumed that most cases of censoring were due to study discontinuations (see Table 2 and Table 11). The exact reasons for most study discontinuations were not described, however. It is assumed that these were potentially informative reasons. In the study, there were overall more cases of censoring for unclear reasons than events at the time of the data cut-off at hand, both for overall survival and for recurrences.

It remains unclear for the other outcomes to what extent the incomplete observations of the patients (potentially informative reasons) led to missing values.

Limitations resulting from the open-label study design are described in Section 2.1.2.2 on the outcome-specific risk of bias.

**Transferability of the study results to the German health care context**

In the company's opinion, the results of the NATALEE study are transferable to the German health care context. The company explained that the majority of patients included were white, and that most of them enrolled in study centres in Europe, North America and Australia, i.e. in countries with a high health care standard, which is comparable to that in Germany.

According to the company, the frequency of visits for the clinical evaluation of the patients was largely in line with the recommendations of the German S3 guideline on breast cancer [6]. It added that there was only a slight deviation with regard to the follow-up examinations, which, from 24 months after randomization in the NATALEE study, were carried out at longer intervals than recommended in the S3 guideline. According to an IQWiG report, however, this does not call into question the overall patient relevance of disease-free survival [7], the company stated.

It additionally described that ultrasound of the breast in the NATALEE study was only performed after clinical suspicion of loco-regional recurrence, while the S3 guideline also recommends it in addition to mammography and as an imaging procedure of the ipsilateral breast after mastectomy at least once a year [6]. However, the company evaluated the importance of this deviation to be only marginal. because, among other things, there is insufficient evidence for mortality reduction for ultrasound of the breast according to the S3 guideline [6], and because the German Gynaecological Oncology Group (AGO) does not provide for routine sonography of the ipsilateral breast after mastectomy [8].

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

### 2.1.2 Results

#### 2.1.2.1 Presented outcomes

This addendum presents the following patient-relevant outcomes for premenopausal women in the NATALEE study:

- Mortality
  - Overall survival
- Morbidity
  - Recurrence
  - Symptoms
    - recorded using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)

    - recorded using the EORTC QLQ-Breast Cancer 23 (BR23)
  - Health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - recorded using the EORTC QLQ-C30
  - recorded using the EORTC QLQ-BR23
- Side effects
  - SAEs
  - Severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3)
  - Discontinuation due to AEs
  - Neutropenia (Preferred Term [PT], severe AEs)
  - Other specific AEs, if any

The patient-relevant outcomes selected deviate from those selected by the company, which used additional outcomes in its dossier (Module 4 C).

Table 6 shows for which outcomes data for research question 1 were available from the included study.

Table 6: Matrix of outcomes – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women)

| Study | Outcomes | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Overall survival | Recurrences[a] | Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23) | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23) | SAEs | Severe AEs[b] | Discontinuation due to AEs[c] | Neutropenia (PT, severe AEs[b]) | Further specific AEs[b,d] |
| NATALEE | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

a. Presented using the recurrence rate and the IDFS, includes local breast cancer recurrence, regional invasive breast cancer recurrence, contralateral invasive breast cancer, distant recurrence, second primary cancer (non-breast cancer), and death from any cause.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Discontinuation of ≥ 1 treatment components.
d. The following events are taken into account (coded according to MedDRA): skin and subcutaneous tissue disorders (SOC, AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs), infections and infestations (SOC, severe AEs), gastrointestinal disorders (SOC, severe AEs), general disorders and administration site conditions (SOC, severe AEs) and hepatobiliary toxicity (operationalized via the SMQ "drug related hepatic disorders – comprehensive search", severe AEs).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; IDFS: invasive disease-free survival; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

**Notes on outcomes**

***Recurrence***

The outcome of recurrence is a composite outcome and includes the components of local breast cancer recurrence, regional invasive breast cancer recurrence, contralateral invasive breast cancer, distant recurrence, second primary cancer (non-breast cancer), and death from any cause. The results of the operationalizations "proportion of patients with recurrence" (hereinafter referred to as "recurrence rate") and "invasive-free survival (IDFS)" are presented for the outcome of recurrence. The patients considered in the relevant stage of the disease are a group of patients who were treated with a curative treatment approach. Recurrence in this situation means that the attempt at cure by the curative treatment approach was not successful.

In accordance with the study protocol, events of the recurrence outcome were recorded by the investigator by means of regular physical examinations and mammography. If a recurrence was suspected, this had to be confirmed by additional imaging and histological or cytological examinations.

Due to the unblinded study design, there was a risk of investigator bias in the assessment of the recurrence outcome, as the interpretation of radiological and clinical data by the investigator could be influenced by knowledge of the treatment allocation. An analysis by means of a blinded review was not carried out in the study. This aspect was taken into account in the assessment of the outcome-specific risk of bias (see Section 2.1.2.2).

It should also be noted that at the 29 April 2024 data cut-off used for the benefit assessment, the median observation period in the study was only about 44 months (see Table 3). In the therapeutic indication in question, recurrences can still occur many years after the initial therapy [5,9]. Analysing data from a later data cut-off with a longer observation period would therefore provide more reliable information.

***Patient-reported outcomes in the categories of morbidity and health-related quality of life***

In Module 4 C, the company presented analyses of the EORTC QLQ-C30 and EORTC QLQ-BR23 scales for the outcomes of symptoms and health-related quality of life, and analyses of the EQ-5D VAS for the outcome of health status. For each of these outcomes, the company presented analyses of the mean change from baseline using a mixed-effects model with repeated measures (MMRM). These are suitable for the benefit assessment.

#### 2.1.2.2 Risk of bias

Table 7 shows the risk of bias for the results of the relevant outcomes for the premenopausal women of research question 1.

Table 7: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women)

| Study | | Outcomes | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study level | Overall survival | Recurrences[a] | Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23) | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23) | SAEs | Severe AEs[b] | Discontinuation due to AEs[c] | Neutropenia (PT, severe AEs[b]) | Further specific AEs[b, d] |
| NATALEE | H | H[e] | H[e, f] | H[e, f] | H[e, f] | H[e, f] | H[e] | H[e] | H[e, g] | H[e] | H[e, f] |

a. Presented using the recurrence rate and the IDFS, includes the events of local breast cancer recurrence, regional invasive breast cancer recurrence, contralateral invasive breast cancer, distant recurrence, second primary cancer (non-breast cancer), and death from any cause.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Discontinuation of a treatment component.
d. The following events are taken into account (coded according to MedDRA): skin and subcutaneous tissue disorders (SOC, AEs), respiratory, thoracic and mediastinal disorders (SOC, AEs), infections and infestations (SOC, severe AEs), gastrointestinal disorders (SOC, severe AEs), general disorders and administration site conditions (SOC, severe AEs) and hepatobiliary toxicity (operationalized via the SMQ "drug related hepatic disorders – comprehensive search", severe AEs).
e. High risk of bias across outcomes.
f. Lack of blinding for subjective outcome assessment (in the category of other specific AEs, this applies exclusively to the following AEs: skin and subcutaneous tissue disorders [SOC, AEs] and respiratory, thoracic and mediastinal disorders [SOC, AEs]).
g. Lack of blinding in subjective decision to discontinue (for non-severe/non-serious AEs).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; IDFS: invasive disease-free survival; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias for the results of all outcomes was rated as high. One reason for this is the high risk of bias across outcomes, which results from a high proportion of censorings (see Table 5). On an outcome-specific basis, the following additional aspects also contribute to the high risk of bias:

The outcome-specific risk of bias is high for the outcome of recurrence due to the unblinded outcome assessment by the investigator (see Section 2.1.2.1).

The risk of bias for the patient-reported outcomes in the categories of symptoms, anxiety symptoms and depressive symptoms, health status and health-related quality of life, as well as for the non-severe/non-serious AEs is also considered to be high due to the lack of blinding in subjective outcome assessment.

For the results of the outcome of discontinuation due to AEs, the lack of blinding in the presence of subjective decision to discontinue treatment also contributed to the high risk of bias.

#### 2.1.2.3 Results

Table 8 and Table 9 summarize the results of the comparison of ribociclib + anastrozole or letrozole versus anastrozole or letrozole for the adjuvant treatment of premenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves for the time-to-event analyses of the outcomes of overall survival and invasive disease-free survival are presented in Appendix A.1, and the results on common AEs, SAEs, severe AEs, and discontinuations due to AEs can be found in Appendix B.1.

Table 8: Results (mortality, morbidity, side effects) – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| Study<br>Outcome category<br>Outcome | Ribociclib + anastrozole or letrozole | | Anastrozole or letrozole | | Ribociclib + anastrozole or letrozole vs. anastrozole or letrozole |
|---|---|---|---|---|---|
| | N | Patients with event<br>n (%) | N | Patients with event<br>n (%) | RR [95% CI]; p-value[a] |
| **NATALEE (29 April 2024 data cut-off)** | | | | | |
| **Mortality** | | | | | |
| Overall survival | 1115 | 31 (2.8)<br>Median time to event: NA | 1123 | 46 (4.1)<br>Median time to event: NA | HR: 0.63 [0.40; 1.00]; 0.049[b] |
| **Morbidity** | | | | | |
| Recurrence | | | | | |
| Recurrence rate[c] | 1115 | 99 (8.9) | 1123 | 136 (12.1) | 0.73 [0.57; 0.93]; 0.012[d] |
| Death from any cause | 1115 | 4 (0.4) | 1123 | 3 (0.3) | – |
| Local breast cancer recurrence | 1115 | 4 (0.4) | 1123 | 3 (0.3) | – |
| Regional invasive breast cancer recurrence | 1115 | 12 (1.1) | 1123 | 18 (1.6) | – |
| Contralateral invasive breast cancer | 1115 | 3 (0.3) | 1123 | 6 (0.5) | – |
| Distant recurrence | 1115 | 66 (5.9) | 1123 | 103 (9.2) | – |
| Second primary cancer (non-breast cancer) | 1115 | 15 (1.3) | 1123 | 13 (1.2) | – |
| Invasive disease-free survival (IDFS)[e] | 1115 | 99 (8.9)<br>Median time to event: NA | 1123 | 136 (12.1)<br>Median time to event: NA | HR: 0.67 [0.52; 0.87]; 0.002[b] |
| **Side effects** | | | | | |
| AEs (supplementary information)[f] | 1108 | 1093 (98.6) | 1070 | 964 (90.1) | – |
| SAEs[f] | 1108 | 145 (13.1) | 1070 | 105 (9.8) | 1.33 [1.05; 1.69]; 0.017 |
| Severe AEs[f, g] | 1108 | 734 (66.2) | 1070 | 200 (18.7) | 3.54 [3.11; 4.04]; < 0.001 |
| Discontinuation due to AEs[f, h] | 1108 | 190 (17.1) | 1070 | 60 (5.6) | 3.06 [2.32; 4.04]; < 0.001 |
| Neutropenia (PT, severe AEs[g]) | 1108 | 335 (30.2) | 1070 | 9 (0.8) | 35.95 [18.64; 69.32]; < 0.001 |

Table 8: Results (mortality, morbidity, side effects) – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| Study<br>Outcome category<br>Outcome | Ribociclib + anastrozole or letrozole | | Anastrozole or letrozole | | Ribociclib + anastrozole or letrozole vs. anastrozole or letrozole |
|---|---|---|---|---|---|
| | N | Patients with event n (%) | N | Patients with event n (%) | RR [95% CI]; p-value[a] |
| Skin and subcutaneous tissue disorders (SOC, AEs) | 1108 | 416 (37.5) | 1070 | 227 (21.2) | 1.77 [1.54; 2.03]; < 0.001 |
| Respiratory, thoracic and mediastinal disorders (SOC, AEs) | 1108 | 339 (30.6) | 1070 | 186 (17.4) | 1.76 [1.50; 2.06]; < 0.001 |
| Infections and infestations (SOC, severe AEs[g]) | 1108 | 57 (5.1) | 1070 | 29 (2.7) | 1.90 [1.22; 2.94]; 0.004 |
| Gastrointestinal disorders (SOC, severe AEs[g]) | 1108 | 24 (2.2) | 1070 | 9 (0.8) | 2.58 [1.20; 5.51]; 0.012 |
| General disorders and administration site conditions (SOC, severe AEs[g]) | 1108 | 24 (2.2) | 1070 | 9 (0.8) | 2.58 [1.20; 5.51]; 0.012 |
| Hepatobiliary toxicity (SMQ, severe AEs[g])[i] | 1108 | 75 (6.8) | 1070 | 21 (2.0) | 3.45 [2.14; 5.55]; < 0.001 |

a. Institute's calculation of RR, 95% CI and p-value, unconditional exact test (CSZ method according to [10]).
b. Effect and CI: Cox proportional hazards model; p-value: log-rank test. Each stratified by AJCC anatomic stage, prior neoadjuvant/adjuvant chemotherapy, and region.
c. The individual components are presented in the lines below.
d. Effect and CI: Cochran-Mantel-Haenszel method, p-value: 2-sided Cochran-Mantel-Haenszel chi-square test. Each stratified by AJCC anatomic stage, prior neoadjuvant/adjuvant chemotherapy, and region.
e. Operationalized as time from the day of randomization to the first occurrence of an event, for individual components see recurrence rate.
f. Without disease-related events (the events of breast cancer recurrence and progression of malignancy were not taken into account).
g. Operationalized as CTCAE grade ≥ 3.
h. Discontinuation of a treatment component.
i. Operationalized via severe AEs of the SMQ “drug related hepatic disorders – comprehensive search” coded according to MedDRA.

AE: adverse event; AJCC: American Joint Committee on Cancer; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; N: number of analysed patients; NA: not achieved; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: standardized MedDRA query: SOC: System Organ Class

Table 9: Results (morbidity, health-related quality of life) – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| Study<br>Outcome category<br>Outcome | Ribociclib + anastrozole or letrozole | | | Anastrozole or letrozole | | | Ribociclib + anastrozole or letrozole vs. anastrozole or letrozole |
|---|---|---|---|---|---|---|---|
| | N[a] | Values at baseline mean (SD) | Mean change in the course of the study mean[b] (SE) | N[a] | Values at baseline mean (SD) | Mean change in the course of the study mean[b] (SE) | MD [95% CI]; p-value[b] |
| **NATALEE (29 April 2024 data cut-off)** | | | | | | | |
| **Morbidity** | | | | | | | |
| Symptoms (EORTC QLQ-C30)[c] | | | | | | | |
| Fatigue | 1059 | 29.0 (21.5) | 4.1 (0.5) | 1004 | 28.1 (20.7) | 1.3 (0.5) | 2.81 [1.40; 4.21]; < 0.001<br>SMD: 0.17 [0.09; 0.26] |
| Nausea and vomiting | 1059 | 3.3 (9.3) | 2.3 (0.2) | 1005 | 3.5 (9.3) | 1.3 (0.2) | 1.02 [0.39; 1.66]; 0.002<br>SMD: 0.14 [0.05; 0.23] |
| Pain | 1060 | 23.1 (22.3) | 3.3 (0.5) | 1004 | 21.5 (21.7) | 2.5 (0.5) | 0.78 [–0.66; 2.23]; 0.288 |
| Dyspnoea | 1057 | 10.7 (19.6) | 3.5 (0.5) | 1004 | 10.6 (18.6) | 2.6 (0.5) | 0.93 [–0.34; 2.20]; 0.150 |
| Insomnia | 1060 | 33.6 (29.7) | 2.7 (0.7) | 1005 | 33.3 (29.9) | 2.6 (0.7) | 0.09 [–1.74; 1.91]; 0.927 |
| Appetite loss | 1059 | 7.8 (18.3) | 2.2 (0.4) | 1005 | 7.6 (17.5) | 1.7 (0.4) | 0.53 [–0.56; 1.63]; 0.339 |
| Constipation | 1055 | 10.6 (21.0) | 4.6 (0.5) | 1004 | 11.6 (21.7) | 3.1 (0.5) | 1.54 [0.16; 2.93]; 0.029<br>SMD: 0.10 [0.01; 0.18] |
| Diarrhoea | 1055 | 4.6 (13.2) | 2.1 (0.3) | 1003 | 4.5 (12.8) | 1.7 (0.3) | 0.37 [–0.54; 1.27]; 0.427 |
| Symptoms (EORTC QLQ-BR23)[c] | | | | | | | |
| Side effects of systemic therapy | 1060 | 17.9 (13.1) | 5.8 (0.4) | 1003 | 17.8 (13.7) | 3.3 (0.4) | 2.52 [1.53; 3.52]; < 0.001<br>SMD: 0.22 [0.13; 0.31] |
| Breast symptoms | 1052 | 21.0 (18.8) | –4.8 (0.4) | 1001 | 20.1 (18.4) | –5.8 (0.4) | 1.01 [0.04; 1.99]; 0.041<br>SMD: 0.09 [0.00; 0.18] |

Table 9: Results (morbidity, health-related quality of life) – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| Study<br>Outcome category<br>Outcome | Ribociclib + anastrozole or letrozole | | | Anastrozole or letrozole | | | Ribociclib + anastrozole or letrozole vs. anastrozole or letrozole |
|---|---|---|---|---|---|---|---|
| | N[a] | Values at baseline mean (SD) | Mean change in the course of the study mean[b] (SE) | N[a] | Values at baseline mean (SD) | Mean change in the course of the study mean[b] (SE) | MD [95% CI]; p-value[b] |
| Arm symptoms | 1054 | 24.9 (21.6) | –0.3 (0.4) | 1000 | 24.8 (20.8) | –2.1 (0.5) | 1.78 [0.54; 3.03]; 0.005<br>SMD: 0.12 [0.04; 0.21] |
| Upset by hair loss | No suitable data[d] | | | | | | |
| Health status (EQ-5D VAS)[f] | 1051 | 78.2 (14.7) | –1.2 (0.4) | 999 | 77.6 (15.1) | –0.5 (0.4) | –0.64 [–1.70; 0.41]; 0.232 |
| **Health-related quality of life** | | | | | | | |
| EORTC QLQ-C30[f] | | | | | | | |
| Global health status | 1056 | 73.7 (17.3) | –3.5 (0.4) | 1003 | 74.4 (16.8) | –2.4 (0.4) | –1.16 [–2.31; –0.02]; 0.047<br>SMD: –0.09 [–0.17; –0.00] |
| Physical functioning | 1060 | 85.9 (14.3) | –1.5 (0.3) | 1003 | 86.3 (13.8) | –0.3 (0.3) | –1.22 [–2.15; –0.30]; 0.010<br>SMD: –0.11 [–0.20; –0.03] |
| Role functioning | 1059 | 83.0 (21.8) | –2.9 (0.5) | 1004 | 83.6 (20.6) | –1.3 (0.5) | –1.64 [–3.06; –0.22]; 0.023<br>SMD: –0.10 [–0.19; –0.01] |
| Emotional functioning | 1056 | 77.6 (20.3) | –5.8 (0.5) | 1003 | 78.5 (19.1) | –5.4 (0.5) | –0.48 [–1.85; 0.89]; 0.494 |
| Cognitive functioning | 1056 | 81.4 (20.7) | –6.2 (0.5) | 1003 | 81.6 (20.2) | –5.2 (0.5) | –1.05 [–2.49; 0.38]; 0.150 |
| Social functioning | 1056 | 80.4 (24.3) | –0.2 (0.5) | 1002 | 81.7 (22.0) | 1.9 (0.5) | –2.08 [–3.52; –0.64]; 0.005<br>SMD: –0.12 [–0.21; –0.04] |

Table 9: Results (morbidity, health-related quality of life) – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| Study<br>Outcome category<br>Outcome | Ribociclib + anastrozole or letrozole | | | Anastrozole or letrozole | | | Ribociclib + anastrozole or letrozole vs. anastrozole or letrozole |
|---|---|---|---|---|---|---|---|
| | N[a] | Values at baseline mean (SD) | Mean change in the course of the study mean[b] (SE) | N[a] | Values at baseline mean (SD) | Mean change in the course of the study mean[b] (SE) | MD [95% CI]; p-value[b] |
| EORTC QLQ-BR23[f] | | | | | | | |
| Body image | 1060 | 69.3 (28.1) | 2.1 (0.6) | 1000 | 69.6 (27.4) | 3.5 (0.6) | –1.35 [–2.98; 0.29]; 0.106 |
| Sexual functioning | 1047 | 25.6 (23.1) | –5.0 (0.4) | 994 | 25.1 (22.4) | –4.42 (0.46) | –0.57 [–1.82; 0.68]; 0.372 |
| Sexual enjoyment | No suitable data[g] | | | | | | |
| Future perspective | 1058 | 45.3 (31.6) | 10.0 (0.7) | 997 | 46.0 (31.5) | 11.3 (0.7) | –1.32 [–3.21; 0.58]; 0.174 |

a. Number of patients taken into account in the effect estimation; baseline values may be based on different patient numbers.
b. MMRM adjusted for AJCC anatomic stage, prior neoadjuvant/adjuvant chemotherapy, and region.
c. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 0 to 100).
d. Only 299 (27%) patients in the intervention arm vs. 256 (23%) patients in the control arm were included in the analysis.
e. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 0 to 21).
f. Higher (increasing) values indicate better health status/health-related quality of life; positive effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 0 to 100).
g. Only 630 (57%) patients in the intervention arm vs. 598 (53%) patients in the control arm were included in the analysis.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; VAS: visual analogue scale

When interpreting the following results of the NATALEE study, the high risk of bias across outcomes must be taken into account.

