Abemaciclib
(breast cancer; adjuvant therapy)

Addendum to Project A26-17
(dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CDK	cyclin-dependent kinase
FACIT-Fatigue	Functional Assessment of Chronic Illness Therapy – Fatigue
FACT-B	Functional Assessment of Cancer Therapy – Breas
FACT-ES	Functional Assessment of Cancer Therapy – Endocrine Symptoms
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GnRH	gonadotropin-releasing hormone
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomised controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)

1 Background

On 08 July 2026, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A26-17 (Abemaciclib – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the MONARCH-E study, taking into account the analyses submitted by the pharmaceutical company (hereinafter referred to as 'the company') in the commenting procedure and the information contained in the dossier.

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

The company presented the randomised controlled trial (RCT) MONARCH-E for the benefit assessment of abemaciclib in combination with endocrine therapy versus the appropriate comparator therapy (ACT) for the adjuvant treatment of patients with hormone receptor (HR)-positive, human epidermal growth factor receptor 2(HER2)-negative, node-positive early breast cancer at high risk of recurrence. The MONARCH-E study is an ongoing, open-label multicentre RCT comparing abemaciclib in combination with standard endocrine therapy with standard endocrine therapy. The study included patients with node-positive, HR-positive, HER2-negative early breast cancer who had undergone definitive surgery, without distant metastases and at high risk of recurrence. A detailed description of the study can be found in dossier assessment A26-17 [1].

In its dossier [2], the company presented subpopulations of the pre- and postmenopausal patients respectively. In the dossier assessment, the study was classified as principally relevant for the benefit assessment; however, the company's dossier [2] lacked crucial information required for the benefit assessment, particularly with regard to the formation of the subpopulations of pre- and post-menopausal women. An adequate assessment of the study data was therefore not possible, so that the results of the MONARCH-E study were overall not used for the benefit assessment.

In its comments [3], the company subsequently submitted further information on the MONARCH-E study, as well as new analyses of sub,-populations of the pre- and postmenopausal patients from the MONARCH-E study. The following section describes and categorises the key information subsequently provided by the company in its written submission and during the oral hearing [4].

2.1 Information subsequently submitted by the company

Time of the allocation of endocrine therapy

For the formation of adequate subpopulations of premenopausal and postmenopausal women from the MONARCH-E study for the benefit assessment, patients in both subpopulations had to be further selected on the basis of the endocrine therapies they had received. To ensure that the study arms remain structurally equal, it had to be ensured that the patients' endocrine therapy was determined prior to randomisation, or that any endocrine therapy already existing before randomisation was continued at the start of the study. This was not clear from the information provided in the company's dossier [2], including the study protocol. In its comments [3], the company states that 63% of the patients were already receiving endocrine therapy prior to enrolment in the study and continued this treatment during the study. In its comments, the company provides no information about the time point of allocation of endocrine therapy (before or after randomisation) for the remaining 37% of

patients. At the oral hearing [4], the company explained that the endocrine therapy had been determined for all patients at a very early stage, even before the patient had been consulted about the study inclusion.

There remains some uncertainty because the time of allocation is not specified in the study protocol, and it is therefore unclear whether this was implemented at all study centres. Nevertheless, it is assumed that the structural equality between the study arms was sufficiently maintained in the formation of the subpopulations presented.

Implementation of the ACT

The information in the company's dossier allowed no adequate assessment of the implementation of the G-BA's ACT for the patients included in the presented subpopulations of the MONARCH-E study. In its comments [3], the company subsequently submitted detailed information on the endocrine therapies administered to the subpopulations presented, as well as on the gonadotropin-releasing hormone (GnRH) analogues administered to premenopausal patients.

Therefore, it is assumed that the ACT was adequately implemented in the presented subpopulations of the MONARCH-E study.

Concomitant treatment

The company provides details on the proportion of patients who were receiving treatment with bisphosphonates or denosumab at the start of the study. In accordance with the G-BA's notes on the ACT, postmenopausal patients with HR-positive breast cancer should be offered adjuvant bisphosphonate therapy. This also corresponds to the guideline recommendations [5,6]. It was already noted in the EPAR [7] that the number of bisphosphonate treatments administered in the study appears to be low. According to the data on the presented subpopulation of postmenopausal women, approx. 9.6% of patients in the intervention arm and approx. 8.5% in the comparator arm received bisphosphonates or denosumab.

It is therefore questionable whether the patients in the MONARCH-E study received guideline-compliant treatment with bisphosphonates or denosumab. As the proportions of patients receiving treatment with bisphosphonates or denosumab is almost equally distributed between the study arms, it is not assumed that the interpretability of the study results is limited to a relevant extent.