**Mortality**

***Overall survival***

A statistically significant difference in favour of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole was shown for the outcome of overall survival. When interpreting the effects for this outcome, the high risk of bias due to censoring for potentially informative reasons in conjunction with the small effect size must be taken into account in particular. These already occurred to a relevant extent early and continuously in the course of the study (see Section 2.1.1).

**Morbidity**

***Recurrence***

For the outcome of recurrence, a statistically significant difference between the study arms for both the recurrence rate and the IDFS was shown in favour of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole. When interpreting the effects for this outcome, the high risk of bias due to censoring for potentially informative reasons in conjunction with the small effect size must be taken into account in particular. These already occurred to a relevant extent early and continuously in the course of the study (see Section 2.1.1).

***Symptoms (recorded with the EORTC QLQ-C30)***

*Fatigue*

The analyses based on the mean difference showed a statistically significant difference between the study arms for the outcome of fatigue. However, there was an effect modification by the characteristic of American Joint Committee on Cancer (AJCC) anatomic stage (see Section 2.1.2.4). For stage I/II patients, there was no advantage or disadvantage of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole. For stage III patients, there was a disadvantage of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

*Nausea and vomiting, constipation*

The analyses based on the mean differences showed statistically significant differences between the study arms for the outcomes of nausea and vomiting, and constipation. The standardized mean difference (SMD) was considered to check the relevance of the results. The 95% confidence interval (CI) of the SMD was not completely outside the irrelevance range of −0.2 to 0.2. The effects can therefore not be inferred to be relevant. There are no advantages or disadvantages of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

*Pain, dyspnoea, insomnia, appetite loss and diarrhoea*

For the outcomes of pain, dyspnoea, insomnia, appetite loss and diarrhoea, the analyses based on the mean differences showed no statistically significant differences between the study arms. There are no advantages or disadvantages of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

***Symptoms (recorded with the EORTC QLQ-BR23)***

*Side effects of systemic therapy*

The analyses based on the mean difference showed a statistically significant difference between the study arms for the outcome of side effects of systemic therapy. However, there was an effect modification by the characteristic of AJCC anatomic stage (see Section 2.1.2.4). For stage I/II patients, there was no advantage or disadvantage of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole. For stage III patients, there was a disadvantage of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

*Breast symptoms, arm symptoms*

The analyses based on the mean differences showed statistically significant differences between the study arms for the outcomes of breast symptoms and arm symptoms. The SMD was considered to check the relevance of the results. The 95% CI of the SMD was not completely outside the irrelevance range of −0.2 to 0.2. The effects can therefore not be inferred to be relevant. There are no advantages or disadvantages of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

*Upset by hair loss*

No suitable data were available for the outcome of upset by hair loss. There is therefore no advantage or disadvantage of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

***Health status (recorded using the EQ-5D VAS)***

The analyses based on the mean difference showed no statistically significant difference between the study arms for the outcome of health status (recorded using the EQ-5D VAS). There is no advantage or disadvantage of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

**Health-related quality of life**

***EORTC QLQ-C30***

*Global health status, physical functioning, role functioning, social functioning*

The analyses based on the mean differences showed a statistically significant difference between the study arms for each of the following outcomes: global health status, physical functioning, role functioning and social functioning. The SMD was considered to check the relevance of the results. The 95% CI of the SMD was not completely outside the irrelevance range of −0.2 to 0.2. The effects can therefore not be inferred to be relevant. There are no advantages or disadvantages of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

*Emotional functioning, cognitive functioning*

The analyses based on the mean differences showed no statistically significant differences between the study arms for the outcomes of emotional functioning and cognitive functioning. There are no advantages or disadvantages of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

***EORTC QLQ-BR23***

*Body image, sexual functioning, future perspective*

The analyses based on the mean differences showed no statistically significant differences between the study arms for the outcomes of body image, sexual functioning and future perspective. There are no advantages or disadvantages of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

*Sexual enjoyment*

No suitable data were available for the outcome of sexual enjoyment. There is therefore no advantage or disadvantage of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

**Side effects**

***SAEs, severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs, neutropenia (AEs)***

A statistically significant difference to the disadvantage of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole was shown for each of the outcomes of SAEs, severe AEs (CTCAE grade ≥ 3), discontinuation due to AEs, and neutropenia (severe AEs).

***Other specific AEs***

*Skin and subcutaneous tissue disorders (AEs), respiratory, thoracic and mediastinal disorders (AEs), infections and infestations (severe AEs), gastrointestinal disorders (severe AEs), general disorders and administration site conditions (severe AEs), hepatobiliary toxicity (severe AEs)*

A statistically significant difference to the disadvantage of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole was shown for the outcomes of skin and subcutaneous tissue disorders (AEs), respiratory, thoracic and mediastinal disorders (AEs), infections and infestations (severe AEs), gastrointestinal disorders (severe AEs), general disorders and administration site conditions (severe AEs) and hepatobiliary toxicity (severe AEs).

#### 2.1.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered in the present addendum:

- Age (< 45 versus 45 to 54 versus 55 to 64 versus ≥ 65)
- AJCC anatomic stages (II versus III)

In the NATALEE study, these subgroup characteristics were predefined for the IDFS outcome. For the subgroup characteristic of age (< 45 versus 45 to 54 versus 55 to 64 versus ≥ 65), subgroup analyses were also predefined for the outcomes in the category of side effects. For the other outcomes relevant for the benefit assessment, subgroup analyses based on the selected characteristics were conducted post hoc.

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

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

The results are presented in Table 10.

Table 10: Subgroups (morbidity) – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1, premenopausal women)

| Study<br>Outcome<br>Characteristic<br>Subgroup | Ribociclib + anastrozole or letrozole | | | Anastrozole or letrozole | | | Ribociclib + anastrozole or letrozole vs. anastrozole or letrozole |
|---|---|---|---|---|---|---|---|
| | N[a] | Values at baseline mean (SD) | Mean change in the course of the study mean[b] (SE) | N[a] | Values at baseline mean (SD) | Mean change in the course of the study mean[b] (SE) | MD [95% CI]; p-value[b] |
| **NATALEE** | | | | | | | |
| **Morbidity** | | | | | | | |
| **Symptoms (EORTC QLQ-C30)[c]** | | | | | | | |
| Fatigue | | | | | | | |
| AJCC anatomic stages | | | | | | | |
| I/II | 394 | ND | 2.5 (0.8) | 398 | ND | 3.8 (0.8) | –1.20 [–3.40; 0.99]; 0.282 |
| III | 665 | ND | 5.0 (0.6) | 606 | ND | –0.2 (0.6) | 5.18 [3.46; 6.91]; < 0.001<br>SMD: 0.33 [0.22; 0.44] |
| Total | | | | | | Interaction: | p-value < 0.001 |
| **Symptoms (EORTC QLQ-BR23)[c]** | | | | | | | |
| Side effects of systemic therapy | | | | | | | |
| AJCC anatomic stages | | | | | | | |
| I/II | 395 | ND | 5.3 (0.6) | 397 | ND | 4.5 (0.6) | 0.73 [–0.89; 2.35]; 0.377 |
| III | 665 | ND | 6.0 (0.4) | 606 | ND | 2.4 (0.5) | 3.61 [2.37; 4.84]; < 0.001<br>SMD: 0.32 [0.21; 0.43] |
| Total | | | | | | Interaction: | p-value = 0.002 |

a. Number of patients taken into account in the effect estimation; baseline values may be based on different patient numbers.
b. MMRM model with the treatment group, the visit and the interactions between visit and treatment group as fixed effects.
c. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 0 to 100).

AJCC: American Joint Committee on Cancer; CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; ND: no data, QLQ-BR23: Quality of Life Questionnaire-Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference

**Morbidity**

***Fatigue (recorded with the EORTC QLQ-C30)***

A statistically significant effect modification by the characteristic of AJCC anatomic stages was shown for the outcome of fatigue. The analyses based on the mean difference showed no statistically significant difference between the study arms for stage I/II patients. There is therefore no advantage or disadvantage of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole for this subgroup. However, a statistically significant difference between the study arms was shown for stage III patients. The SMD was considered to check the relevance of the results. The 95% CI of the SMD was completely outside the irrelevance range of −0.2 to 0.2. This was interpreted to be a relevant effect. For stage III patients, there was a disadvantage of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

***Side effects of systemic therapy (recorded with the EORTC QLQ-BR23)***

A statistically significant effect modification by the characteristic of AJCC anatomic stages was also shown for the outcome of side effects of systemic therapy. The analyses based on the mean difference showed no statistically significant difference between the study arms for stage I/II patients. There is therefore no advantage or disadvantage of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole for this subgroup. However, a statistically significant difference between the study arms was shown for stage III patients. The SMD was considered to check the relevance of the results. The 95% CI of the SMD was completely outside the irrelevance range of −0.2 to 0.2. This was interpreted to be a relevant effect. For stage III patients, there was a disadvantage of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

### 2.1.3 Summary of the results

Overall, at the 29 April 2024 data cut-off, advantages of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole in the premenopausal women from research question 1 were shown for the following outcomes:

- Overall survival
- Recurrence

There are disadvantages of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole for the following outcomes:

- Fatigue (patients with AJCC anatomic stage III)
- Side effects of systemic therapy (patients with AJCC anatomic stage III)
- SAEs

- Severe AEs, including
  - neutropenia
  - infections and infestations
  - gastrointestinal disorders
  - general disorders and administration site conditions
  - hepatobiliary toxicity
- Discontinuation due to AEs
- Skin and subcutaneous tissue disorders (AEs)
- Respiratory, thoracic and mediastinal disorders (AEs)

## 2.2 Research question 2: Postmenopausal women

### 2.2.1 Study characteristics

A detailed description of the NATALEE study, including information on study design, intervention and data cut-offs conducted to date, can be found in dossier assessment A24-124 [1].

***Subpopulation relevant to the assessment of research question 2***

Both pre- and postmenopausal women and men were included in the NATALEE study (N = 5101). For the assessment of research question 2, the company presented the subpopulation of postmenopausal women. This subpopulation consisted of 2844 patients in total, of which 1424 patients were included in the intervention arm and 1420 patients in the comparator arm.

**Planned duration of follow-up observation**

For a description of the planned duration of follow-up observation in the NATALEE study, see Table 1 and the corresponding description in Section 2.1.1.

**Patient characteristics**

Table 11 shows the characteristics of the postmenopausal patients in the study included.

Table 11: Characterization of the study population and of study/treatment discontinuation – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| Study Characteristic<br>Category | Ribociclib + anastrozole or letrozole<br>N = 1424 | Anastrozole or letrozole<br>N = 1420 |
|---|---|---|
| **NATALEE** | | |
| Age [years], mean (SD) | 60 (8) | 59 (9) |
| Family origin, n (%) | | |
| Asian | 129 (9) | 134 (9) |
| Black or African American | 25 (2) | 25 (2) |
| White | 1114 (78) | 1103 (78) |
| Other | 76 (5)[a] | 90 (6)[a] |
| No data | 80 (6) | 68 (5) |
| ECOG PS, n (%) | | |
| 0 | 1131 (79) | 1148 (81) |
| 1 | 292 (21) | 271 (19) |
| No data | 1 (< 1) | 1 (< 1) |
| Disease stage[b], n (%) | | |
| IA | 0 (0) | 3 (< 1) |
| IB | 6 (< 1) | 2 (< 1) |
| IIA | 306 (22) | 315 (22) |
| IIB | 280 (20) | 283 (20) |
| IIIA | 488 (34) | 476 (34) |
| IIIB | 100 (7) | 86 (6) |
| IIIC | 243 (17) | 254 (18) |
| Missing value | 1 (< 1) | 1 (< 1) |
| Hormone receptor status, n (%) | | |
| ER+/PR+ | 1191 (84) | 1166 (82) |
| ER+/PR- | 221 (16) | 241 (17) |
| ER-/PR+ | 1 (< 1) | 6 (< 1) |
| Missing value | 11 (< 1) | 7 (< 1) |
| Prior radiotherapy, n (%) | 1267 (89) | 1259 (89) |
| Prior chemotherapy, n (%) | 1209 (85) | 1199 (84) |
| Adjuvant | 702 (49) | 705 (50) |
| Neoadjuvant | 535 (38) | 524 (37) |
| Prior endocrine therapy, n (%) | 964 (68) | 977 (69) |
| Antioestrogens | 81 (6) | 96 (7) |
| Aromatase inhibitors | 927 (65) | 938 (66) |
| GnRH analogues | 24 (2) | 22 (2) |

Table 11: Characterization of the study population and of study/treatment discontinuation – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| Study Characteristic Category | Ribociclib + anastrozole or letrozole N = 1424 | Anastrozole or letrozole N = 1420 |
|---|---|---|
| Treatment discontinuation of all components, n (%)[c] | 372 (26)[d] | 461 (34)[d] |
| Ribociclib[e] | 588 (42)[d] | – |
| Anastrozole or letrozole[f] | 434 (31)[d] | 461 (34)[d] |
| Goserelin | 3 (< 1)[d] | 4 (< 1)[d] |
| Study discontinuation, n (%)[g] | 279 (20) | 323 (23) |

a. Includes Native Americans, Native Hawaiians/Other Pacific Islanders and Others; Institute's calculation.
b. Staging according to AJCC classification, 8th edition.
c. 13 (0.9%) of the randomized patients in the intervention arm vs. 60 (4.2%) of the randomized patients in the control arm did not receive any treatment. The percentages therefore refer to the patients who received treatment (intervention arm: 1411, control arm: 1360).
d. Institute's calculation.
e. Common reasons for the discontinuation of ribociclib in the intervention arm were the following (percentages refer to patients who discontinued ribociclib; Institute's calculation): AEs (55%), recurrence (13%), patient's decision (15%), end of study participation (8%). The data additionally include 5 patients who died during the treatment with the study medication.
f. Common reasons for the discontinuation of anastrozole or letrozole in the intervention vs. control arm were the following (percentages refer to patients who discontinued anastrozole or letrozole; Institute's calculation): AEs (21% vs. 15%), recurrence (28% vs. 34%), patient's decision (23% vs. 19%), end of study participation (19% vs. 22%). The data additionally include patients who died during the treatment with the study medication (intervention arm: 7 vs. control arm: 5).
g. A common reason for study discontinuation in the intervention vs. control arm was the following (percentages refer to randomized patients): end of study participation (12% vs. 15%). The data additionally include patients who died during the course of the study (intervention arm: 5% vs. control arm: 5%).

AE: adverse event; AJCC: American Joint Committee on Cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status; ER: oestrogen receptor; GnRH: gonadotropin-releasing hormone; n: number of patients in the category; N: number of randomized patients; PR: progesterone receptor; RCT: randomized controlled trial; SD: standard deviation

The demographic and clinical characteristics of the postmenopausal patients were largely balanced between the intervention and the comparator arm of the NATALEE study. The mean patient ages were 60 and 59 years respectively, and most patients were of white family origin (78% in each arm). The majority of patients had stage II (42% in both study arms) or III (58% in both study arms) disease. 89% of patients in each study arm had already received radiotherapy, 85% versus 84% chemotherapy, and 68% versus 69% endocrine therapy.

The proportion of patients who discontinued all treatment components was slightly lower in the intervention arm than in the comparator arm (26% vs. 34%). In the intervention arm, 42% of patients discontinued treatment with ribociclib, primarily due to the occurrence of AEs. Approximately one-third of patients from both study arms discontinued treatment with

anastrozole or letrozole, most frequently due to recurrence. The number of patients who discontinued the study was sufficiently similar in both study arms (20% versus 23%), the main reason in each case being the end of study participation.

**Information on the course of the study**

Table 12 shows the postmenopausal patients' median and mean treatment durations and the median and mean observation periods for individual outcomes.