Implementation of the intention-to-treat (ITT) principle

The analyses of the respective subpopulations presented in the dossier included only those patients who had received endocrine therapy corresponding to the ACT at the start of the study and throughout the entire observation period up to the data cut. Consequently, the ITT principle was breached in the analyses submitted. In its comments [3], the company provided

analyses of the subpopulations of all pre- and postmenopausal patients who were being treated with endocrine therapy in accordance with the G-BA's ACT at the start of the study. The analyses submitted with the comments suggest that the ITT principle was adequately implemented.

Duration of treatment with the endocrine therapy

In the MONARCH-E study, endocrine therapy was to be continued in both study arms for at least 5 years after the start of the study. According to current guidelines [5,6,8,9], a significantly longer duration of adjuvant endocrine therapy is recommended for patients at high risk of recurrence (up to 10 years for premenopausal women, and 7 to 8 years for postmenopausal women).

In its dossier, the company presented data on the treatment duration only for the first two years of the study, even though the patients had been followed up for a median period of slightly over six years at the time of the data cut. The company's written comments [3] include contradictory statements regarding the duration of treatment with endocrine therapy. Firstly, the company stated that detailed information on the endocrine therapy was only available for the period of treatment with abemaciclib in the study during the first two years following randomisation. Information on the concrete duration of individual endocrine therapy outside the study treatment period was not recorded. However, elsewhere it is stated that endocrine therapy was continued for at least 5 years by approx. 85% of premenopausal and approx. 82% of postmenopausal patients. At the oral hearing [4], the company explained that the data submitted on endocrine therapy refer to a treatment duration of at least 5 years. Given the median observation period of 6 years, it is therefore assumed that the duration of treatment was sufficiently long for this assessment.

2.2 Research question 1: Premenopausal women

2.2.1 Study characteristics

A detailed description of the MONARCH-E study can be found in dossier assessment A26-17 [1].

The company presented analyses of a subpopulation of 1715 premenopausal patients, 864 of whom were treated with abemaciclib in combination with endocrine therapy and 851 with endocrine therapy alone.

Data cuts

The MONARCH-E study is an ongoing study. So far, 7 data cuts are available:

- First data cut (27 September 2019): planned interim analysis after 195 invasive disease-free survival (IDFS) events

- Second data cut (16 March 2020): planned interim analysis after 293 IDFS events
- Third data cut (8 July 2020): planned final IDFS analysis after 390 IDFS events
- Fourth data cut (1 April 2021): post hoc interim analysis on overall survival requested by the regulatory authorities
- Fifth data cut (1 July 2022): planned interim analysis of overall survival 2 years after the final IDFS analysis
- Sixth data cut (3 July 2023): planned interim analysis of overall survival 3 years after the final IDFS analysis
- Seventh data cut (15 July 2025): planned final analysis on overall survival after 650 events
- The study is ongoing. The company used the analysis at the seventh data cut (15 July 2025) for the benefit assessment. According to the company, this is the final analysis on overall survival. Patient-reported outcomes were only recorded up to 1 July 2022. For the analysis of patient-reported outcomes (symptoms, health status and health-related quality of life), the company therefore used the 5th data cut (1 July 2022).

Planned duration of follow-up

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

Table 1: Planned duration of follow-up – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy

Study **outcome category** **outcome**	**Planned follow-up**
MONARCH-E	
Mortality	
Overall survival	Until death, maximum 10 years or end of study
Morbidity	
Recurrence[a]	Up to 10 years or end of study
Symptoms (FACIT-Fatigue)	Up to 12 months after end of treatment[b]
Health status (EQ-5D-5L VAS)	Up to 12 months after end of treatment[b]
Health-related quality of life	
FACT-B, FACT-ES	Up to 12 months after end of treatment[b]
Side effects	
AEs, discontinuation due to AEs	Up to 30 days after end of treatment[b]
SAEs	Up to 5 years after the start of the study

a. Presented based on the recurrence rate and disease-free survival, includes the events of local breast cancer recurrence, regional invasive recurrence, distant recurrence, contralateral invasive breast cancer, second primary carcinoma, and death without recurrence.
b. The observed period refers to the end of treatment with any study medication within the first 2 years after the start of the study.

FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; RCT: randomised controlled trial; VAS: visual analogue scale

In the study, only the outcomes of overall survival and recurrence are recorded until the end of the study. The observation periods for the outcomes symptoms, health status, health-related quality of life and side effects are systematically shortened because they were only recorded for the time period of treatment with the study medication in the first two years following the start of the study (plus 30 days or 12 months or 5 years). For these outcomes, data are therefore available only for a shortened observation period, depending on the course of the study. However, to draw a reliable conclusion on the total study period or the time to patient death, it would also be necessary to record these outcomes for the total period, as was done for survival.