Table 12: Information on the course of the study – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| **Study**<br>**Duration of the study phase**<br>**Drug or outcome category/outcome** | **Ribociclib + anastrozole or letrozole**<br>**N = 1424[a]** | **Anastrozole or letrozole**<br>**N = 1420[a]** |
|---|---|---|
| **NATALEE (29 April 2024 data cut-off)** | | |
| Treatment duration [months] | | |
| Ribociclib | N = 1409 | – |
| Median [Q1; Q3] | 35.7 [8.7; 35.7] | – |
| Mean (SD) | 25.2 (14.1) | – |
| Anastrozole or letrozole | N = 1411 | N = 1360 |
| Median [Q1; Q3] | 45.0 [34.5; 51.3] | 45.0 [30.5; 51.5] |
| Mean (SD) | 38.8 (16.9) | 38.4 (17.5) |
| Goserelin | N = 5 | N = 8 |
| Median [Q1; Q3] | 5.5 [4.6; 23.8] | 16.1 [4.3; 28.9] |
| Mean (SD) | 14.5 (15.3) | 17.7 (14.7) |
| Observation period [months] | | |
| Overall survival[b] | N = 1424 | N = 1420 |
| Median [Q1; Q3] | 44.3 [38.6; 49.7] | 44.2 [35.9; 49.7] |
| Mean (SD) | 40.9 (13.9) | 39.3 (15.9) |
| Recurrence | N = 1424 | N = 1420 |
| Median [Q1; Q3] | 44.2 [33.4; 49.7] | 44.2 [29.9; 49.7] |
| Mean (SD) | 38.5 (15.6) | 36.3 (17.4) |
| Symptoms (EORTC QLQ-C30)[c] | N = 1328 | N = 1263 |
| Median [Q1; Q3] | 44.4 [33.7; 49.9] | 44.4 [33.6; 49.9] |
| Mean (SD) | 39.7 (13.7) | 40.1 (13.6) |
| Symptoms (EORTC QLQ-BR23)[c] | N = 1329 | N = 1257 |
| Median [Q1; Q3] | 44.4 [33.7; 49.9] | 44.4 [33.6; 49.9] |
| Mean (SD) | 39.7 (13.7) | 40.1 (13.5) |

Table 12: Information on the course of the study – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| **Study**<br>**Duration of the study phase**<br>**Drug or outcome category/outcome** | **Ribociclib + anastrozole or letrozole**<br>**N = 1424[a]** | **Anastrozole or letrozole**<br>**N = 1420[a]** |
|---|---|---|
| Health status (EQ-5D VAS) | N = 1323 | N = 1259 |
| Median [Q1; Q3] | 44.4 [33.7; 49.9] | 44.4 [33.6; 49.9] |
| Mean (SD) | 39.7 (13.7) | 40.1 (13.6) |
| Health-related quality of life (EORTC QLQ-C30)[c] | N = 1326 | N = 1264 |
| Median [Q1; Q3] | 44.4 [33.7; 49.9] | 44.4 [33.6; 49.9] |
| Mean (SD) | 39.7 (13.7) | 40.1 (13.5) |
| Health-related quality of life (EORTC QLQ-BR23)[c] | N = 1327 | N = 1254 |
| Median [Q1; Q3] | 44.4 [33.7; 49.9] | 44.4 [33.6; 49.9] |
| Mean (SD) | 39.7 (13.7) | 40.1 (13.5) |
| Side effects | N = 1409[d] | N = 1362[d] |
| Median [Q1; Q3] | 45.1 [36.0; 51.3] | 45.1 [31.3; 51.4] |
| Mean (SD) | 39.1 (16.6) | 38.5 (17.3) |

a. Number of patients in the ITT population, any deviating numbers are indicated in the relevant place.
b. Inverse Kaplan-Meier method.
c. Partially deviating information between the subscales.
d. Number of randomized patients who received at least one dose of the study medication.

EORTC: European Organisation for Research and Treatment of Cancer; ITT: intention to treat; N: number of analysed patients; Q1: 1st quartile; Q3: 3rd quartile; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

The median treatment duration for ribociclib in the intervention arm was approximately 36 months. The study documents show that at the time of the data cut-off, all postmenopausal patients in the intervention arm had either completed the 3-year treatment with ribociclib according to the study protocol or had discontinued this treatment prematurely. The median treatment duration for anastrozole or letrozole was 45 months in both study arms. The median treatment duration for goserelin differed between the intervention and the comparator arm (5.5 months versus 16.1 months). However, since according to the information in Module 4 C only 5 and 8 patients respectively received treatment with goserelin, this had no consequences for the benefit assessment.

The median observation periods for the individual outcomes are comparable between the study arms.

### Subsequent therapies

Table 13 shows which subsequent therapies postmenopausal patients received after discontinuing one component or the entire study medication. Data are only available for all treatments regardless of the line of treatment.

Table 13: Information on subsequent therapies (≥ 2 patients in one treatment arm) – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| Study<br>Drug class[a] | Patients with subsequent therapy n (%)[b] | |
|---|---|---|
| | Ribociclib + anastrozole or letrozole<br>N = 1424 | Anastrozole or letrozole<br>N = 1420 |
| **NATALEE (29 April 2024 data cut-off)** | | |
| Total | 255 (17.9) | 283 (19.9) |
| Anthracyclines and related substances | 10 (3.9) | 10 (3.5) |
| Antioestrogens | 83 (32.5) | 135 (47.7) |
| Aromatase inhibitors | 143 (56.1) | 133 (47.0) |
| Bisphosphonates | 8 (3.1) | 6 (2.1) |
| CDK inhibitors | 32 (12.5) | 115 (40.6) |
| Detoxifying agents for treatment with cytostatics | 4 (1.6) | 1 (0.4) |
| Folic acid analogues | 1 (0.4) | 2 (0.7) |
| Folic acid and its derivatives | 0 (0) | 2 (0.7) |
| GnRH analogues | 1 (0.4) | 2 (0.7) |
| HER2 inhibitors | 11 (4.3) | 14 (4.9) |
| mTOR kinase inhibitors | 5 (2.0) | 3 (1.1) |
| Nitrogen mustard analogues | 9 (3.5) | 12 (4.2) |
| Other antineoplastic agents | 14 (5.5) | 17 (6.0) |
| Other drugs affecting bone structure and mineralization | 12 (4.7) | 7 (2.5) |
| Other immunosuppressants | 2 (0.8) | 2 (0.7) |
| Other monoclonal antibodies and antibody drug conjugates | 5 (2.0) | 5 (1.8) |
| Other protein kinase inhibitors | 3 (1.2) | 0 (0) |
| PD-1/PD-L1 inhibitors | 4 (1.6) | 2 (0.7) |
| pi3k inhibitors | 6 (2.4) | 3 (1.1) |
| Platinum compounds | 16 (6.3) | 18 (6.4) |
| PARP inhibitors | 3 (1.2) | 3 (1.1) |
| Pyrimidine analogues | 46 (18.0) | 46 (16.3) |
| Taxanes | 33 (12.9) | 37 (13.1) |
| TOP1 inhibitors | 3 (1.2) | 1 (0.4) |
| VEGF/VEGFR inhibitors | 5 (2.0) | 5 (1.8) |
| Vinca alkaloids and analogues | 6 (2.4) | 4 (1.4) |

Table 13: Information on subsequent therapies (≥ 2 patients in one treatment arm) – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| Study<br>Drug class[a] | Patients with subsequent therapy n (%)[b] | |
|---|---|---|
| | Ribociclib + anastrozole or letrozole<br>N = 1424 | Anastrozole or letrozole<br>N = 1420 |
| Radiotherapy | 28 (11.0) | 17 (6.0) |
| Surgical therapy | 26 (10.2) | 17 (6.0) |

a. Drug classes according to the Anatomical Therapeutic Chemical Classification.
b. The percentages at the level of the drug classes were calculated by the Institute and refer to patients with subsequent therapy (intervention arm vs. control arm: n = 255 vs. n = 283).

CDK: cyclin-dependent kinase; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor 2; mTOR: mammalian target of rapamycin; n: number of patients with subsequent therapy; N: number of randomized patients; PARP: poly(adenosine diphosphate-ribose) polymerase; PD-1: programmed cell death protein 1; PD-L1: programmed cell death ligand 1; Pi3K: phosphatidylinositol-3-kinase; RCT: randomized controlled trial; TOP1: topoisomerase 1; VEGF: vascular endothelial growth factor; VEGFR: vascular endothelial growth factor receptor

In the NATALEE study, subsequent antineoplastic therapies were permitted without restrictions in both study arms. The proportion of postmenopausal patients who received at least one subsequent therapy was approx. 18% in the intervention arm and 20% in the comparator arm, and was thus notably higher than the proportion of patients with recurrence (approx. 11% and 14%, see also Table 16). This is assumed to be due to the fact that, for example, switching a component of endocrine therapy after discontinuation due to AEs was also included in this analysis. The most common subsequent therapies in both study arms were antioestrogens and aromatase inhibitors, and in the comparator arm also CDK inhibitors. Many patients also received chemotherapy.

According to the S3 Guideline on Breast Cancer [5], surgery and, if necessary, radiotherapy or systemic treatment (endocrine therapy or chemotherapy) are indicated if local recurrence occurs. Postmenopausal women with distant recurrence are recommended a combination of an aromatase inhibitor or fulvestrant with a CDK4/6 inhibitor as first-line treatment if this substance group has not yet been used [5]. The company's dossier shows that the recurrences that occurred in both study arms were mainly distant recurrences (73% in each arm). Overall, the subsequent therapies appeared to be largely consistent with the recommendations of the S3 guideline and were therefore considered adequate.

**Risk of bias across outcomes (study level)**

The risk of bias across outcomes (risk of bias at study level) is described in Table 5 in Section 2.1.1 and was rated as high.

Limitations resulting from the open-label study design are described in Section 2.2.2.2 on the outcome-specific risk of bias.

**Transferability of the study results to the German health care context**

The company's assessment regarding the transferability of the study results to the German health care context is described in Section 2.1.1.

### 2.2.2 Results

#### 2.2.2.1 Outcomes included

The following patient-relevant outcomes for the postmenopausal women of research question 2 were to be included in the present addendum.

- Mortality
  - Overall survival
- Morbidity
  - Recurrence
  - Symptoms
    - recorded using the EORTC QLQ-C30
    - recorded using the EORTC QLQ-BR23
  - Health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the EORTC QLQ-C30
  - recorded using the EORTC QLQ-BR23
- Side effects
  - SAEs
  - Severe AEs (CTCAE grade ≥ 3)
  - Discontinuation due to AEs
  - Neutropenia (PT, severe AEs)
  - Other specific AEs, if any

The patient-relevant outcomes selected deviate from those selected by the company, which used additional outcomes in its dossier (Module 4 C).

Table 14 shows for which outcomes data for research question 2 were available in the included study.

Table 14: Matrix of outcomes – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women)

| Study | Outcomes | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Overall survival | Recurrences[a] | Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23) | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23) | SAEs | Severe AEs[b] | Discontinuation due to AEs[c] | Neutropenia (PT, severe AEs[b]) | Further specific AEs[b, d] |
| NATALEE | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes | Yes |

a. Presented using the recurrence rate and the IDFS, includes local breast cancer recurrence, regional invasive breast cancer recurrence, contralateral invasive breast cancer, distant recurrence, second primary cancer (non-breast cancer), and death from any cause.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Discontinuation of a treatment component.
d. The following events are taken into account (coded according to MedDRA): gastrointestinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), respiratory, thoracic and mediastinal disorders (SOC, SAEs), infections and infestations (SOC, severe AEs), nervous system disorders (SOC, severe AEs), fatigue (PT, severe AEs), hepatobiliary toxicity (operationalized via the SMQ "drug related hepatic disorders – comprehensive search", severe AEs), and renal toxicity (operationalized via the SMQ "acute renal failure", severe AEs).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; IDFS: invasive disease-free survival; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

**Notes on outcomes**

***Recurrence***

The outcome of recurrence is a composite outcome and includes the components of local breast cancer recurrence, regional invasive breast cancer recurrence, contralateral invasive breast cancer, distant recurrence, second primary cancer (non-breast cancer), and death from any cause. The results of the operationalizations "proportion of patients with recurrence" (hereinafter referred to as "recurrence rate") and "IDFS" are presented for the outcome of

recurrence. The patients considered in the relevant stage of the disease are a group of patients who were treated with a curative treatment approach. Recurrence in this situation means that the attempt at cure by the curative treatment approach was not successful.

In accordance with the study protocol, events of the recurrence outcome were recorded by the investigator by means of regular physical examinations and mammography. If a recurrence was suspected, this had to be confirmed by additional imaging and histological or cytological examinations.

Due to the unblinded study design, there was a risk of investigator bias in the assessment of the recurrence outcome, as the interpretation of radiological and clinical data by the investigator could be influenced by knowledge of the treatment allocation. An analysis by means of a blinded review was not carried out in the study. This aspect was taken into account in the assessment of the outcome-specific risk of bias (see Section 2.2.2.2).

It should also be noted, that, at the 29 April 2024 data cut-off used for the benefit assessment, the median observation period in the study was only about 44 months (see Table 12). In the therapeutic indication in question, recurrences can still occur many years after the initial therapy [5,9]. Analysing data from a later data cut-off with a longer observation period would therefore provide more reliable information.

***Patient-reported outcomes in the categories of morbidity and health-related quality of life***

In Module 4 C, the company presented analyses of the EORTC QLQ-C30 and EORTC QLQ-BR23 scales for the outcomes of symptoms and health-related quality of life, and analyses of the EQ-5D VAS for the outcome of health status. For each of these outcomes, the company presented analyses of the mean change from baseline using a mixed-effects model with repeated measures (MMRM). These are suitable for the benefit assessment.

#### 2.2.2.2 Risk of bias

Table 15 shows the risk of bias for the results of the relevant outcomes for the postmenopausal women of research question 2.

Table 15: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women)

| Study | | Outcomes | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study level | Overall survival | Recurrences[a] | Symptoms (EORTC QLQ-C30, EORTC QLQ-BR23) | Health status (EQ-5D VAS) | Health-related quality of life (EORTC QLQ-C30, EORTC QLQ-BR23) | SAEs | Severe AEs[b] | Discontinuation due to AEs[c] | Neutropenia (PT, severe AEs[b]) | Further specific AEs[b, d] |
| NATALEE | H | H[e] | H[e, f] | H[e, f] | H[e, f] | H[e, f] | H[e] | H[e] | H[e, g] | H[e] | H[e, f] |

a. Presented using the recurrence rate and the IDFS, includes the events of local breast cancer recurrence, regional invasive breast cancer recurrence, contralateral invasive breast cancer, distant recurrence, second primary cancer (non-breast cancer), and death from any cause.
b. Severe AEs are operationalized as CTCAE grade ≥ 3.
c. Discontinuation of a treatment component.
d. The following events are taken into account (coded according to MedDRA): gastrointestinal disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AEs), respiratory, thoracic and mediastinal disorders (SOC, SAEs), infections and infestations (SOC, severe AEs), nervous system disorders (SOC, severe AEs), fatigue (PT, severe AEs), hepatobiliary toxicity (operationalized via the SMQ “drug related hepatic disorders – comprehensive search", severe AEs), and renal toxicity (operationalized via the SMQ “acute renal failure”, severe AEs).
e. High risk of bias across outcomes.
f. Lack of blinding for subjective outcome assessment (in the category of other specific AEs, this applies exclusively to the following AEs: gastrointestinal disorders [SOC, AEs], skin and subcutaneous tissue disorders [SOC, AEs]).
g. Lack of blinding in subjective decision to discontinue (for non-severe/non-serious AEs).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; EORTC: European Organisation for Research and Treatment of Cancer; H: high; IDFS: invasive disease-free survival; L: low; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: Standardized MedDRA Query; SOC: System Organ Class; VAS: visual analogue scale

The risk of bias for the results of all outcomes was rated as high. One reason for this is the high risk of bias across outcomes, which results from a high proportion of censorings (see Table 5). On an outcome-specific basis, the following additional aspects also contribute to the high risk of bias:

The outcome-specific risk of bias is high for the outcome of recurrence due to the unblinded outcome assessment by the investigator (see Section 2.2.2.1).

The risk of bias for the patient-reported outcomes in the categories of symptoms, anxiety symptoms and depressive symptoms, health status and health-related quality of life, as well

as for the non-severe/non-serious AEs is also considered to be high due to the lack of blinding in subjective outcome assessment.

For the results of the outcome of discontinuation due to AEs, the lack of blinding in the presence of subjective decision to discontinue treatment also contributed to the high risk of bias.

#### 2.2.2.3 Results

Table 16 and Table 17 summarize the results of the comparison of ribociclib + anastrozole or letrozole versus anastrozole or letrozole for the adjuvant treatment of postmenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence. Where necessary, IQWiG calculations are provided to supplement the data from the company's dossier.

The Kaplan-Meier curves for the time-to-event analyses of the outcomes of overall survival and invasive disease-free survival are presented in Appendix A.2, and the results on common AEs, SAEs, severe AEs, and discontinuations due to AEs can be found in Appendix B.2.

Table 16: Results (mortality, morbidity, side effects) – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| Study<br>Outcome category<br>Outcome | Ribociclib + anastrozole or letrozole | | Anastrozole or letrozole | | Ribociclib + anastrozole or letrozole vs. anastrozole or letrozole |
|---|---|---|---|---|---|
| | N | Patients with event<br>n (%) | N | Patients with event<br>n (%) | RR [95% CI]; p-value[a] |
| **NATALEE (29 April 2024 data cut-off)** | | | | | |
| **Mortality** | | | | | |
| Overall survival | 1424 | 74 (5.2)<br>Median time to event: NA | 1420 | 75 (5.3)<br>Median time to event: NA | HR: 0.94 [0.68; 1.30]; 0.724[b] |
| **Morbidity** | | | | | |
| Recurrence | | | | | |
| Recurrence rate[c] | 1424 | 164 (11.5) | 1420 | 203 (14.3) | 0.81 [0.67; 0.98]; 0.027[d] |
| Death from any cause | 1424 | 13 (0.9) | 1420 | 8 (0.6) | – |
| Local breast cancer recurrence | 1424 | 4 (0.3) | 1420 | 6 (0.4) | – |
| Regional invasive breast cancer recurrence | 1424 | 13 (0.9) | 1420 | 31 (2.2) | – |
| Contralateral invasive breast cancer | 1424 | 8 (0.6) | 1420 | 4 (0.3) | – |
| Distant recurrence | 1424 | 110 (7.7) | 1420 | 142 (10.0) | – |
| Second primary cancer (non-breast cancer) | 1424 | 24 (1.7) | 1420 | 27 (1.9) | – |
| Invasive disease-free survival (IDFS)[e] | 1424 | 164 (11.5)<br>Median time to event: NA | 1420 | 203 (14.3)<br>Median time to event: NA | HR: 0.75 [0.61; 0.92]; 0.005[b] |
| **Side effects** | | | | | |
| AEs (supplementary information)[f] | 1409 | 1376 (97.7) | 1362 | 1183 (86.9) | – |
| SAEs[f] | 1409 | 229 (16.3) | 1362 | 162 (11.9) | 1.37 [1.13; 1.65]; < 0.001 |
| Severe AEs[f, g] | 1409 | 883 (62.7) | 1362 | 280 (20.6) | 3.05 [2.73; 3.41]; < 0.001 |
| Discontinuation due to AEs[f, h] | 1409 | 340 (24.1) | 1362 | 68 (5.0) | 4.83 [3.77; 6.20]; < 0.001 |
| Neutropenia (PT, severe AEs[g]) | 1409 | 374 (26.5) | 1362 | 4 (0.3) | 90.38 [33.84; 241.39]; < 0.001 |

Table 16: Results (mortality, morbidity, side effects) – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| Study<br>Outcome category<br>Outcome | Ribociclib + anastrozole or letrozole | | Anastrozole or letrozole | | Ribociclib + anastrozole or letrozole vs. anastrozole or letrozole |
|---|---|---|---|---|---|
| | N | Patients with event n (%) | N | Patients with event n (%) | RR [95% CI]; p-value[a] |
| Gastrointestinal disorders (SOC, AEs) | 1409 | 760 (53.9) | 1362 | 384 (28.2) | 1.91 [1.74; 2.11]; < 0.001 |
| Skin and subcutaneous tissue disorders (SOC, AEs) | 1409 | 536 (38.0) | 1362 | 274 (20.1) | 1.89 [1.67; 2.14]; < 0.001 |
| Respiratory, thoracic and mediastinal disorders (SOC, SAEs) | 1409 | 34 (2.4) | 1362 | 16 (1.2) | 2.05 [1.14; 3.70]; 0.015 |
| Infections and infestations (SOC, severe AEs[g]) | 1409 | 89 (6.3) | 1362 | 51 (3.7) | 1.69 [1.21; 2.36]; 0.002 |
| Nervous system disorders (SOC, severe AEs[g]) | 1409 | 40 (2.8) | 1362 | 16 (1.2) | 2.42 [1.36; 4.29]; 0.002 |
| Fatigue (PT, severe AEs[g]) | 1409 | 15 (1.1) | 1362 | 3 (0.2) | 4.83 [1.40; 16.66]; 0.006 |
| Hepatobiliary toxicity (SMQ, severe AEs[g])[i] | 1409 | 142 (10.1) | 1362 | 21 (1.5) | 6.54 [4.16; 10.27]; < 0.001 |
| Renal toxicity (SMQ, severe AEs[g])[j] | 1409 | 7 (0.5) | 1362 | 0 (0) | 14,50 [0.83; 253.63] 0.009[k] |

a. Institute's calculation of RR, 95% CI and p-value, unconditional exact test (CSZ method according to [10]).
b. Effect and CI: Cox proportional hazards model; p-value: log-rank test. Each stratified by AJCC anatomic stage, prior neoadjuvant/adjuvant chemotherapy, and region.
c. The individual components are presented in the lines below.
d. Effect and CI: Cochran-Mantel-Haenszel method, p-value: 2-sided Cochran-Mantel-Haenszel chi-square test. Each stratified by AJCC anatomic stage, prior neoadjuvant/adjuvant chemotherapy, and region.
e. Operationalized as time from the day of randomization to the first occurrence of an event, for individual components see recurrence rate.
f. Without disease-related events (the events of breast cancer recurrence and progression of malignancy were not taken into account).
g. Operationalized as CTCAE grade ≥ 3.
h. Discontinuation of a treatment component.
i. Operationalized via severe AEs of the SMQ “drug related hepatic disorders – comprehensive search” coded according to MedDRA.
j. Operationalized via severe AEs of the SMQ “acute renal failure” coded according to MedDRA.
k. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.

AE: adverse event; AJCC: American Joint Committee on Cancer; CI: confidence interval; CSZ: convexity, symmetry, z-score; CTCAE: Common Terminology Criteria for Adverse Events; IDFS: invasive disease-free survival; MedDRA: Medical Dictionary for Regulatory Activities; N: number of analysed patients; NA: not achieved; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SMQ: standardized MedDRA query: SOC: System Organ Class

Table 17: Results (morbidity, health-related quality of life) – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| Study<br>Outcome category<br>Outcome | Ribociclib + anastrozole or letrozole | | | Anastrozole or letrozole | | | Ribociclib + anastrozole or letrozole vs. anastrozole or letrozole |
|---|---|---|---|---|---|---|---|
| | N[a] | Values at baseline mean (SD) | Mean change in the course of the study mean[b] (SE) | N[a] | Values at baseline mean (SD) | Mean change in the course of the study mean[b] (SE) | MD [95% CI]; p-value[b] |
| **NATALEE (29 April 2024 data cut-off)** | | | | | | | |
| **Morbidity** | | | | | | | |
| Symptoms (EORTC QLQ-C30)[c] | | | | | | | |
| Fatigue | 1325 | 26.6 (20.3) | 2.8 (0.4) | 1263 | 27.4 (20.9) | 2.7 (0.4) | 0.05 [–1.13; 1.22]; 0.939 |
| Nausea and vomiting | 1325 | 3.1 (9.2) | 2.0 (0.2) | 1263 | 3.2 (9.0) | 1.1 (0.2) | 0.88 [0.33; 1.44]; 0.002<br>SMD: 0.12 [0.05; 0.20] |
| Pain | 1328 | 21.3 (21.8) | 3.0 (0.5) | 1263 | 21.3 (22.2) | 4.5 (0.5) | −1.52 [−2.82; −0.21]; 0.022<br>SMD: −0.09 [−0.17; −0.01] |
| Dyspnoea | 1322 | 11.1 (19.0) | 3.5 (0.4) | 1260 | 12.5 (20.9) | 3.4 (0.4) | 0.11 [–1.08; 1.30]; 0.853 |
| Insomnia | 1322 | 30.2 (29.6) | 2.2 (0.5) | 1261 | 29.3 (28.5) | 3.4 (0.6) | –1.22 [–2.75; 0.30]; 0.116 |
| Appetite loss | 1325 | 8.1 (18.5) | 1.1 (0.4) | 1261 | 8.9 (19.2) | 0.6 (0.4) | 0.47 [–0.51; 1.44]; 0.349 |
| Constipation | 1323 | 10.9 (20.8) | 4.1 (0.4) | 1263 | 11.3 (21.5) | 1.3 (0.4) | 2.78 [1.57; 3.98]; < 0.001<br>SMD: 0.18 [0.10; 0.26] |
| Diarrhoea | 1322 | 5.8 (14.4) | 1.2 (0.3) | 1259 | 5.4 (14.2) | 1.8 (0.3) | –0.58 [–1.36; 0.20]; 0.144 |
| Symptoms (EORTC QLQ-BR23)[c] | | | | | | | |
| Side effects of systemic therapy | 1329 | 16.0 (13.5) | 4.2 (0.3) | 1257 | 16.2 (13.7) | 3.0 (0.3) | 1.22 [0.37; 2.07]; 0.005<br>SMD: 0.11 [0.03; 0.19] |
| Breast symptoms | 1322 | 18.9 (17.8) | –5.5 (0.3) | 1259 | 19.8 (18.7) | –5.5 (0.3) | 0.01 [–0.87; 0.89]; 0.981 |

Table 17: Results (morbidity, health-related quality of life) – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| Study<br>Outcome category<br>Outcome | Ribociclib + anastrozole or letrozole | | | Anastrozole or letrozole | | | Ribociclib + anastrozole or letrozole vs. anastrozole or letrozole |
|---|---|---|---|---|---|---|---|
| | N[a] | Values at baseline mean (SD) | Mean change in the course of the study mean[b] (SE) | N[a] | Values at baseline mean (SD) | Mean change in the course of the study mean[b] (SE) | MD [95% CI]; p-value[b] |
| Arm symptoms | 1323 | 22.2 (20.6) | 0.3 (0.4) | 1261 | 24.0 (21.7) | –0.3 (0.4) | 0.58 [–0.58; 1.74]; 0.329 |
| Upset by hair loss | No suitable data[d] | | | | | | |
| Health status (EQ-5D VAS)[f] | 1323 | 78.6 (14.9) | –1.6 (0.3) | 1259 | 78.2 (14.8) | –1.3 (0.3) | –0.27 [–1.13; 0.59]; 0.540 |
| **Health-related quality of life** | | | | | | | |
| EORTC QLQ-C30[f] | | | | | | | |
| Global health status | 1322 | 74.0 (17.7) | –2.8 (0.4) | 1258 | 73.2 (18.4) | –2.4 (0.4) | –0.43 [–1.40; 0.54]; 0.388 |
| Physical functioning | 1326 | 84.5 (15.2) | –2.2 (0.3) | 1264 | 83.5 (15.5) | –2.8 (0.3) | 0.64 [–0.27; 1.56]; 0.168 |
| Role functioning | 1325 | 84.8 (21.0) | –3.0 (0.4) | 1264 | 84.3 (21.5) | –3.5 (0.4) | 0.57 [–0.63; 1.78]; 0.353 |
| Emotional functioning | 1323 | 80.4 (19.6) | –2.8 (0.4) | 1259 | 80.6 (19.5) | –3.8 (0.4) | 0.98 [–0.14; 2.10]; 0.088 |
| Cognitive functioning | 1322 | 85.2 (18.7) | –4.5 (0.4) | 1260 | 84.0 (19.4) | –5.1 (0.4) | 0.62 [–0.50; 1.75]; 0.278 |
| Social functioning | 1323 | 85.9 (20.4) | 0.4 (0.3) | 1259 | 84.6 (22.2) | 0.5 (0.3) | –0.05 [–0.90; 0.80]; 0.911 |
| EORTC QLQ-BR23[f] | | | | | | | |
| Body image | 1327 | 74.3 (25.9) | 2.7 (0.5) | 1254 | 74.3 (26.4) | 2.1 (0.5) | 0.57 [–0.76; 1.90]; 0.401 |
| Sexual functioning | 1297 | 18.3 (21.7) | –1.9 (0.4) | 1221 | 16.8 (21.2) | –2.1 (0.4) | 0.12 [–0.88; 1.13]; 0.808 |
| Sexual enjoyment | No suitable data[g] | | | | | | |
| Future perspective | 1327 | 52.2 (31.2) | 9.1 (0.5) | 1252 | 51.3 (31.7) | 8.1 (0.5) | 0.94 [–0.55; 2.43]; 0.215 |

Table 17: Results (morbidity, health-related quality of life) – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| Study<br>Outcome category<br>Outcome | Ribociclib + anastrozole or letrozole | | | Anastrozole or letrozole | | | Ribociclib + anastrozole or letrozole vs. anastrozole or letrozole |
|---|---|---|---|---|---|---|---|
| | N[a] | Values at baseline mean (SD) | Mean change in the course of the study mean[b] (SE) | N[a] | Values at baseline mean (SD) | Mean change in the course of the study mean[b] (SE) | MD [95% CI]; p-value[b] |

a. Number of patients taken into account in the effect estimation; baseline values may be based on different patient numbers.
b. MMRM adjusted for AJCC anatomic stage, prior neoadjuvant/adjuvant chemotherapy, and region.
c. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 0 to 100).
d. Only 356 (25%) patients in the intervention arm vs. 351 (25%) patients in the control arm were included in the analysis.
e. Lower (decreasing) values indicate improved symptoms; negative effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 0 to 21).
f. Higher (increasing) values indicate better health status/health-related quality of life; positive effects (intervention minus comparison) indicate an advantage of the intervention (scale range: 0 to 100).
g. Only 583 (41%) patients in the intervention arm vs. 513 (36%) patients in the control arm were included in the analysis.

CI: confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; VAS: visual analogue scale

On the basis of the available information, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

### Mortality

#### *Overall survival*

No statistically significant difference between the study arms was shown for the outcome of overall survival. There was no hint of an added benefit of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

**Morbidity**

***Recurrence***

For the outcome of recurrence (operationalized via the recurrence rate and IDFS), a statistically significant difference between the study arms for both the recurrence rate and the IDFS was shown in favour of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole. When interpreting the effects for this outcome, the high risk of bias due to censoring for potentially informative reasons in conjunction with the small effect size must be taken into account in particular. These already occurred to a relevant extent early and continuously in the course of the study (see Section 2.1.1). For this outcome, there was a hint of an added benefit of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

***Symptoms (recorded with the EORTC QLQ-C30)***

*Nausea and vomiting, pain, constipation*

The analyses based on the mean differences showed statistically significant differences between the study arms for the outcomes of nausea and vomiting, pain, and constipation. The SMD was considered to check the relevance of the results. The 95% CI of the SMD was not completely outside the irrelevance range of −0.2 to 0.2. The effects can therefore not be inferred to be relevant. In each case, there was no hint of an added benefit of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

*Fatigue, dyspnoea, insomnia, appetite loss, diarrhoea*

For the outcomes of fatigue, dyspnoea, insomnia, appetite loss and diarrhoea, the analyses based on the mean differences showed no statistically significant differences between the study arms. In each case, there was no hint of an added benefit of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

***Symptoms (recorded with the EORTC QLQ-BR23)***

*Side effects of systemic therapy*

The analyses based on the mean difference showed a statistically significant difference between the study arms for the outcome of side effects of systemic therapy. The SMD was considered to check the relevance of the results. The 95% CI of the SMD was not completely outside the irrelevance range of −0.2 to 0.2. The effects can therefore not be inferred to be relevant. There was no hint of an added benefit of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

*Breast symptoms, arm symptoms*

The analyses based on the mean differences showed no statistically significant differences between the study arms for the outcomes of breast symptoms and arm symptoms. In each case, there was no hint of an added benefit of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

*Upset by hair loss*

No suitable data were available for the outcome of upset by hair loss. Hence, there was no hint of an added benefit of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

***Health status (recorded using the EQ-5D VAS)***

The analyses based on the mean difference showed no statistically significant difference between the study arms for the outcome of health status (recorded using the EQ-5D VAS). There was no hint of an added benefit of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

**Health-related quality of life**

***EORTC QLQ-C30***

*Global health status, physical functioning, role functioning, emotional functioning, cognitive functioning, social functioning*

The analyses based on the mean difference showed no statistically significant difference between the study arms for any of the following outcomes: global health status, physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning. In each case, there was no hint of an added benefit of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

***EORTC QLQ-BR23***

*Body image, sexual functioning, future perspective*

The analyses based on the mean differences showed no statistically significant differences between the study arms for the outcomes of body image, sexual functioning and future perspective. In each case, there was no hint of an added benefit of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

*Sexual enjoyment*

No suitable data were available for the outcome of sexual enjoyment. Hence, there was no hint of an added benefit of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole; an added benefit is therefore not proven.

**Side effects**

***SAEs, severe AEs (CTCAE grade ≥ 3)***

A statistically significant difference to the disadvantage of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole was shown for both of the outcomes of SAEs and severe AEs (CTCAE grade ≥ 3). In each case, there was a hint of greater harm of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

***Discontinuation due to AEs***

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

***Neutropenia (severe AEs)***

A statistically significant difference to the disadvantage of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole was shown for the outcome of neutropenia (severe AEs). There was a hint of greater harm of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

***Other specific AEs***

*Gastrointestinal disorders (AEs), skin and subcutaneous tissue disorders (AEs)*

A statistically significant difference to the disadvantage of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole was shown for each of the outcomes of gastrointestinal disorders (AEs) and skin and subcutaneous tissue disorders (AEs). In each case, there was a hint of greater harm of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

*Respiratory, thoracic and mediastinal disorders (SAEs), infections and infestations (severe AEs), nervous system disorders (severe AEs), fatigue (severe AEs), hepatobiliary toxicity (severe AEs), renal toxicity (severe AEs)*

A statistically significant difference to the disadvantage of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole was shown for each of the outcomes of respiratory, thoracic and mediastinal disorders (SAEs), infections and infestations (severe AEs), nervous system disorders (severe AEs), fatigue (severe AEs), hepatobiliary toxicity

(severe AEs) and renal toxicity (severe AEs). In each case, there was a hint of greater harm of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

#### 2.2.2.4 Subgroups and other effect modifications

The subgroup characteristics considered and the methods for evaluating the subgroup analyses are identical for research questions 1 and 2 and are described in Section 2.1.2.4.

Applying the methods described in Section 2.1.2.4, no effects relevant for the benefit assessment were shown.

### 2.2.3 Probability and extent of added benefit

The probability and extent of added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [11].

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

#### 2.2.3.1 Assessment of added benefit at outcome level

The extent of the respective added benefit at outcome level was assessed based on the results presented in Section 2.2.2.3 (see Table 18).

**Determination of the outcome category for the side effects outcomes**

***Discontinuation due to AEs***

For the outcome of discontinuation due to AEs, insufficient severity data are available which would allow them to be classified as serious/severe. The outcome was therefore assigned to the outcome category of non-serious/non-severe side effects.