Patient characteristics

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

Table 2: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study characteristic category	**Abemaciclib + endocrine therapy N=864**	**Endocrine therapy N=851**
MONARCH-E		
Age [years], mean (SD)	43 (6)	43 (6)
Median [min; max]	44 [23; 57]	44 [24; 59]
Sex [F/M], %	100/0	100/0
Family origin, n (%)		
Asian	286 (34)	267 (32)
White/Caucasian	531 (62)	528 (63)
Other[a]	47 (5)[b]	56 (7)[b]
Region, n (%)		
North America/Europe	404 (47)	388 (46)
Asia	248 (29)	245 (29)
Other	212 (25)	218 (26)
ECOG PS, n (%)		
0	762 (88)	753 (89)
1	102 (12)	98 (12)
Primary tumour size by radiology prior to any systemic treatment, n (%)		
< 20 millimeters	212 (25)	211 (25)
≥ 20 to < 50 mm	420 (49)	420 (49)
≥ 50 millimeters	197 (23)	190 (22)
Missing	35 (4)	30 (4)
Number of positive lymph nodes, n (%)		
0	5 (< 1)	1 (< 1)
1–3	304 (35)	319 (38)
4–9	388 (45)	379 (45)
≥ 10	167 (19)	152 (18)
Histopathological grading at diagnosis, n (%)		
G1 – well differentiated	71 (8)	65 (8)
G2 – moderately differentiated	383 (44)	384 (45)
G3 – poorly differentiated	360 (42)	356 (42)
Gx – cannot be assessed	47 (5)	44 (5)
Missing	3 (< 1)	2 (< 1)
Tumour stage at first diagnosis, n (%)		
Stage IA	1 (< 1)	0 (0)
Stage IIA	88 (10)	90 (11)

Table 2: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study characteristic category	**Abemaciclib + endocrine therapy N=864**	**Endocrine therapy N=851**
Stage IIB	86 (10)	107 (13)
Stage IIIA	380 (44)	341 (40)
Stage IIIB	24 (3)	22 (3)
Stage IIIC	281 (33)	289 (34)
Missing	4 (< 1)	2 (< 1)
Oestrogen receptor status, n (%)		
Positive	858 (99)	849 (100)
Negative	4 (< 1)	2 (< 1)
Unknown	1 (< 1)	0 (0)
Missing	1 (< 1)	0 (0)
Progesterone receptor status, n (%)		
Positive	757 (88)	751 (88)
Negative	73 (8)	71 (8)
Unknown	9 (1)	9 (1)
Missing	25 (3)	20 (2)
HER2 status at time of first diagnosis, n (%)		
Positive	0 (0)	0 (0)
Negative	864 (100)	851 (100)
Prior chemotherapy, n (%)		
Adjuvant chemotherapy	500 (58)	486 (57)
Neoadjuvant chemotherapy	354 (41)	356 (42)
No chemotherapy	10 (1)	9 (1)
Endocrine therapy at baseline, n (%)		
Aromatase inhibitors	234 (27)[c]	212 (25)[c]
Anastrozole	71 (8)	62 (7)
Exemestane	14 (2)	16 (2)
Letrozole	148 (17)	135 (16)
Antioestrogens	630 (73)	630 (73)
Tamoxifen	630 (73)	639 (75)
GnRH analogues	424 (49)	427 (50)
Goserelin	304 (35)	305 (36)
Leuprorelin	146 (17)	135 (16)
Triptorelin	22 (3)	31 (4)
Treatment discontinuation, n (%)[d]	124 (14)[b]	161 (19)[b]
Study discontinuation, n (%)[d]	200 (28)[b]	234 (27)[b]

Table 2: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study characteristic category	Abemaciclib + endocrine therapy N=864	Endocrine therapy N=851

a. Other includes Native American/Native Alaskan, Black/African American, Native Hawaiian or Pacific Islander, multiple and missing data.
b. Institute's calculation.
c. Deviating information in various tables of the company.
d. Common reasons for treatment discontinuation in the intervention arm vs. the comparator arm were the following (percentages refer to randomised patients who received at least one dose of the study medication): AEs (4.9% vs. 0.7%), recurrence (4.5% vs. 10.9%), withdrawal of consent (3.8% vs. 6.0%). The data on the reasons for study discontinuation are incomplete.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; GnRH: gonadotropin-releasing hormone;
HER2: human epidermal growth factor receptor 2; f: female; m: male; n: number of patients in the category; N: number of randomised patients; RCT: randomised controlled trial; SD: standard deviation

The demographic and clinical characteristics of the patients in both treatment arms are comparable.