Table 18: Extent of added benefit at outcome level: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| **Outcome category**<br>**Outcome** | **Ribociclib + anastrozole or letrozole vs. anastrozole or letrozole**<br>**Median time to event (months) or proportion of events (%) or mean change**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| **Outcomes with observation over the entire study duration** | | |
| **Mortality** | | |
| Overall survival | NA vs. NA<br>HR: 0.94 [0.68; 1.30];<br>p = 0.724 | Lesser/added benefit not proven |
| **Morbidity** | | |
| Recurrence | | Outcome category: serious/severe symptoms/late complications<br>$0.90 \leq CI_u < 1.00$<br>added benefit, extent: minor |
| Recurrence rate | 11.5% vs. 14.3%<br>RR: 0.81 [0.67; 0.98]<br>p = 0.027<br>probability: hint | |
| Invasive disease-free survival (IDFS) | NA vs. NA<br>HR: 0.75 [0.61; 0.92];<br>p = 0.005<br>probability: hint | |
| **Outcomes with shortened observation period** | | |
| **Morbidity** | | |
| Symptoms (EORTC QLQ-C30) | | |
| Fatigue | 2.8 vs. 2.7<br>MD: 0.05 [–1.13; 1.22]<br>p = 0.939 | Lesser/added benefit not proven |
| Nausea and vomiting | 2.0 vs. 1.1<br>MD: 0.88 [0.33; 1.44];<br>p = 0.002<br>SMD: 0.12 [0.05; 0.20][c] | Lesser/added benefit not proven |
| Pain | 3.0 vs. 4.5<br>MD: −1.52 [−2.82; −0.21];<br>p = 0.022<br>SMD: −0.09 [−0.17; −0.01][c] | Lesser/added benefit not proven |
| Dyspnoea | 3.5 vs. 3.4<br>MD: 0.11 [–1.08; 1.30]<br>p = 0.853 | Lesser/added benefit not proven |
| Insomnia | 2.2 vs. 3.4<br>MD: –1.22 [–2.75; 0.30]<br>p = 0.116 | Lesser/added benefit not proven |

Table 18: Extent of added benefit at outcome level: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| **Outcome category**<br>**Outcome** | **Ribociclib + anastrozole or letrozole vs. anastrozole or letrozole**<br>**Median time to event (months) or proportion of events (%) or mean change**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| Appetite loss | 1.1 vs. 0.6<br>MD: 0.47 [–0.51; 1.44]<br>p = 0.349 | Lesser/added benefit not proven |
| Constipation | 4.1 vs. 1.3<br>MD: 2.78 [1.57; 3.98];<br>p < 0.001<br>SMD: 0.18 [0.10; 0.26][c] | Lesser/added benefit not proven |
| Diarrhoea | 1.2 vs. 1.8<br>MD: –0.58 [–1.36; 0.20]<br>p = 0.144 | Lesser/added benefit not proven |
| Symptoms (EORTC QLQ-BR23) | | |
| Side effects of systemic therapy | 4.2 vs. 3.0<br>MD: 1.22 [0.37; 2.07];<br>p = 0.005<br>SMD: 0.11 [0.03; 0.19][c] | Lesser/added benefit not proven |
| Breast symptoms | –5.5 vs. –5.5<br>MD: 0.01 [–0.87; 0.89]<br>p = 0.981 | Lesser/added benefit not proven |
| Arm symptoms | 0.3 vs. –0.3<br>MD: 0.58 [–0.58; 1.74]<br>p = 0.329 | Lesser/added benefit not proven |
| Upset by hair loss | No suitable data | Lesser/added benefit not proven |
| Health status | | |
| EQ-5D VAS | −1.6 vs. −1.3<br>MD: −0.27 [−1.13; 0.59];<br>p = 0.540 | Lesser/added benefit not proven |
| **Health-related quality of life** | | |
| EORTC QLQ-C30 | | |
| Global health status | –2.8 vs. –2.4<br>MD: –0.43 [–1.40; 0.54]<br>p = 0.388 | Lesser/added benefit not proven |
| Physical functioning | –2.2 vs. –2.8<br>MD: 0.64 [–0.27; 1.56]<br>p = 0.168 | Lesser/added benefit not proven |
| Role functioning | –3.0 vs. –3.5<br>MD: 0.57 [–0.63; 1.78]<br>p = 0.353 | Lesser/added benefit not proven |

Table 18: Extent of added benefit at outcome level: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| **Outcome category**<br>**Outcome** | **Ribociclib + anastrozole or letrozole vs. anastrozole or letrozole**<br>**Median time to event (months) or proportion of events (%) or mean change**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| Emotional functioning | –2.8 vs. –3.8<br>MD: 0.98 [–0.14; 2.10]<br>p = 0.088 | Lesser/added benefit not proven |
| Cognitive functioning | –4.5 vs. –5.1<br>MD: 0.62 [–0.50; 1.75]<br>p = 0.278 | Lesser/added benefit not proven |
| Social functioning | 0.4 vs. 0.5<br>MD: –0.05 [–0.90; 0.80]<br>p = 0.911 | Lesser/added benefit not proven |
| EORTC QLQ-BR23 | | |
| Body image | 2.7 vs. 2.1<br>MD: 0.57 [–0.76; 1.90]<br>p = 0.401 | Lesser/added benefit not proven |
| Sexual functioning | –1.9 vs. –2.1<br>MD: 0.12 [–0.88; 1.13]<br>p = 0.808 | Lesser/added benefit not proven |
| Sexual enjoyment | No suitable data | Lesser/added benefit not proven |
| Future perspective | 9.1 vs. 8.1<br>MD: 0.94 [–0.55; 2.43]<br>p = 0.215 | Lesser/added benefit not proven |
| **Side effects** | | |
| SAEs | 16.3% vs. 11.9%<br>RR: 1.37 [1.13; 1.65];<br>RR: 0.73 [0.61; 0.88][d];<br>p < 0.001<br>probability: hint | Outcome category: serious/severe side effects<br>$0.75 < CI_u < 0.90$<br>Greater harm, extent: considerable |
| Severe AEs | 62.7% vs. 20.6%<br>RR: 3.05 [2.73; 3.41];<br>RR: 0.33 [0.29; 0.37][d];<br>p < 0.001<br>probability: hint | Outcome category: serious/severe side effects<br>$CI_u < 0.75$, risk ≥ 5%<br>Greater harm, extent: major |
| Discontinuation due to AEs | 24.1% vs. 5.0%<br>RR: 4.83 [3.77; 6.20];<br>RR: 0.21 [0.16; 0.27][d];<br>p < 0.001<br>probability: hint | Outcome category: non-serious/non-severe side effects<br>$CI_u < 0.80$<br>greater harm, extent: considerable |

Table 18: Extent of added benefit at outcome level: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| **Outcome category**<br>**Outcome** | **Ribociclib + anastrozole or letrozole vs. anastrozole or letrozole**<br>**Median time to event (months) or proportion of events (%) or mean change**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| Neutropenia (severe AEs) | 26.5% vs. 0.3%<br>RR: 90.38 [33.84; 241.39];<br>RR: 0.01 [0.004; 0.03][d];<br>p < 0.001<br>probability: hint | Outcome category: serious/severe side effects<br>$CI_u$ < 0.75, risk ≥ 5%<br>greater harm, extent: major |
| Gastrointestinal disorders (AEs) | 53.9% vs. 28.2%<br>RR: 1.91 [1.74; 2.11];<br>RR: 0.52 [0.47; 0.57][d];<br>p < 0.001<br>probability: hint | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>greater harm, extent: considerable |
| Skin and subcutaneous tissue disorders (AEs) | 38.0% vs. 20.1%<br>RR: 1.89 [1.67; 2.14];<br>RR: 0.53 [0.47; 0.60][d];<br>p < 0.001<br>probability: hint | Outcome category: non-serious/non-severe side effects<br>$CI_u$ < 0.80<br>greater harm, extent: considerable |
| Respiratory, thoracic and mediastinal disorders (SAEs) | 2.4% vs. 1.2%<br>RR: 2.05 [1.14; 3.70];<br>RR: 0.49 [0.27; 0.88][d];<br>p = 0.015<br>probability: hint | Outcome category: serious/severe side effects<br>0.75 ≤ $CI_u$ < 0.90<br>greater harm, extent: considerable |
| Infections and infestations (severe AEs) | 6.3% vs. 3.7%<br>RR: 1.69 [1.21; 2.36];<br>RR: 0.59 [0.42; 0.83][d];<br>p = 0.002<br>probability: hint | Outcome category: serious/severe side effects<br>0.75 ≤ $CI_u$ < 0.90<br>greater harm, extent: considerable |
| Nervous system disorders (severe AEs) | 2.8% vs. 1.2%<br>RR: 2.42 [1.36; 4.29];<br>RR: 0.41 [0.23; 0.74][d];<br>p = 0.002<br>probability: hint | Outcome category: serious/severe side effects<br>$CI_u$ < 0.75, risk< 5%<br>greater harm, extent: considerable |
| Fatigue (severe AEs) | 1.1% vs. 0.2%<br>RR: 4.83 [1.40; 16.66];<br>RR: 0.21 [0.06; 0.71][d];<br>p = 0.006<br>probability: hint | Outcome category: serious/severe side effects<br>$CI_u$ < 0.75, risk< 5%<br>greater harm, extent: considerable |
| Hepatobiliary toxicity (severe AEs) | 10.1% vs. 1.5%<br>RR: 6.54 [4.16; 10.27];<br>RR: 0.15 [0.10; 0.24][d];<br>p < 0.001<br>probability: hint | Outcome category: serious/severe side effects<br>$CI_u$ < 0.75, risk ≥ 5%<br>greater harm, extent: major |

Table 18: Extent of added benefit at outcome level: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| **Outcome category**<br>**Outcome** | **Ribociclib + anastrozole or letrozole vs. anastrozole or letrozole**<br>**Median time to event (months) or proportion of events (%) or mean change**<br>**Effect estimation [95% CI];**<br>**p-value**<br>**Probability**[a] | **Derivation of extent**[b] |
|---|---|---|
| Renal toxicity (severe AEs) | 0.5% vs. 0%<br>RR: 14.50 [0.83; 253.63];<br>RR: 0.07 [0.004; 1.20][d, e];<br>p = 0.009<br>probability: hint | Outcome category: serious/severe side effects<br>greater harm, extent: minor[e] |

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category and the scale of the outcome, the effect size is estimated with different limits based on the upper or lower limit of the confidence interval ($CI_u$ or $CI_L$).
c. If the CI for the SMD is fully outside the irrelevance range [–0.2; 0.2], this is interpreted to be a relevant effect. In other cases, the presence of a relevant effect cannot be derived.
d. Institute's calculation; reversed direction of effect to enable the use of limits to derive the extent of added benefit.
e. Discrepancy between p-value and CI due to different calculation methods; the lowest possible extent of added benefit is assumed here.

AE: adverse event; CI: confidence interval; $CI_L$: lower limit of confidence interval; $CI_u$: upper limit of confidence interval; EORTC: European Organisation for Research and Treatment of Cancer; IDFS: invasive disease-free survival; QLQ-BR23: Quality of Life Questionnaire-Breast Cancer 23; QLQ-C30: Quality of Life Questionnaire-Core 30; RR: relative risk; SAE: serious adverse event; SMD: standardized mean difference; VAS: visual analogue scale

### 2.2.3.2 Overall conclusion on added benefit

Table 19 summarizes the results taken into account for the overall conclusion on the extent of added benefit.

Table 19: Positive and negative effects from the assessment of ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women)

| **Positive effects** | **Negative effects** |
|---|---|
| **Outcomes with observation over the entire study duration** | |
| Morbidity<br>serious/severe symptoms/late complications<br>Recurrence: hint of an added benefit – extent: minor | – |
| **Outcomes with shortened observation period** | |
| – | Serious/severe side effects<br>▪ SAEs: hint of greater harm – extent: considerable, including<br>▫ respiratory, thoracic and mediastinal disorders: hint of greater harm – extent: considerable<br>▪ Severe AEs: hint of greater harm – extent: major, including<br>▫ neutropenia: hint of greater harm – extent: major<br>▫ infections and infestations: hint of greater harm – extent: considerable<br>▫ nervous system disorders: hint of greater harm – extent: considerable<br>▫ fatigue: hint of greater harm – extent: considerable<br>▫ hepatobiliary toxicity: hint of greater harm – extent: major<br>▫ renal toxicity: hint of greater harm – extent: minor<br>Non-serious/non-severe side effects<br>▪ discontinuation due to AEs: hint of greater harm – extent: considerable<br>▪ gastrointestinal disorders: hint of greater harm – extent: considerable<br>▪ skin and subcutaneous tissue disorders: hint of greater harm – extent: considerable |
| AE: adverse event; SAE: serious adverse event | |

Overall, there is one positive and several negative effects of ribociclib + anastrozole or letrozole in comparison with anastrozole or letrozole.

No conclusions can be drawn about longer-term effects of therapy with ribociclib in the therapeutic indication in question, as the observation period in the NATALEE study was only 44 months at the 29 April 2024 data cut-off.

In terms of positive effects, there is a hint of a minor added benefit for the outcome of recurrence. The significance of this effect should be viewed in the context of several biasing factors (see Section 2.2.2.2) and the overall minor effect size. On the other hand, there are

clear negative effects: There are hints of greater harm of minor to major extent in the outcome category of serious/severe side effects, and hints of greater harm, each with considerable extent, for the category of non-serious/non-severe side effects. The numerous negative effects outweigh the positive effect on recurrences.

In summary, there is a hint of lesser benefit of ribociclib in combination with an aromatase inhibitor compared with the ACT for the adjuvant treatment of postmenopausal women with HR-positive, HER2-negative early breast cancer at high risk of recurrence.

## 2.3 Summary

As a result of the information presented by the company in the commenting procedure and the oral hearing, the data from the 29 April 2024 data cut-off were used for research question 2. The conclusion on the added benefit of ribociclib in combination with an aromatase inhibitor from the dossier assessment A24-124 [1] changes. Whereas the added benefit was not proven in dossier assessment A24-124 [1], the present assessment shows a hint of a lesser benefit.

Table 20 below shows the result of the benefit assessment of ribociclib in combination with an aromatase inhibitor under consideration of dossier assessment A24-124 and the present addendum.

Table 20: Ribociclib in combination with an aromatase inhibitor – probability and extent of added benefit

| 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 | Pre-menopausal women[b, c, d] | ▪ tamoxifen (where appropriate in addition to ovarian function suppression), or<br>▪ abemaciclib in combination with endocrine therapy (only for patients with node-positive breast cancer), or<br>▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations) | Added benefit not proven |
| 2 | Post-menopausal women[c, d, e] | ▪ an aromatase inhibitor (anastrozole or letrozole) alone, where appropriate tamoxifen if aromatase inhibitors are unsuitable, or<br>▪ an aromatase inhibitor (anastrozole or exemestane) in sequence after tamoxifen, or<br>▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline BRCA1/2 mutations) | Hint of lesser benefit[g] |
| 3 | men[b, c, d, f] | ▪ tamoxifen, or<br>▪ abemaciclib in combination with endocrine therapy (only for patients with node-positive breast cancer), or<br>▪ 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.
g. The NATALEE study included only patients with an ECOG PS of 0 or 1. It remains unclear whether the observed effects are transferable to patients with an ECOG PS ≥ 2.

ACT: appropriate comparator therapy; BRCA: breast cancer associated gene; ECOG PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; LH-RH: luteinizing hormone-releasing hormone

The G-BA decides on the added benefit.

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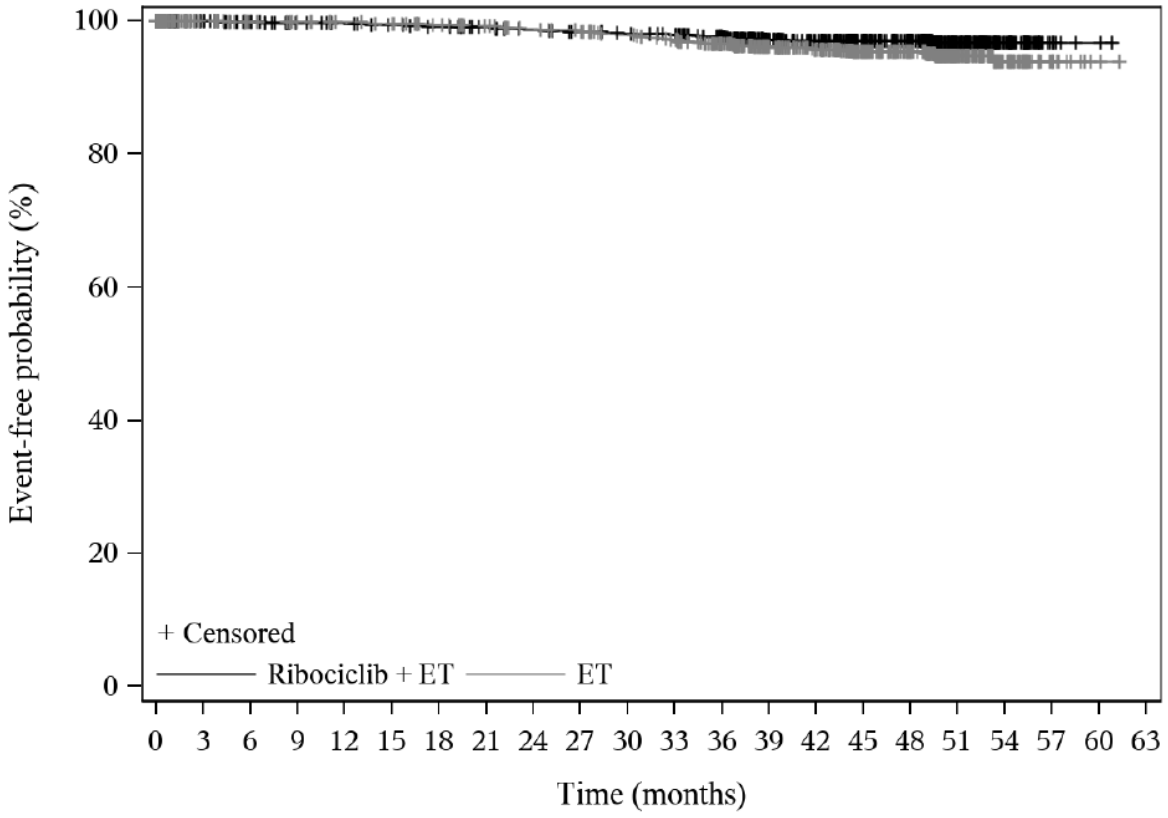
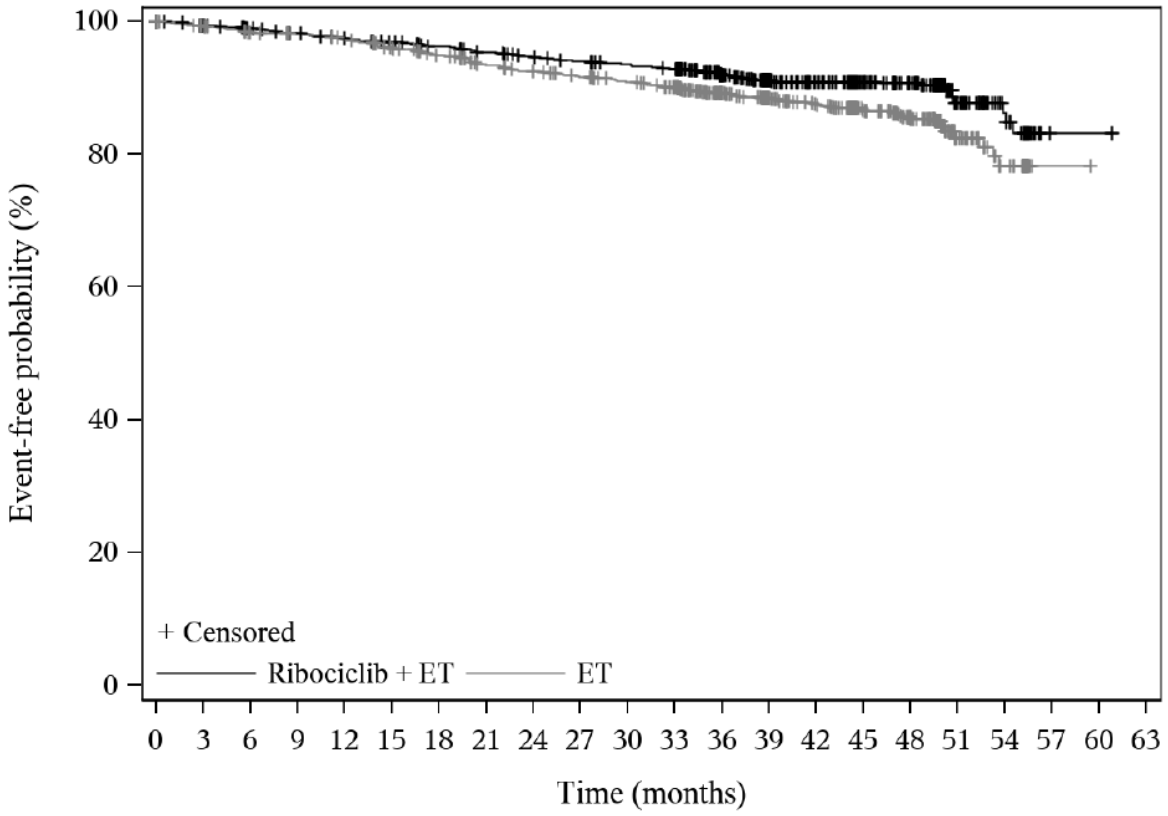
# Appendix A Kaplan-Meier curves

## A.1 Research question 1: Premenopausal women




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ribociclib + ET | 1115 | 1055 | 1034 | 1022 | 1004 | 989 | 938 | 738 | 446 | 84 | 3 |
| ET | 1123 | 1012 | 1000 | 984 | 963 | 941 | 874 | 686 | 413 | 84 | 2 |

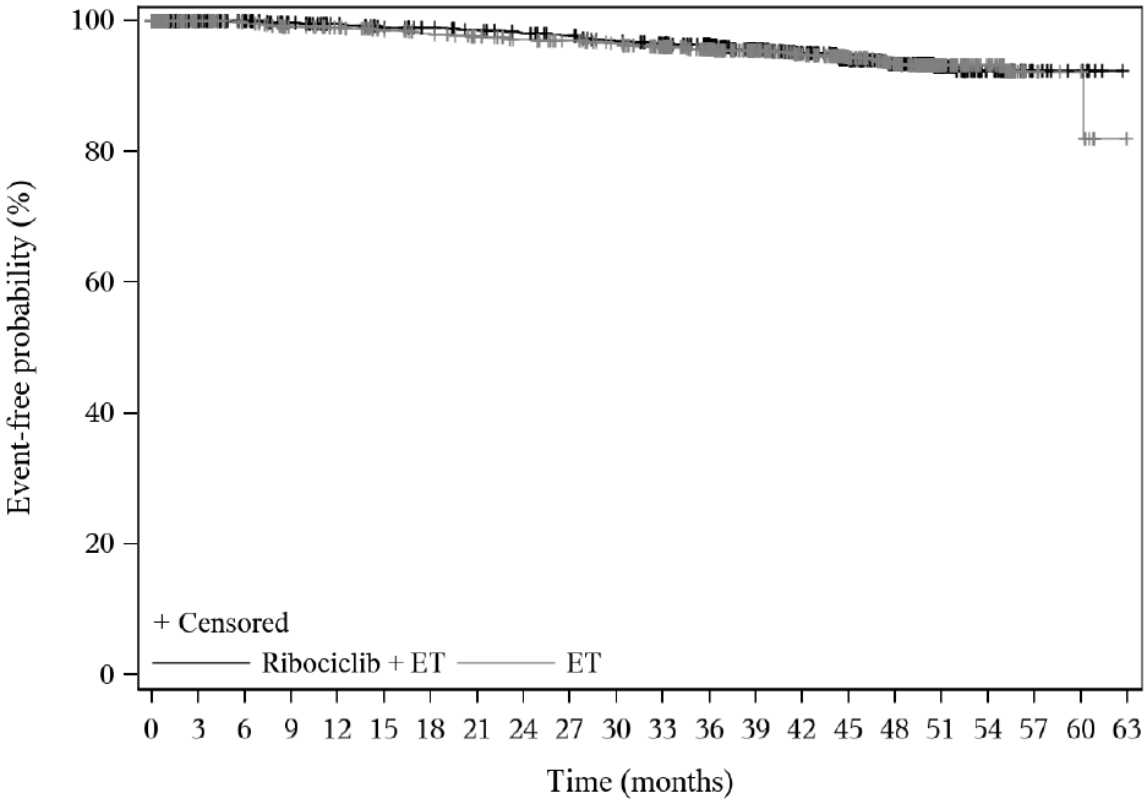
Figure 1: Kaplan-Meier curves for the outcome of overall survival in the subpopulation of premenopausal women (research question 1) from the NATALEE study (29 April 2024 data cut-off)




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ribociclib + ET | 1115 | 1038 | 1013 | 987 | 958 | 939 | 810 | 646 | 375 | 59 | 2 |
| ET | 1123 | 994 | 974 | 932 | 894 | 864 | 736 | 592 | 350 | 52 | |

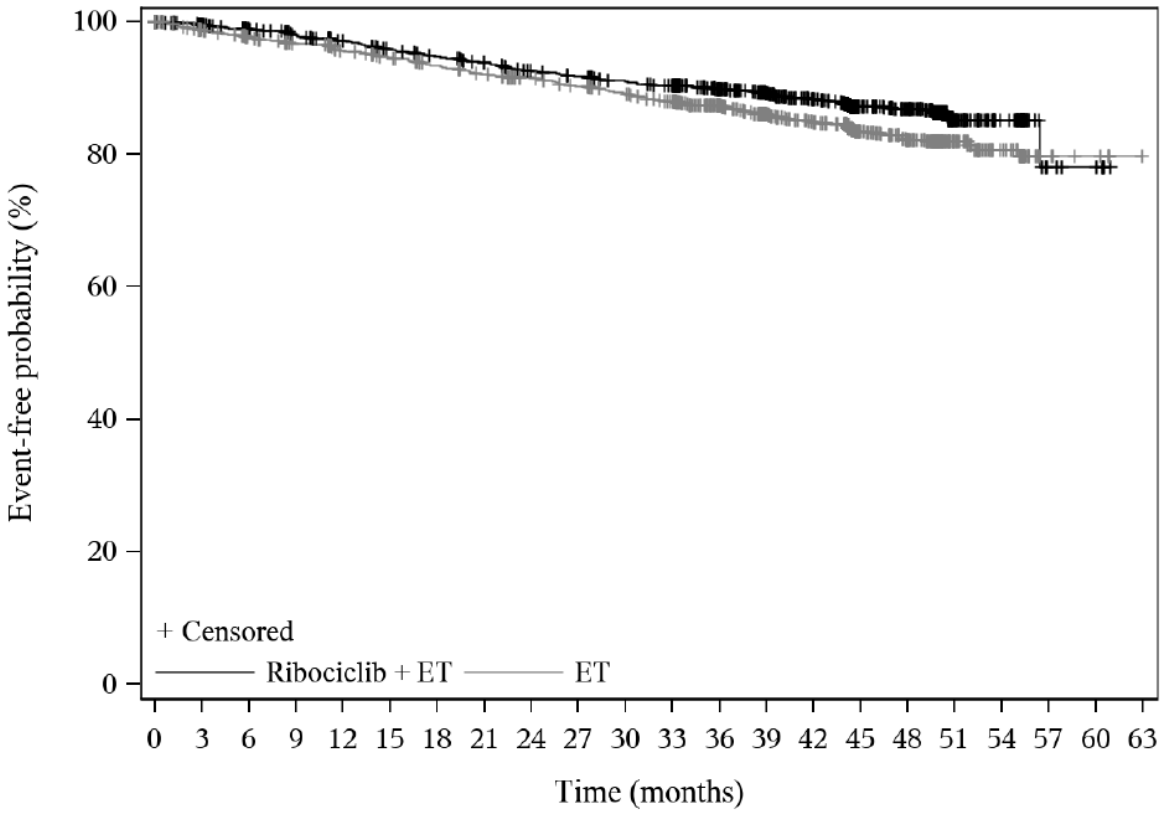
Figure 2: Kaplan-Meier curves for the outcome of invasive disease-free survival in the subpopulation of premenopausal women (research question 1) from the NATALEE study (29 April 2024 data cut-off)

## A.2 Research question 2: Postmenopausal women




| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Ribociclib + ET | 1424 | 1341 | 1294 | 1270 | 1248 | 1220 | 1134 | 904 | 580 | 109 | 8 |
| ET | 1420 | 1281 | 1247 | 1218 | 1193 | 1168 | 1063 | 878 | 573 | 117 | 10 |

Figure 3: Kaplan-Meier curves for the outcome of overall survival in the subpopulation of postmenopausal women (research question 2) from the NATALEE study (29 April 2024 data cut-off)




| | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Ribociclib + ET | 1424 | 1305 | 1254 | 1212 | 1167 | 1133 | 1027 | 830 | 535 | 96 | 6 |
| ET | 1420 | 1237 | 1187 | 1143 | 1105 | 1064 | 944 | 768 | 495 | 96 | 6 |

Figure 4: Kaplan-Meier curves for the outcome of invasive disease-free survival in the subpopulation of postmenopausal women (research question 2) from the NATALEE study (29 April 2024 data cut-off)

## Appendix B Results on side effects

For the overall rates of AEs, SAEs, and severe AEs (Common Terminology Criteria for Adverse Events [CTCAE] grade ≥ 3), the following tables present events for System Organ Classes (SOCs) and PTs according to the Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity): events that occurred in at least 10% of patients in one study arm
- Overall rates of severe AEs (e.g. CTCAE grade ≥ 3) and SAEs: events that occurred in at least 5% of patients in one study arm
- Additionally, for all events irrespective of severity: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, all events (SOCs/PTs) that resulted in discontinuation are presented.

## B.1 Research question 1: Premenopausal women

Table 21: Common AEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | Ribociclib + anastrozole or letrozole (N = 1108) | Anastrozole or letrozole N = 1070 |
| **NATALEE** | | |
| **Overall AE rate** | 1093 (98.6) | 964 (90.1) |
| Investigations | 742 (67.0) | 390 (36.4) |
| Neutrophil count decreased | 308 (27.8) | 28 (2.6) |
| SARS-CoV-2 test positive | 294 (26.5) | 180 (16.8) |
| Alanine aminotransferase increased | 194 (17.5) | 67 (6.3) |
| Aspartate aminotransferase increased | 172 (15.5) | 63 (5.9) |
| White blood cell count decreased | 130 (11.7) | 26 (2.4) |
| SARS-CoV-2 test negative | 64 (5.8) | 40 (3.7) |
| Electrocardiogram QT prolonged | 54 (4.9) | 9 (0.8) |
| Blood alkaline phosphatase increased | 43 (3.9) | 25 (2.3) |
| Gamma-glutamyltransferase increased | 41 (3.7) | 23 (2.1) |
| Weight increased | 41 (3.7) | 38 (3.6) |
| Lymphocyte count decreased | 32 (2.9) | 14 (1.3) |
| Blood bilirubin increased | 28 (2.5) | 13 (1.2) |
| Blood magnesium decreased | 28 (2.5) | 13 (1.2) |
| Weight decreased | 27 (2.4) | 19 (1.8) |
| Blood creatinine increased | 24 (2.2) | 4 (0.4) |
| Platelet count decreased | 23 (2.1) | 5 (0.5) |
| Lipase increased | 21 (1.9) | 11 (1.0) |
| Blood lactate dehydrogenase increased | 20 (1.8) | 12 (1.1) |
| Blood cholesterol increased | 9 (0.8) | 19 (1.8) |
| Blood phosphorus increased | 18 (1.6) | 10 (0.9) |
| Amylase increased | 11 (1.0) | 17 (1.6) |
| Blood sodium decreased | 9 (0.8) | 16 (1.5) |
| Adjusted calcium decreased | 14 (1.3) | 2 (0.2) |
| Blood calcium decreased | 13 (1.2) | 5 (0.5) |
| Musculoskeletal and connective tissue disorders | 716 (64.6) | 712 (66.5) |
| Arthralgia | 471 (42.5) | 505 (47.2) |
| Back pain | 132 (11.9) | 124 (11.6) |
| Pain in extremity | 123 (11.1) | 90 (8.4) |
| Myalgia | 104 (9.4) | 99 (9.3) |
| Osteoporosis | 36 (3.2) | 52 (4.9) |

Table 21: Common AEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b] PT[b]** | **Ribociclib + anastrozole or letrozole (N = 1108)** | **Anastrozole or letrozole N = 1070** |
| Bone pain | 50 (4.5) | 39 (3.6) |
| Osteopenia | 35 (3.2) | 47 (4.4) |
| Musculoskeletal chest pain | 44 (4.0) | 31 (2.9) |
| Neck pain | 42 (3.8) | 24 (2.2) |
| Joint stiffness | 34 (3.1) | 37 (3.5) |
| Muscle spasms | 29 (2.6) | 18 (1.7) |
| Musculoskeletal pain | 27 (2.4) | 23 (2.1) |
| Spinal pain | 20 (1.8) | 23 (2.1) |
| Musculoskeletal stiffness | 16 (1.4) | 20 (1.9) |
| Tendonitis | 12 (1.1) | 16 (1.5) |
| Osteoarthritis | 15 (1.4) | 12 (1.1) |
| Periarthritis | 6 (0.5) | 14 (1.3) |
| General disorders and administration site conditions | 625 (56.4) | 421 (39.3) |
| Fatigue | 238 (21.5) | 144 (13.5) |
| Asthenia | 185 (16.7) | 133 (12.4) |
| Pyrexia | 159 (14.4) | 83 (7.8) |
| Influenza like illness | 65 (5.9) | 21 (2.0) |
| Oedema peripheral | 51 (4.6) | 27 (2.5) |
| Mucosal inflammation | 36 (3.2) | 5 (0.5) |
| Pain | 35 (3.2) | 34 (3.2) |
| Chest pain | 27 (2.4) | 17 (1.6) |
| Non-cardiac chest pain | 26 (2.3) | 10 (0.9) |
| Axillary pain | 25 (2.3) | 16 (1.5) |
| Peripheral swelling | 23 (2.1) | 25 (2.3) |
| Chills | 18 (1.6) | 10 (0.9) |
| Malaise | 17 (1.5) | 8 (0.7) |
| Infections and infestations | 580 (52.3) | 421 (39.3) |
| COVID-19 | 306 (27.6) | 189 (17.7) |
| Upper respiratory tract infection | 72 (6.5) | 30 (2.8) |
| Urinary tract infection | 63 (5.7) | 53 (5.0) |
| Nasopharyngitis | 61 (5.5) | 43 (4.0) |
| Sinusitis | 35 (3.2) | 14 (1.3) |
| Herpes zoster | 28 (2.5) | 25 (2.3) |
| Oral herpes | 22 (2.0) | 2 (0.2) |
| Suspected COVID-19 | 20 (1.8) | 15 (1.4) |

Table 21: Common AEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Ribociclib + anastrozole or letrozole (N = 1108)** | **Anastrozole or letrozole N = 1070** |
| Influenza | 18 (1.6) | 11 (1.0) |
| Cystitis | 17 (1.5) | 17 (1.6) |
| Pneumonia | 17 (1.5) | 10 (0.9) |
| Mastitis | 16 (1.4) | 7 (0.7) |
| Respiratory tract infection viral | 8 (0.7) | 16 (1.5) |
| Bronchitis | 13 (1.2) | 15 (1.4) |
| Cellulitis | 14 (1.3) | 4 (0.4) |
| Conjunctivitis | 14 (1.3) | 3 (0.3) |
| Gastroenteritis | 12 (1.1) | 9 (0.8) |
| Skin infection | 12 (1.1) | 8 (0.7) |
| respiratory tract infection | 12 (1.1) | 10 (0.9) |
| Gastrointestinal disorders | 578 (52.2) | 349 (32.6) |
| Nausea | 247 (22.3) | 92 (8.6) |
| Constipation | 149 (13.4) | 55 (5.1) |
| Diarrhoea | 126 (11.4) | 49 (4.6) |
| Vomiting | 82 (7.4) | 47 (4.4) |
| Abdominal pain upper | 74 (6.7) | 45 (4.2) |
| Abdominal pain | 71 (6.4) | 62 (5.8) |
| Dyspepsia | 53 (4.8) | 41 (3.8) |
| Dry mouth | 47 (4.2) | 29 (2.7) |
| Gastrooesophageal reflux disease | 45 (4.1) | 23 (2.1) |
| Stomatitis | 45 (4.1) | 10 (0.9) |
| Toothache | 22 (2.0) | 6 (0.6) |
| Haemorrhoids | 20 (1.8) | 13 (1.2) |
| Abdominal distension | 17 (1.5) | 10 (0.9) |
| Mouth ulceration | 17 (1.5) | 3 (0.3) |
| Gastritis | 16 (1.4) | 8 (0.7) |
| Abdominal pain lower | 10 (0.9) | 12 (1.1) |
| Blood and lymphatic system disorders | 537 (48.5) | 105 (9.8) |
| Neutropenia | 470 (42.4) | 39 (3.6) |
| Leukopenia | 123 (11.1) | 29 (2.7) |
| Anaemia | 81 (7.3) | 34 (3.2) |
| Thrombocytopenia | 36 (3.2) | 21 (2.0) |
| Lymphopenia | 17 (1.5) | 10 (0.9) |
| Nervous system disorders | 481 (43.4) | 390 (36.4) |