The median age of the subpopulation of premenopausal patients in the MONARCH-E study analysed by the company was 44 years at study entry. About 3 quarters of the patients had tumour stage III (A–C) at first diagnosis. Almost 60 % of the patients were pretreated with adjuvant chemotherapy and about 40 % with neoadjuvant chemotherapy.

In the intervention arm, patients discontinued treatment less frequently (14% vs. 19%). The most common reasons for treatment discontinuation were recurrences (4.5% vs. 10.9%), withdrawal of consent (3.8% vs. 6.0 %) and AEs (4.9% vs. 0.7%). The number of study discontinuations was nearly balanced between the study arms (28% vs. 27%). Data regarding the reasons for the study discontinuation are still incomplete.

Information on the course of the study

Table 3 shows the median treatment duration of the patients and the median observation period for individual outcomes of the MONARCH-E study.

Table 3: Information on the course of the study – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women)

Study **duration of the study phase** **outcome category /** **outcome**	**Abemaciclib + endocrine therapy** **N=864**	**Endocrine therapy** **N=851**
MONARCH-E		
Duration of treatment[a] with abemaciclib [months]	N=863	N=852
Median [Q1; Q3]	23.7 [23.3; 23.8][b]	–
Duration of treatment[a] with endocrine therapy [months]	N=861	N=852
Median [Q1; Q3]	N D[c]	N D[c]
Observation period [months]		
Overall survival[a, d]		
Median [Q1; Q3]	76.6 [72.5; 82.3]	76.5 [72.3; 83.2]
Morbidity		
Failure of the curative treatment approach[a]		
Median [Q1; Q3]	76.7 [72.6; 82.2]	76.8 [72.5; 83.6]
Symptoms (FACIT-Fatigue)[e]	N=863	N=852
Median [Q1; Q3]	8.3 [7.1; 8.5][b]	8.3 [7.0; 8.5][b]
Health status (EQ-5D VAS)[e]		
Median [Q1; Q3]	8.3 [7.1; 8.5][b]	8.3 [7.0; 8.5][b]
Health-related quality of lifee		
FACT-B		
Median [Q1; Q3]	8.3 [7.1; 8.5][b]	8.3 [7.1; 8.5][b]
FACT-ES		
Median [Q1; Q3]	8.3 [7.1; 8.5][b]	8.3 [7.1; 8.5][b]
Side effects[a, f]		
Median [Q1; Q3]	5.7 [5.6; 5.7][b]	5.7 [5.6; 5.7][b]

a. The information refers to the data cut from 15 July 2025.
b. Institute's calculation from weeks to months.
c. Conclusive information on the median treatment duration is not available. However, the data subsequently submitted show that 687 (87%) of the patients in the intervention arm and 599 (82%) of the patients in the comparator arm received endocrine therapy for ≥ 5 years.
d. The observation period is calculated using a Kaplan-Meier curve in which deceased patients were censored at the time of death, while non-deceased patients were categorised as an event at the end of the observation period.
e. Information refers to the fifth data cut of 01 July 2022.
f. SAEs related to the treatment were followed up for up to 5 years after the start of the study. Data on the observation period of SAEs are not available.

FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomised controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Patients in the intervention arm of the MONARCH-E study were treated with abemaciclib for approximately 2 years. No data are available on the treatment duration with the endocrine therapy for either study arm (see Section 2.1).

In both study arms, the observation period until the data cut of 15 July 2025 is approximately 77 months for both the outcomes overall survival and failure of the curative treatment approach.

The median observation periods for the outcomes symptoms, health-related quality of life (Functional Assessment of Cancer Therapy – Breast [FACT-B], Functional Assessment of Cancer Therapy – Endocrine Symptoms [FACT-ES]), symptoms (Functional Assessment of Chronic Illness Therapy – Fatigue [FACIT-Fatigue]) and health status (EQ-5D VAS) are shortened compared to the outcome overall survival. The median follow-up durations between the study arms are comparable for these outcomes.

For the outcome category side effects, the median observation periods are balanced between the study arms (approx. 6 months in each case), but are also significantly shorter than for the outcome overall survival.

Information on subsequent therapies

Table 4 shows the subsequent therapies patients received after discontinuing the study medication.