Table 21: Common AEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Ribociclib + anastrozole or letrozole (N = 1108)** | **Anastrozole or letrozole N = 1070** |
| Headache | 314 (28.3) | 230 (21.5) |
| Dizziness | 101 (9.1) | 51 (4.8) |
| Paraesthesia | 42 (3.8) | 28 (2.6) |
| Dysgeusia | 26 (2.3) | 8 (0.7) |
| Neuropathy peripheral | 21 (1.9) | 24 (2.2) |
| Disturbance in attention | 21 (1.9) | 10 (0.9) |
| Hypoaesthesia | 21 (1.9) | 13 (1.2) |
| Memory impairment | 19 (1.7) | 20 (1.9) |
| Amnesia | 19 (1.7) | 9 (0.8) |
| Migraine | 18 (1.6) | 17 (1.6) |
| Anosmia | 16 (1.4) | 10 (0.9) |
| Carpal tunnel syndrome | 2 (0.2) | 13 (1.2) |
| Peripheral sensory neuropathy | 13 (1.2) | 10 (0.9) |
| Sciatica | 7 (0.6) | 12 (1.1) |
| Vascular disorders | 417 (37.6) | 405 (37.9) |
| Hot flush | 261 (23.6) | 270 (25.2) |
| Hypertension | 92 (8.3) | 84 (7.9) |
| Lymphoedema | 87 (7.9) | 86 (8.0) |
| Skin and subcutaneous tissue disorders | 416 (37.5) | 227 (21.2) |
| Alopecia | 155 (14.0) | 47 (4.4) |
| Rash | 99 (8.9) | 32 (3.0) |
| Pruritus | 80 (7.2) | 36 (3.4) |
| Dry skin | 44 (4.0) | 14 (1.3) |
| Dermatitis | 15 (1.4) | 7 (0.7) |
| Erythema | 14 (1.3) | 14 (1.3) |
| Scar pain | 7 (0.6) | 14 (1.3) |
| Madarosis | 14 (1.3) | 3 (0.3) |
| Rash maculo-papular | 12 (1.1) | 3 (0.3) |
| Urticaria | 12 (1.1) | 4 (0.4) |
| Respiratory, thoracic and mediastinal disorders | 339 (30.6) | 186 (17.4) |
| Cough | 170 (15.3) | 92 (8.6) |
| Oropharyngeal pain | 92 (8.3) | 48 (4.5) |
| Dyspnoea | 55 (5.0) | 37 (3.5) |
| Rhinorrhoea | 39 (3.5) | 11 (1.0) |
| Nasal congestion | 31 (2.8) | 13 (1.2) |

Table 21: Common AEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Ribociclib + anastrozole or letrozole (N = 1108)** | **Anastrozole or letrozole N = 1070** |
| Productive cough | 22 (2.0) | 10 (0.9) |
| Rhinitis allergic | 20 (1.8) | 12 (1.1) |
| Epistaxis | 18 (1.6) | 8 (0.7) |
| Dysphonia | 14 (1.3) | 4 (0.4) |
| Psychiatric disorders | 306 (27.6) | 322 (30.1) |
| Insomnia | 142 (12.8) | 161 (15.0) |
| Anxiety | 77 (6.9) | 78 (7.3) |
| Depression | 51 (4.6) | 62 (5.8) |
| Sleep disorder | 23 (2.1) | 20 (1.9) |
| Libido decreased | 14 (1.3) | 13 (1.2) |
| Mood altered | 5 (0.5) | 14 (1.3) |
| Metabolism and nutrition disorders | 308 (27.8) | 143 (13.4) |
| Hypokalaemia | 56 (5.1) | 13 (1.2) |
| Hypocalcaemia | 54 (4.9) | 6 (0.6) |
| Decreased appetite | 50 (4.5) | 13 (1.2) |
| Hypomagnesaemia | 49 (4.4) | 10 (0.9) |
| Hyperkalaemia | 31 (2.8) | 10 (0.9) |
| Hyperglycaemia | 29 (2.6) | 20 (1.9) |
| Hypercalcaemia | 19 (1.7) | 8 (0.7) |
| Hypercholesterolaemia | 16 (1.4) | 17 (1.6) |
| Hypertriglyceridaemia | 15 (1.4) | 8 (0.7) |
| Hyperuricaemia | 15 (1.4) | 6 (0.6) |
| Vitamin D deficiency | 8 (0.7) | 14 (1.3) |
| Hyperphosphataemia | 12 (1.1) | 2 (0.2) |
| Reproductive system and breast disorders | 202 (18.2) | 214 (20.0) |
| Vulvovaginal dryness | 67 (6.0) | 89 (8.3) |
| Breast pain | 62 (5.6) | 62 (5.8) |
| Vaginal haemorrhage | 12 (1.1) | 20 (1.9) |
| Dyspareunia | 6 (0.5) | 19 (1.8) |
| Vaginal discharge | 9 (0.8) | 11 (1.0) |
| Injury, poisoning and procedural complications | 184 (16.6) | 118 (11.0) |
| Procedural pain | 36 (3.2) | 26 (2.4) |
| Contusion | 17 (1.5) | 10 (0.9) |
| Seroma | 12 (1.1) | 6 (0.6) |

Table 21: Common AEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b] PT[b]** | **Ribociclib + anastrozole or letrozole (N = 1108)** | **Anastrozole or letrozole N = 1070** |
| Eye disorders | 134 (12.1) | 72 (6.7) |
| Dry eye | 47 (4.2) | 16 (1.5) |
| Lacrimation increased | 24 (2.2) | 4 (0.4) |
| Vision blurred | 22 (2.0) | 4 (0.4) |
| Cardiac disorders | 76 (6.9) | 57 (5.3) |
| Palpitations | 42 (3.8) | 16 (1.5) |
| Tachycardia | 9 (0.8) | 11 (1.0) |
| Renal and urinary disorders | 75 (6.8) | 45 (4.2) |
| Dysuria | 15 (1.4) | 13 (1.2) |
| Ear and labyrinth disorders | 63 (5.7) | 41 (3.8) |
| Vertigo | 24 (2.2) | 21 (2.0) |
| Tinnitus | 17 (1.5) | 9 (0.8) |
| Ear pain | 13 (1.2) | 7 (0.7) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 57 (5.1) | 44 (4.1) |
| Hepatobiliary disorders | 52 (4.7) | 35 (3.3) |
| Hepatic steatosis | 12 (1.1) | 5 (0.5) |
| Endocrine disorders | 28 (2.5) | 30 (2.8) |
| Hypothyroidism | 15 (1.4) | 14 (1.3) |
| Immune system disorders | 20 (1.8) | 14 (1.3) |

a. Events that occurred in ≥ 1% of patients in at least one study arm.
b. MedDRA version 21.1; SOC and PT notation taken from Module 4 without adaptation.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 22: Common SAEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women)

| Study | Patients with event n (%) | |
|---|---|---|
| **SOC[b] PT[b]** | **Ribociclib + anastrozole or letrozole N = 1108** | **Anastrozole or letrozole N = 1070** |
| **NATALEE** | | |
| **Overall SAE rate** | 145 (13.1) | 105 (9.8) |
| Infections and infestations | 50 (4.5) | 29 (2.7) |
| Injury, poisoning and procedural complications | 20 (1.8) | 14 (1.3) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 16 (1.4) | 13 (1.2) |
| Reproductive system and breast disorders | 16 (1.4) | 6 (0.6) |
| Nervous system disorders | 9 (0.8) | 13 (1.2) |
| Hepatobiliary disorders | 12 (1.1) | 8 (0.7) |

a. Events that occurred in ≥ 1% of patients in at least one study arm.
b. MedDRA version 21.1; SOC and PT notation taken from Module 4 without adaptation.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse events; SOC: System Organ Class

Table 23: Common severe AEs (CTCAE grade ≥ 3)[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Ribociclib + anastrozole or letrozole**<br>**N = 1108** | **Anastrozole or letrozole**<br>**N = 1070** |
| **NATALEE** | | |
| **Overall rate of severe AEs** | 734 (66.2) | 200 (18.7) |
| Blood and lymphatic system disorders | 348 (31.4) | 12 (1.1) |
| Neutropenia | 335 (30.2) | 9 (0.8) |
| Leukopenia | 38 (3.4) | 1 (0.1) |
| Investigations | 335 (30.2) | 38 (3.6) |
| Neutrophil count decreased | 245 (22.1) | 5 (0.5) |
| Alanine aminotransferase increased | 72 (6.5) | 12 (1.1) |
| White blood cell count decreased | 56 (5.1) | 3 (0.3) |
| Aspartate aminotransferase increased | 43 (3.9) | 8 (0.7) |
| Infections and infestations | 57 (5.1) | 29 (2.7) |
| Nervous system disorders | 21 (1.9) | 29 (2.7) |
| Vascular disorders | 28 (2.5) | 23 (2.1) |
| Hypertension | 21 (1.9) | 19 (1.8) |
| Gastrointestinal disorders | 24 (2.2) | 9 (0.8) |
| General disorders and administration site conditions | 24 (2.2) | 9 (0.8) |
| Musculoskeletal and connective tissue disorders | 23 (2.1) | 22 (2.1) |
| Arthralgia | 10 (0.9) | 14 (1.3) |
| Injury, poisoning and procedural complications | 22 (2.0) | 15 (1.4) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 17 (1.5) | 13 (1.2) |
| Reproductive system and breast disorders | 16 (1.4) | 8 (0.7) |
| Hepatobiliary disorders | 13 (1.2) | 8 (0.7) |
| Metabolism and nutrition disorders | 12 (1.1) | 8 (0.7) |

a. Events that occurred in ≥ 1% of patients in at least one study arm.
b. MedDRA version 21.1; SOC and PT notation taken from Module 4 without adaptation.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 24: Common discontinuations due to AEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Ribociclib + anastrozole or letrozole**<br>**N = 1108** | **Anastrozole or letrozole**<br>**N = 1070** |
| **NATALEE** | | |
| **Overall rate of discontinuations due to AEs** | 190 (17.1) | 60 (5.6) |
| Investigations | 89 (8.0) | 3 (0.3) |
| Alanine aminotransferase increased | 69 (6.2) | 1 (0.1) |
| Aspartate aminotransferase increased | 25 (2.3) | 0 (0) |
| Neutrophil count decreased | 4 (0.4) | 0 (0) |
| Electrocardiogram QT prolonged | 3 (0.3) | 0 (0) |
| Blood bilirubin increased | 2 (0.2) | 0 (0) |
| White blood cell count decreased | 2 (0.2) | 0 (0) |
| Weight increased | 1 (0.1) | 1 (0.1) |
| Musculoskeletal and connective tissue disorders | 13 (1.2) | 35 (3.3) |
| Arthralgia | 12 (1.1) | 25 (2.3) |
| Bone pain | 0 (0) | 3 (0.3) |
| Myalgia | 0 (0) | 3 (0.3) |
| General disorders and administration site conditions | 20 (1.8) | 3 (0.3) |
| Fatigue | 8 (0.7) | 2 (0.2) |
| Asthenia | 3 (0.3) | 0 (0) |
| Blood and lymphatic system disorders | 12 (1.1) | 0 (0) |
| Neutropenia | 10 (0.9) | 0 (0) |
| Febrile neutropenia | 2 (0.2) | 0 (0) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 11 (1.0) | 7 (0.7) |
| Acute myeloid leukaemia | 0 (0.0) | 2 (0.2) |
| Malignant melanoma | 2 (0.2) | 0 (0) |
| Papillary thyroid cancer | 2 (0.2) | 0 (0) |
| Metabolism and nutrition disorders | 9 (0.8) | 0 (0) |
| Hypercalcaemia | 3 (0.3) | 0 (0) |
| Hypokalaemia | 2 (0.2) | 0 (0) |
| Hypomagnesaemia | 2 (0.2) | 0 (0) |
| Hepatobiliary disorders | 8 (0.7) | 1 (0.1) |
| Hepatotoxicity | 3 (0.3) | 0 (0) |
| Drug-induced liver injury | 2 (0.2) | 0 (0) |
| Hyperbilirubinaemia | 1 (0.1) | 1 (0.1) |

Table 24: Common discontinuations due to AEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 1: premenopausal women) (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Ribociclib + anastrozole or letrozole**<br>**N = 1108** | **Anastrozole or letrozole**<br>**N = 1070** |
| Nervous system disorders | 6 (0.5) | 8 (0.7) |
| Headache | 3 (0.3) | 4 (0.4) |
| Dizziness | 2 (0.2) | 0 (0) |
| Paraesthesia | 1 (0.1) | 1 (0.1) |
| Skin and subcutaneous tissue disorders | 8 (0.7) | 2 (0.2) |
| Alopecia | 2 (0.2) | 0 (0) |
| Rash | 2 (0.2) | 1 (0.1) |
| Infections and infestations | 7 (0.6) | 0 (0) |
| COVID-19 | 2 (0.2) | 0 (0) |
| Gastrointestinal disorders | 6 (0.5) | 3 (0.3) |
| Nausea | 4 (0.4) | 0 (0) |
| Abdominal pain upper | 1 (0.1) | 1 (0.1) |
| Diarrhoea | 1 (0.1) | 1 (0.1) |
| Respiratory, thoracic and mediastinal disorders | 5 (0.5) | 0 (0) |
| Pneumonitis | 2 (0.2) | 0 (0) |
| Vascular disorders | 5 (0.5) | 0 (0) |
| Hot flush | 3 (0.3) | 0 (0) |
| Psychiatric disorders | 4 (0.4) | 4 (0.4) |
| Depression | 2 (0.2) | 0 (0) |
| Anxiety | 1 (0.1) | 1 (0.1) |
| Reproductive system and breast disorders | 2 (0.2) | 4 (0.4) |
| Vulvovaginal dryness | 2 (0.2) | 1 (0.1) |
| Cardiac disorders | 3 (0.3) | 0 (0) |
| Ear and labyrinth disorders | 0 (0) | 2 (0.2) |
| Vertigo | 0 (0) | 2 (0.2) |
| Eye disorders | 2 (0.2) | 0 (0) |

a. Discontinuation of one treatment component; events that occurred in ≥ 2 patients (irrespective of the study arm assignment).
b. MedDRA version 21.1; SOC and PT notation taken from Module 4 without adaptation.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

## B.2 Research question 2: Postmenopausal women

Table 25: Common AEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b] PT[b]** | **Ribociclib + anastrozole or letrozole** | **Anastrozole or letrozole** |
| | **N = 1409** | **N = 1362** |
| **NATALEE** | | |
| **Overall AE rate** | 1376 (97.7) | 1183 (86.9) |
| Investigations | 902 (64.0) | 417 (30.6) |
| Alanine aminotransferase increased | 302 (21.4) | 71 (5.2) |
| Neutrophil count decreased | 302 (21.4) | 13 (1.0) |
| Aspartate aminotransferase increased | 261 (18.5) | 78 (5.7) |
| SARS-CoV-2 test positive | 256 (18.2) | 159 (11.7) |
| White blood cell count decreased | 116 (8.2) | 14 (1.0) |
| SARS-CoV-2 test negative | 84 (6.0) | 42 (3.1) |
| Gamma-glutamyltransferase increased | 77 (5.5) | 44 (3.2) |
| Blood creatinine increased | 75 (5.3) | 19 (1.4) |
| Electrocardiogram QT prolonged | 55 (3.9) | 10 (0.7) |
| Blood magnesium decreased | 53 (3.8) | 18 (1.3) |
| Weight increased | 43 (3.1) | 32 (2.3) |
| Blood bilirubin increased | 38 (2.7) | 16 (1.2) |
| Blood lactate dehydrogenase increased | 38 (2.7) | 24 (1.8) |
| Blood alkaline phosphatase increased | 36 (2.6) | 37 (2.7) |
| Lipase increased | 36 (2.6) | 25 (1.8) |
| Weight decreased | 35 (2.5) | 21 (1.5) |
| Glomerular filtration rate decreased | 32 (2.3) | 11 (0.8) |
| Platelet count decreased | 32 (2.3) | 6 (0.4) |
| Lymphocyte count decreased | 30 (2.1) | 11 (0.8) |
| Blood uric acid increased | 25 (1.8) | 23 (1.7) |
| Blood cholesterol increased | 15 (1.1) | 24 (1.8) |
| Blood urea increased | 23 (1.6) | 24 (1.8) |
| Blood sodium decreased | 23 (1.6) | 15 (1.1) |
| Amylase increased | 22 (1.6) | 19 (1.4) |
| Adjusted calcium decreased | 20 (1.4) | 6 (0.4) |
| Blood calcium decreased | 17 (1.2) | 8 (0.6) |
| Blood glucose increased | 12 (0.9) | 17 (1.2) |
| Blood phosphorus increased | 16 (1.1) | 16 (1.2) |
| Blood potassium increased | 15 (1.1) | 2 (0.1) |

Table 25: Common AEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Ribociclib + anastrozole or letrozole**<br>**N = 1409** | **Anastrozole or letrozole**<br>**N = 1362** |
| Musculoskeletal and connective tissue disorders | 832 (59.0) | 861 (63.2) |
| Arthralgia | 504 (35.8) | 575 (42.2) |
| Back pain | 146 (10.4) | 129 (9.5) |
| Pain in extremity | 140 (9.9) | 132 (9.7) |
| Myalgia | 99 (7.0) | 81 (5.9) |
| Bone pain | 54 (3.8) | 63 (4.6) |
| Muscle spasms | 60 (4.3) | 45 (3.3) |
| Osteoporosis | 41 (2.9) | 50 (3.7) |
| Musculoskeletal chest pain | 44 (3.1) | 44 (3.2) |
| Osteopenia | 43 (3.1) | 26 (1.9) |
| Osteoarthritis | 41 (2.9) | 39 (2.9) |
| Joint stiffness | 32 (2.3) | 35 (2.6) |
| Musculoskeletal pain | 23 (1.6) | 33 (2.4) |
| Neck pain | 31 (2.2) | 23 (1.7) |
| Spinal pain | 30 (2.1) | 22 (1.6) |
| Musculoskeletal stiffness | 22 (1.6) | 27 (2.0) |
| Arthritis | 18 (1.3) | 21 (1.5) |
| Tendonitis | 11 (0.8) | 19 (1.4) |
| Joint swelling | 18 (1.3) | 7 (0.5) |
| Flank pain | 15 (1.1) | 7 (0.5) |
| Trigger finger | 13 (0.9) | 14 (1.0) |
| General disorders and administration site conditions | 774 (54.9) | 496 (36.4) |
| Fatigue | 335 (23.8) | 182 (13.4) |
| Asthenia | 241 (17.1) | 159 (11.7) |
| Pyrexia | 133 (9.4) | 70 (5.1) |
| Oedema peripheral | 89 (6.3) | 50 (3.7) |
| Influenza like illness | 43 (3.1) | 25 (1.8) |
| Pain | 43 (3.1) | 19 (1.4) |
| Mucosal inflammation | 35 (2.5) | 5 (0.4) |
| Chest pain | 33 (2.3) | 34 (2.5) |
| Non-cardiac chest pain | 32 (2.3) | 18 (1.3) |
| Peripheral swelling | 30 (2.1) | 24 (1.8) |
| Axillary pain | 28 (2.0) | 21 (1.5) |
| Chills | 25 (1.8) | 10 (0.7) |