Table 4: Information on subsequent antineoplastic therapies (≥ 5% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women)

Study drug class drug	Patients with subsequent therapy, n (%)	
	abemaciclib + endocrine therapy N=864	endocrine therapy N=851
MONARCH-E		
Surgical procedure	31 (4)	43 (5)
Radiotherapy	34 (4)	41 (5)
First subsequent systemic therapy	811 (94)	793 (93)
Endocrine therapy[a]	792 (98)	763 (96)
Anastrozole	88 (11)	74 (9)
Exemestane	33 (4)	43 (5)
Goserelin	143 (18)	132 (17)
Letrozole	172 (21)	170 (21)
Leuprorelin	88 (11)	91 (11)
Tamoxifen	478 (59)	438 (55)
Targeted therapy[a]	8 (1)	38 (5)
Any subsequent systemic therapy	811 (94)	793 (93)
Chemotherapy[a]	64 (8)	96 (12)
Capecitabine	29 (4)	53 (7)
Paclitaxel	26 (3)	45 (6)
Endocrine therapy[a]	798 (98)	771 (97)
Anastrozole	135 (17)	117 (15)
Exemestane	66 (8)	73 (9)
Fulvestrant	49 (6)	76 (10)
Goserelin	190 (23)	180 (23)
Letrozole	275 (34)	279 (35)
Leuprorelin	114 (14)	110 (14)
Tamoxifen	506 (62)	459 (58)
Targeted therapy[a]	78 (10)	139 (18)
Abemaciclib	12 (1)	48 (6)
Ribociclib	29 (4)	51 (6)

a. Percentages for the drug classes and the drugs listed below: Institute's calculation, based on the number of patients with any subsequent systemic therapy.

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomised controlled trial

In the MONARCH-E study, subsequent antineoplastic therapies were permitted without restrictions in both study arms. The proportion of premenopausal patients who received at

least one subsequent systemic therapy was approx. 90% in both study arms, and was thus notably higher than the proportion of patients with recurrence (approx. 18% and 27%, 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. Accordingly, the most common subsequent therapies were endocrine therapies.

According to the S3 Guideline [5], surgery and, if necessary, radiotherapy or systemic treatment (endocrine therapy or chemotherapy) are indicated if local recurrence occurs. Premenopausal women with distant recurrences are recommended to have endocrine-based therapy with a cyclin-dependent kinase (CDK) 4/6 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. 80% of patients with recurrence, see Table 8). In the comparator arm, however, only about half of the patients with distant recurrence received a CDK-4/6 inhibitor as subsequent therapy. This had already been the subject of critical discussion by the parties submitting the comments during the oral hearing [3,4].

This has consequences regarding the interpretability of the results of the outcome overall survival. For further explanations, see Section 2.2.2.1.

Risk of bias across outcomes (study level)

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

Table 5: Risk of bias across outcomes (study level) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women)

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	Absence of other aspects	Risk of bias at study level
			Patients	Treating staff			
MONARCH-E	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 disease-free survival in Appendix A). It is assumed that the censoring was largely due to study discontinuations.

RCT: randomised controlled trial

In the MONARCH-E study, the risk of bias across outcomes was rated as high for both research questions. 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 (see Figure 1 and Figure 2 of the full dossier assessment). Administrative censoring, for example due to data cuts, also played a subordinate role at most. A similar picture regarding censoring can also be seen for the outcome failure of the curative treatment approach (see Figure 3 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 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 Sections 2.2.2.2, 2.2.2.3 and 2.3.2.2 each under outcome-specific risk of bias.

Transferability of the study results to the German health care context

The company described that the results of the MONARCH-E study are transferable to the German health care context. The characteristics of the patients included in the study did not differ notably from the population of early breast cancer patients in the current German health care context with regard to age, Eastern Cooperative Oncology Group Performance Status; GnRH: gonadotropin-releasing hormone (ECOG PS), tumour characteristics and prior therapies.

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

2.2.2 Results on added benefit

2.2.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - failure of the curative treatment approach
  - symptoms, recorded using the FACIT-Fatigue
  - health status, recorded using the EQ-5D VAS
- Health-related quality of life
  - recorded using the FACT-B and the FACT-ES

- Side effects
  - serious adverse events (SAEs)
  - severe adverse events (AEs) (CTCAE grade ≥3)
  - discontinuation due to AEs
  - diarrhoea, Preferred Term (PT) (severe AEs [CTCAE grade ≥ 3])
  - neutropenia, PT (severe AEs [CTCAE grade ≥ 3])
  - other specific AEs, if any

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

Table 6 shows for which outcomes data were available in the included study.

Table 6: Matrix of outcomes – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women)

Study	Outcomes											
	Overall survival	Failure of the curative treatment approach[a]	Symptoms (FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-B)	Health-related quality of life (FACT-ES)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Diarrhoea (PT, severe AEs[b])	Neutropenia (PT, severe AEs[b])	Further specific AEs[d]
MONARCH-E	No[f]	Yes	Yes	Yes	Yes	No[e]	Yes	Yes	Yes	Yes	Yes	Yes

a. Presented based on the recurrence rate and disease-free survival, includes the events: local breast cancer recurrence, regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, second primary carcinoma (no breast cancer), and death.
b. Severe AEs are operationalised as CTCAE grade ≥3.
c. Discontinuation of at least one of the drugs used.
d. The following events (MedDRa coding) were considered: eye disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AE), gastrointestinal disorders (SOC, severe AEs), general disorders and administration site conditions (SOC, severe AEs), hepatobiliary disorders (SOC, severe AEs), examinations (SOC, severe AEs), metabolism and nutrition disorders
(SOC, severe AEs), reproductive system and breast disorders (SOC, severe AEs), respiratory, thoracic and mediastinal disorders (SOC, severe AEs). In the analyses submitted by the company, the PTs were not assigned to the relevant SOCs and were therefore not taken into account
e. No usable data available (for explanation see running text below, Section 2.2.2.1).
f. Data cannot be interpreted (see the following running text, Section 2.2.2.1)

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term, RCT: randomised controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Overall survival

The overall survival of patients in the present therapeutic indication is composed of a phase of DFS until recurrence and the subsequent stage of advanced and/or metastatic breast cancer.

An observed effect in the outcome “overall survival” is not only influenced by the initial study treatment, but also by the subsequent antineoplastic therapies used after disease progression or recurrence [10,11]. In order for an observed effect in the outcome overall survival to be interpreted meaningfully, adequate guideline-compliant subsequent treatment of patients

after progression or recurrence of the disease is therefore necessary, especially in the adjuvant therapy situation.

The guideline recommendations for the advanced therapy stage of breast cancer are decisive for the assessment of the administered subsequent therapies in the MONARCH-E study. According to the S3 guideline [5], patients with advanced or metastatic breast cancer should receive endocrine-based therapy with a CDK-4/6 inhibitor. In the comparator arm of the MONARCH-E study, however, only about half of the patients with distant recurrence received a CDK-4/6 inhibitor as subsequent therapy. This entails a systematic disadvantage for the patients in the comparator arm.

Given the already high risk of bias across outcomes due to numerous informative censorings, the outcome overall survival is considered not interpretable because of this additional potential bias.

Failure of the curative treatment approach

The outcome failure of the curative treatment approach is a composite outcome and includes the components local breast cancer recurrence, regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, second primary carcinoma (no breast cancer), and death. 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.

For the outcome failure of the curative treatment approach, the results of the operationalisations are presented as the proportion of patients with recurrence (hereinafter referred to as “recurrence rate”) and as disease-free survival.

In accordance with the study protocol, events of the outcome failure of the curative treatment approach 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 outcome failure of the curative treatment approach, 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 Sections 2.2.2.2 and 2.3.2.2). At this final data cut, the outcome failure of the curative treatment approach had been observed in the vast majority of patients for a period of just over 6 years (see Table 3). At that time, the duration of adjuvant endocrine therapy of up to 10 years for premenopausal women at high risk of recurrence recommended in the guidelines

[5,6,8,9] had not yet been reached. The 10-year timeframe recommended in the S3-guideline for patient follow-up has also not yet been reached [5]. This means that only part of this period is covered even at the end of the observation period in the Monarch E study despite a comparatively long observation period. Nor do the Kaplan-Meier curves show any sign of a plateau formation for this outcome. This also contributes to the high risk of bias in the results of this outcome.

Notes on the analyses presented by the company on patient-reported outcomes on symptoms, health status and health-related quality of life

The company presented analyses using a mixed-effects model with repeated measures (MMRM) on course of disease and change from baseline for the outcomes on symptoms (FACIT-Fatigue), health status (EQ-5D visual analogue scale) and health-related quality of life (FACT-B, FACT-ES). As already noted in the previous benefit assessment [12], the company provides deviating data in Module 4 of its dossier regarding the number of patients considered in the respective analyses at individual documentation dates: The descriptive tables on response rates, the graphical curves on the course and the tabulated changes from baseline all contain data that differ from one another. No data are available on the total number of patients included in the MMRM analyses. Based on the patient numbers reported for each time point of measurement in the tabulated changes from baseline, it is assumed that a sufficient number of female patients were included in the MMRM analyses. Therefore, the present MMRM analyses of the outcomes on symptoms (FACIT-Fatigue), health status (EQ-5D VAS) and health-related quality of life (FACT-B, FACT-ES) can be used, despite the limitations mentioned.

As the company did not present any responder analyses for the patient-reported outcomes, the MMRM analyses were used for the assessment.

FACT-ES

The company presented analyses of two scales, which it refers to as FACT-ES 19 and FACT-ESS 18.

The FACT-ES is composed of the scales from the FACT-G and the Endocrine Symptom Scale (ESS-19). According to the manual, a total score should be calculated [13]. Instead, the company only presented the results of the ESS-19 subscale. The ESS-18 subscale, which was also submitted, corresponds to the ESS-19 scale shortened by the last question. This form of analysis also does not correspond to the specifications for the analysis of the FACT-ES. . The ESS-19 and the ESS-18 were therefore not used for the benefit assessment. The results for the ESS-19 subscale are presented as supplementary information in the results tables.