Table 25: Common AEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Ribociclib + anastrozole or letrozole**<br>**N = 1409** | **Anastrozole or letrozole**<br>**N = 1362** |
| Chest discomfort | 19 (1.3) | 11 (0.8) |
| Malaise | 17 (1.2) | 7 (0.5) |
| Gastrointestinal disorders | 760 (53.9) | 384 (28.2) |
| Nausea | 346 (24.6) | 99 (7.3) |
| Diarrhoea | 241 (17.1) | 86 (6.3) |
| Constipation | 187 (13.3) | 70 (5.1) |
| Vomiting | 119 (8.4) | 51 (3.7) |
| Abdominal pain | 89 (6.3) | 42 (3.1) |
| Abdominal pain upper | 67 (4.8) | 43 (3.2) |
| Dyspepsia | 66 (4.7) | 32 (2.3) |
| Dry mouth | 58 (4.1) | 30 (2.2) |
| Stomatitis | 49 (3.5) | 6 (0.4) |
| Gastrooesophageal reflux disease | 41 (2.9) | 30 (2.2) |
| Toothache | 26 (1.8) | 8 (0.6) |
| Abdominal distension | 25 (1.8) | 6 (0.4) |
| Haemorrhoids | 23 (1.6) | 6 (0.4) |
| Mouth ulceration | 18 (1.3) | 2 (0.1) |
| Abdominal discomfort | 15 (1.1) | 12 (0.9) |
| Infections and infestations | 694 (49.3) | 477 (35.0) |
| COVID-19 | 263 (18.7) | 168 (12.3) |
| Urinary tract infection | 109 (7.7) | 75 (5.5) |
| Nasopharyngitis | 81 (5.7) | 57 (4.2) |
| Upper respiratory tract infection | 61 (4.3) | 39 (2.9) |
| Herpes zoster | 36 (2.6) | 29 (2.1) |
| Sinusitis | 33 (2.3) | 27 (2.0) |
| Suspected COVID-19 | 29 (2.1) | 11 (0.8) |
| Pneumonia | 24 (1.7) | 16 (1.2) |
| Respiratory tract infection viral | 23 (1.6) | 14 (1.0) |
| Bronchitis | 22 (1.6) | 18 (1.3) |
| Cellulitis | 22 (1.6) | 15 (1.1) |
| Tooth infection | 20 (1.4) | 12 (0.9) |
| Gastroenteritis | 19 (1.3) | 10 (0.7) |
| Conjunctivitis | 17 (1.2) | 10 (0.7) |
| Cystitis | 17 (1.2) | 11 (0.8) |

Table 25: Common AEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Ribociclib + anastrozole or letrozole**<br>**N = 1409** | **Anastrozole or letrozole**<br>**N = 1362** |
| Influenza | 16 (1.1) | 13 (1.0) |
| Oral herpes | 15 (1.1) | 11 (0.8) |
| Blood and lymphatic system disorders | 686 (48.7) | 114 (8.4) |
| Neutropenia | 581 (41.2) | 31 (2.3) |
| Leukopenia | 215 (15.3) | 21 (1.5) |
| Anaemia | 136 (9.7) | 42 (3.1) |
| Thrombocytopenia | 75 (5.3) | 23 (1.7) |
| Lymphopenia | 52 (3.7) | 6 (0.4) |
| Nervous system disorders | 548 (38.9) | 411 (30.2) |
| Headache | 265 (18.8) | 189 (13.9) |
| Dizziness | 129 (9.2) | 63 (4.6) |
| Neuropathy peripheral | 33 (2.3) | 34 (2.5) |
| Dysgeusia | 30 (2.1) | 7 (0.5) |
| Paraesthesia | 25 (1.8) | 30 (2.2) |
| Amnesia | 24 (1.7) | 16 (1.2) |
| Migraine | 21 (1.5) | 7 (0.5) |
| Peripheral sensory neuropathy | 20 (1.4) | 17 (1.2) |
| Sciatica | 20 (1.4) | 17 (1.2) |
| Taste disorder | 18 (1.3) | 6 (0.4) |
| Memory impairment | 17 (1.2) | 14 (1.0) |
| Cerebrovascular disorder | 16 (1.1) | 13 (1.0) |
| Disturbance in attention | 16 (1.1) | 10 (0.7) |
| Anosmia | 15 (1.1) | 6 (0.4) |
| Carpal tunnel syndrome | 10 (0.7) | 15 (1.1) |
| Hypoaesthesia | 15 (1.1) | 9 (0.7) |
| Skin and subcutaneous tissue disorders | 536 (38.0) | 274 (20.1) |
| Alopecia | 231 (16.4) | 66 (4.8) |
| Pruritus | 108 (7.7) | 43 (3.2) |
| Rash | 102 (7.2) | 38 (2.8) |
| Dry skin | 46 (3.3) | 18 (1.3) |
| Erythema | 29 (2.1) | 19 (1.4) |
| Scar pain | 18 (1.3) | 23 (1.7) |
| Rash maculo-papular | 16 (1.1) | 7 (0.5) |

Table 25: Common AEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Ribociclib + anastrozole or letrozole**<br>**N = 1409** | **Anastrozole or letrozole**<br>**N = 1362** |
| Metabolism and nutrition disorders | 460 (32.6) | 233 (17.1) |
| Hypomagnesaemia | 108 (7.7) | 30 (2.2) |
| Hyperkalaemia | 82 (5.8) | 18 (1.3) |
| Decreased appetite | 71 (5.0) | 34 (2.5) |
| Hypocalcaemia | 62 (4.4) | 8 (0.6) |
| Hyperglycaemia | 61 (4.3) | 58 (4.3) |
| Hypokalaemia | 49 (3.5) | 22 (1.6) |
| Hypercalcaemia | 31 (2.2) | 16 (1.2) |
| Hyperuricaemia | 25 (1.8) | 17 (1.2) |
| Hypercholesterolaemia | 21 (1.5) | 22 (1.6) |
| Hypermagnesaemia | 18 (1.3) | 2 (0.1) |
| Type 2 diabetes mellitus | 14 (1.0) | 14 (1.0) |
| Vascular disorders | 433 (30.7) | 419 (30.8) |
| Hot flush | 227 (16.1) | 221 (16.2) |
| Hypertension | 124 (8.8) | 105 (7.7) |
| Lymphoedema | 92 (6.5) | 102 (7.5) |
| Respiratory, thoracic and mediastinal disorders | 416 (29.5) | 257 (18.9) |
| Cough | 172 (12.2) | 114 (8.4) |
| Dyspnoea | 115 (8.2) | 66 (4.8) |
| Oropharyngeal pain | 72 (5.1) | 34 (2.5) |
| Rhinorrhoea | 37 (2.6) | 16 (1.2) |
| Nasal congestion | 29 (2.1) | 14 (1.0) |
| Epistaxis | 23 (1.6) | 7 (0.5) |
| Rhinitis allergic | 21 (1.5) | 14 (1.0) |
| Productive cough | 16 (1.1) | 7 (0.5) |
| Psychiatric disorders | 316 (22.4) | 255 (18.7) |
| Insomnia | 154 (10.9) | 125 (9.2) |
| Anxiety | 72 (5.1) | 51 (3.7) |
| Depression | 68 (4.8) | 40 (2.9) |
| Depressed mood | 22 (1.6) | 16 (1.2) |
| Sleep disorder | 22 (1.6) | 22 (1.6) |
| Injury, poisoning and procedural complications | 198 (14.1) | 192 (14.1) |
| Procedural pain | 28 (2.0) | 40 (2.9) |
| Fall | 18 (1.3) | 34 (2.5) |

Table 25: Common AEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Ribociclib + anastrozole or letrozole**<br>**N = 1409** | **Anastrozole or letrozole**<br>**N = 1362** |
| Contusion | 21 (1.5) | 16 (1.2) |
| Humerus fracture | 15 (1.1) | 6 (0.4) |
| Reproductive system and breast disorders | 165 (11.7) | 195 (14.3) |
| Breast pain | 49 (3.5) | 66 (4.8) |
| Vulvovaginal dryness | 43 (3.1) | 47 (3.5) |
| Eye disorders | 182 (12.9) | 105 (7.7) |
| Dry eye | 49 (3.5) | 21 (1.5) |
| Lacrimation increased | 48 (3.4) | 12 (0.9) |
| Cataract | 15 (1.1) | 26 (1.9) |
| Vision blurred | 17 (1.2) | 8 (0.6) |
| Cardiac disorders | 123 (8.7) | 103 (7.6) |
| Palpitations | 47 (3.3) | 20 (1.5) |
| Tachycardia | 18 (1.3) | 15 (1.1) |
| Atrial fibrillation | 13 (0.9) | 16 (1.2) |
| Renal and urinary disorders | 101 (7.2) | 83 (6.1) |
| Pollakiuria | 17 (1.2) | 10 (0.7) |
| Dysuria | 15 (1.1) | 15 (1.1) |
| Ear and labyrinth disorders | 97 (6.9) | 53 (3.9) |
| Vertigo | 50 (3.5) | 25 (1.8) |
| Hepatobiliary disorders | 76 (5.4) | 44 (3.2) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 63 (4.5) | 76 (5.6) |
| Endocrine disorders | 30 (2.1) | 42 (3.1) |
| Hypothyroidism | 15 (1.1) | 22 (1.6) |
| Immune system disorders | 25 (1.8) | 18 (1.3) |

a. Events that occurred in ≥ 1% of patients in at least one study arm.
b. MedDRA version 21.1; SOC and PT notation taken from Module 4 without adaptation.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 26: Common SAEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b] PT[b]** | **Ribociclib + anastrozole or letrozole N = 1409** | **Anastrozole or letrozole N = 1362** |
| **NATALEE** | | |
| **Overall SAE rate** | 229 (16.3) | 162 (11.9) |
| Infections and infestations | 82 (5.8) | 46 (3.4) |
| Respiratory, thoracic and mediastinal disorders | 34 (2.4) | 16 (1.2) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 23 (1.6) | 27 (2.0) |
| Injury, poisoning and procedural complications | 24 (1.7) | 22 (1.6) |
| Cardiac disorders | 20 (1.4) | 16 (1.2) |
| Nervous system disorders | 19 (1.3) | 12 (0.9) |
| Gastrointestinal disorders | 13 (0.9) | 17 (1.2) |
| General disorders and administration site conditions | 15 (1.1) | 5 (0.4) |
| Hepatobiliary disorders | 15 (1.1) | 1 (0.1) |

a. Events that occurred in ≥ 1% of patients in at least one study arm.
b. MedDRA version 21.1; SOC and PT notation taken from Module 4 without adaptation.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse events; SOC: System Organ Class

Table 27: Common severe AEs (CTCAE grade ≥ 3)[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women)

| Study | Patients with event n (%) | |
|---|---|---|
| SOC[b] PT[b] | Ribociclib + anastrozole or letrozole N = 1409 | Anastrozole or letrozole N = 1362 |
| **NATALEE** | | |
| **Overall rate of severe AEs** | 883 (62.7) | 280 (20.6) |
| Blood and lymphatic system disorders | 396 (28.1) | 13 (1.0) |
| Neutropenia | 374 (26.5) | 4 (0.3) |
| Leukopenia | 56 (4.0) | 1 (0.1) |
| Investigations | 371 (26.3) | 47 (3.5) |
| Neutrophil count decreased | 202 (14.3) | 3 (0.2) |
| Alanine aminotransferase increased | 122 (8.7) | 5 (0.4) |
| Aspartate aminotransferase increased | 74 (5.3) | 6 (0.4) |
| White blood cell count decreased | 39 (2.8) | 3 (0.2) |
| Gamma-glutamyltransferase increased | 19 (1.3) | 13 (1.0) |
| Infections and infestations | 89 (6.3) | 51 (3.7) |
| Vascular disorders | 49 (3.5) | 49 (3.6) |
| Hypertension | 37 (2.6) | 44 (3.2) |
| Musculoskeletal and connective tissue disorders | 42 (3.0) | 34 (2.5) |
| Arthralgia | 15 (1.1) | 17 (1.2) |
| Nervous system disorders | 40 (2.8) | 16 (1.2) |
| Respiratory, thoracic and mediastinal disorders | 38 (2.7) | 23 (1.7) |
| Gastrointestinal disorders | 36 (2.6) | 24 (1.8) |
| General disorders and administration site conditions | 34 (2.4) | 13 (1.0) |
| Fatigue | 15 (1.1) | 3 (0.2) |
| Metabolism and nutrition disorders | 28 (2.0) | 20 (1.5) |
| Injury, poisoning and procedural complications | 25 (1.8) | 24 (1.8) |
| Hepatobiliary disorders | 23 (1.6) | 2 (0.1) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 21 (1.5) | 22 (1.6) |
| Cardiac disorders | 20 (1.4) | 16 (1.2) |

a. Events that occurred in ≥ 1% of patients in at least one study arm.
b. MedDRA version 21.1; SOC and PT notation taken from Module 4 without adaptation.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 28: Common discontinuations due to AEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Ribociclib + anastrozole or letrozole**<br>**N = 1409** | **Anastrozole or letrozole**<br>**N = 1362** |
| **NATALEE** | | |
| **Overall rate of discontinuations due to AEs** | 340 (24.1) | 68 (5.0) |
| Investigations | 165 (11.7) | 2 (0.1) |
| Alanine aminotransferase increased | 113 (8.0) | 1 (0.1) |
| Aspartate aminotransferase increased | 47 (3.3) | 0 (0) |
| Blood creatinine increased | 7 (0.5) | 0 (0) |
| Blood magnesium decreased | 6 (0.4) | 0 (0) |
| Electrocardiogram QT prolonged | 5 (0.4) | 0 (0) |
| Gamma-glutamyltransferase increased | 3 (0.2) | 0 (0) |
| Neutrophil count decreased | 3 (0.2) | 0 (0) |
| Amylase increased | 2 (0.1) | 0 (0) |
| Lipase increased | 2 (0.1) | 0 (0) |
| SARS-CoV-2 test positive | 1 (0.1) | 1 (0.1) |
| Musculoskeletal and connective tissue disorders | 31 (2.2) | 35 (2.6) |
| Arthralgia | 22 (1.6) | 25 (1.8) |
| Arthritis | 0 (0) | 2 (0.1) |
| Back pain | 1 (0.1) | 2 (0.1) |
| Myalgia | 2 (0.1) | 1 (0.1) |
| Osteoporosis | 0 (0) | 2 (0.1) |
| Rheumatoid arthritis | 1 (0.1) | 1 (0.1) |
| General disorders and administration site conditions | 25 (1.8) | 2 (0.1) |
| Fatigue | 12 (0.9) | 0 (0) |
| Asthenia | 9 (0.6) | 0 (0) |
| Gastrointestinal disorders | 18 (1.3) | 3 (0.2) |
| Nausea | 9 (0.6) | 1 (0.1) |
| Diarrhoea | 6 (0.4) | 1 (0.1) |
| Dyspepsia | 3 (0.2) | 0 (0) |
| Abdominal pain | 2 (0.1) | 0 (0) |
| Vomiting | 2 (0.1) | 0 (0) |
| Skin and subcutaneous tissue disorders | 17 (1.2) | 1 (0.1) |
| Rash | 5 (0.4) | 1 (0.1) |
| Alopecia | 3 (0.2) | 0 (0) |
| Rash maculo-papular | 2 (0.1) | 0 (0) |

Table 28: Common discontinuations due to AEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b]**<br>**PT[b]** | **Ribociclib + anastrozole or letrozole**<br>**N = 1409** | **Anastrozole or letrozole**<br>**N = 1362** |
| Hepatobiliary disorders | 16 (1.1) | 0 (0) |
| Hepatotoxicity | 4 (0.3) | 0 (0) |
| Hypertransaminasaemia | 4 (0.3) | 0 (0) |
| Hepatic cytolysis | 2 (0.1) | 0 (0) |
| Nervous system disorders | 16 (1.1) | 4 (0.3) |
| Headache | 4 (0.3) | 0 (0) |
| Cerebrovascular accident | 3 (0.2) | 0 (0) |
| Carpal tunnel syndrome | 2 (0.1) | 0 (0) |
| Migraine | 2 (0.1) | 0 (0) |
| Subarachnoid haemorrhage | 2 (0.1) | 0 (0) |
| Blood and lymphatic system disorders | 15 (1.1) | 0 (0) |
| Neutropenia | 9 (0.6) | 0 (0) |
| Anaemia | 2 (0.1) | 0 (0) |
| Leukopenia | 2 (0.1) | 0 (0) |
| Infections and infestations | 15 (1.1) | 3 (0.2) |
| COVID-19 | 5 (0.4) | 1 (0.1) |
| COVID-19 pneumonia | 3 (0.2) | 0 (0) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | 15 (1.1) | 11 (0.8) |
| Colon cancer | 0 (0) | 2 (0.1) |
| Papillary thyroid cancer | 2 (0.1) | 0 (0) |
| Acute myeloid leukaemia | 1 (0.1) | 1 (0.1) |
| Rectal adenocarcinoma | 1 (0.1) | 1 (0.1) |
| Respiratory, thoracic and mediastinal disorders | 14 (1.0) | 4 (0.3) |
| Pulmonary embolism | 5 (0.4) | 1 (0.1) |
| Pneumonitis | 4 (0.3) | 0 (0) |
| Dyspnoea | 2 (0.1) | 2 (0.1) |
| Metabolism and nutrition disorders | 10 (0.7) | 0 (0) |
| Hyperkalaemia | 4 (0.3) | 0 (0) |
| Hypomagnesaemia | 4 (0.3) | 0 (0) |
| Cardiac disorders | 9 (0.6) | 3 (0.2) |
| Acute myocardial infarction | 2 (0.1) | 0 (0) |
| Myocardial infarction | 1 (0.1) | 1 (0.1) |

Table 28: Common discontinuations due to AEs[a] – RCT, direct comparison: ribociclib + anastrozole or letrozole vs. anastrozole or letrozole (research question 2: postmenopausal women) (multipage table)

| **Study** | **Patients with event n (%)** | |
|---|---|---|
| **SOC[b] PT[b]** | **Ribociclib + anastrozole or letrozole** | **Anastrozole or letrozole** |
| | **N = 1409** | **N = 1362** |
| Injury, poisoning and procedural complications | 4 (0.3) | 1 (0.1) |
| Psychiatric disorders | 4 (0.3) | 2 (0.1) |
| Anxiety | 3 (0.2) | 0 (0) |
| Eye disorders | 3 (0.2) | 1 (0.1) |
| Vascular disorders | 3 (0.2) | 1 (0.1) |
| Hypotension | 2 (0.1) | 0 (0) |
| Renal and urinary disorders | 2 (0.1) | 0 (0) |
| Chronic kidney disease | 2 (0.1) | 0 (0) |

a. Discontinuation of one treatment component; events that occurred in ≥ 2 patients (irrespective of the study arm assignment).
b. MedDRA version 21.1; SOC and PT notation taken from Module 4 without adaptation.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class