2.2.2.2 Risk of bias

Table 7 describes the risk of bias for the results of the relevant outcomes.

Table 7: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (Research question 1: Premenopausal women)

Study		Outcomes											
	Study level	Overall survival	Failure of the curative treatment approach[a]	Symptoms (FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-B)	Health-related quality of life (FACT-ES)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Neutropenia (PT, severe AEs[b])	Diarrhoea (PT, severe AEs[b])	Further specific AEs[d]
MONARCH-E	H	-[e, k]	H[e, f]	H[e, f, g]	H[e, f, g]	H[e, f, g]	-[h]	H[e]	H[e, i]	H[e, f]	H[e, i]	H[e, i]	H[e, j]

a. Presented based on the recurrence rate and disease-free survival, includes the events: local breast cancer recurrence, regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, second primary carcinoma (no breast cancer), and death.
b. Severe AEs are operationalised as CTCAE grade ≥3.
c. Discontinuation of at least one of the drugs used.
d. The following events (MedDRa coding) were considered: eye disorders (SOC, AEs), skin and subcutaneous tissue disorders (SOC, AE), gastrointestinal disorders (SOC, severe AEs), general disorders and administration site conditions (SOC, severe AEs), hepatobiliary disorders (SOC, severe AEs), examinations (SOC, severe AEs), metabolism and nutrition disorders (SOC, severe AEs), reproductive system and breast disorders (SOC, severe AEs), respiratory, thoracic and mediastinal disorders (SOC, severe AEs).
e. High risk of bias across outcomes.
f. Lack of blinding in subjective recording of outcomes.
g. Large proportion of patients not considered in the analysis (> 10%); decrease in the return of questionnaires in the course of the study, and lack of blinding in subjective recording of outcomes.
h. No usable data available (see Section 2.2.2.1).
i. Incomplete observations for potentially informative reasons.
j. Incomplete observations for potentially informative reasons; for non-severe AEs, additionally lack of blinding in subjective recording of outcomes.
k. Data not interpretable (see Section 2.2.2.1).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term, RCT: randomised controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

There was a high risk of bias for the results on all outcomes, as there was already a high risk of bias across outcomes (see Section 2.2.1 on the risk of bias at study level).

The results for the outcome overall survival could not be interpreted due to the high risk of bias. Given the already high risk of bias across outcomes due to numerous informative censorings, a further relevant potential bias arises from the systematic disadvantage of the patients in the comparator arm as a result of inadequate subsequent therapies (see Sections 2.2.1 and 2.2.2.1).

In the results for the outcome failure of the curative treatment approach, there is a high outcome-specific risk of bias due to the unblinded outcome recording by the investigator. Furthermore, the observation period covers only part of the follow-up period (see Section 2.2.2.1).

Furthermore, each of the results on the patient-reported outcomes in the categories symptoms, health status and health-related quality of life are subject to a high risk of bias, due to the lack of blinding in the subjective recording of outcomes, a high proportion of patients not included in the analysis, and a declining response rate to the questionnaires over the course of the study.

There are incomplete observations for potentially informative reasons for the severe/serious adverse event (AE) outcomes, as well as for the non-severe/non-serious specific AE outcomes and the outcome discontinuation due to AEs. For the results on non-severe/non-serious specific AE outcomes and discontinuation due to AEs, another reason for a high risk of bias arises through the open-label study design and the subjective recording of outcomes.

2.2.2.3 Results

Table 8 and Table 9 summarise the results of the comparison of abemaciclib in combination with endocrine therapy against endocrine therapy in premenopausal patients with node-positive, HR-positive, HER2-negative early breast cancer at high risk of recurrence (research question 1). Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves for the time-to-event analyses of the outcomes in the MONARCH-E study are shown in Appendix A.1.1 and Appendix A.2.1 of the full dossier assessment. Results on common AEs can be found in Appendix B.1 of the full dossier assessment.

Table 8: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study **outcome category** **outcome** **timepoint**	**Abemaciclib + endocrine therapy**		**Endocrine therapy**		**Abemaciclib + endocrine therapy vs. endocrine therapy**
	N	**patients with event n (%)**	**N**	**patients with event n (%)**	**RR [95% CI]; p-value[a]**
MONARCH-E[b]					
Mortality					
Supplementary information					
Overall survival	*864*	*72 (8.3)* *median time to event* *NA*	*851*	*101 (11.9)* *median time to event* *NA*	*HR: 0.69 [0.51; 0.93]; 0.014[c]*
Morbidity					
Failure of the curative treatment approach[d]					
Recurrence rate	864	154 (17.8)	851	228 (26.8)	0.67 [0.56; 0.80]; < 0.001
Local breast cancer recurrence	864	9 (1.0)	851	18 (2.1)	–
Regional invasive breast cancer recurrence	864	7 (0.8)	851	9 (1.1)	–
Distant recurrence	864	124 (14.4)	851	182 (21.4)	–
Contralateral invasive breast cancer	864	6 (0.7)	851	11 (1.3)	–
Second primary cancer (non-breast cancer)	864	8 (0.9)	851	9 (1.1)	–
Death	864	2 (0.2)	851	6 (0.7)	–
Disease-free survival[e]	864	154 (17.8) median time to event NA	851	228 (26.8) median time to event NA	HR: 0.61 [0.50; 0.75]; < 0.001[c]
Side effects					
AEs (supplementary information)	863	848 (98.3)	852	756 (88.7)	–
SAEs	863	118 (13.7)	852	77 (9.0)	1.51 [1.15; 1.98]; 0.003
Severe AEs[f]	863	420 (48.7)	852	144 (16.9)	2.88 [2.44; 3.39]; < 0.001

Table 8: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study outcome category outcome timepoint	Abemaciclib + endocrine therapy		Endocrine therapy		Abemaciclib + endocrine therapy vs. endocrine therapy
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
Discontinuation due to AEs	863	101 (11.7)	852	7 (0.8)	14.24 [6.66; 30.46]; < 0.001
Neutropenia (PT, severe AEs[f])	863	66 (7.6)	852	6 (0.7)	10.86 [4.73; 24.91]; < 0.001
Eye disorders (SOC, AE)	863	122 (14.1)	852	61 (7.2)	1.97 [1.47; 2.65]; < 0.001
Skin and subcutaneous tissue disorders (SOC, AE)	863	347 (40.2)	852	189 (22.2)	1.81 [1.56; 2.11]; < 0.001
Gastrointestinal disorders (SOC, severe AEsf)	863	68 (7.9)	852	8 (0.9)	8.39 [4.06; 17.35]; < 0.001
Diarrhoea (PT, severe AEs[f])	863	49 (5.7)	852	3 (0.4)	16.13 [5.05; 51.53]; < 0.001
General disorders and administration site conditions (SOC, severe AEs[f])	863	21 (2.4)	852	8 (0.9)	2.59 [1.15; 5.82]; 0.017
Hepatobiliary disorders (SOC, severe AEsf)	863	11 (1.3)	852	3 (0.4)	3.62 [1.01; 12.93]; 0.035
Investigations (SOC, severe AEs[f])	863	181 (21.0)	852	21 (2.5)	8.51 [5.47; 13.24]; < 0.001
Metabolism and nutrition disorders (SOC, severe AEs[f])	863	19 (2.2)	852	7 (0.8)	2.68 [1.13; 6.34]; 0.020
Reproductive system and breast disorders (SOC, severe AEs[f])	863	7 (0.8)	852	17 (2.0)	0.41 [0.17; 0.98]; 0.039
Respiratory, thoracic and mediastinal disorders (SOC, severe AEs)	863	14 (1.6)	852	3 (0.4)	4.61 [1.33; 15.97]; 0.008

Table 8: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study outcome category outcome timepoint	Abemaciclib + endocrine therapy		Endocrine therapy		Abemaciclib + endocrine therapy vs. endocrine therapy
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
a. Institute's calculation, unconditional exact test (CSZ method according to [14]). b. Data cut: 15 July 2025. c. p-value: log-rank test. No information on the model; presumably unstratified Cox proportional hazards model. d. The individual components are presented in the lines below. The sum of the individual components is greater than the number of events used to calculate the recurrence rate. Therefore, the individual components presumably include all events, rather than just the qualifying ones. e. For individual components, see failure of the curative treatment approach. f. Operationalised as CTCAE grade ≥ 3. AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; PT: Preferred Term; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class					

Table 9: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study outcome category outcome	Abemaciclib + endocrine therapy			Endocrine therapy			Abemaciclib + endocrine therapy vs. endocrine therapy
	N	values at baseline mean (SD)	change mean[a] (SE)	N	values at baseline mean (SD)	change mean[a] (SE)	MD [95% CI]; p-value[a]; SMD [95% CI]
MONARCH-E[b]							
Morbidity							
Symptoms (FACIT-Fatigue)[c]	754	40.7 (9.1)	-0.7 (0.2)	738	40.3 (9.1)	0.5 (0.2)	-1.23 [-1.86; -0.60]; < 0.001; -0.20 [-0.30; -0.10]
Health status (EQ-5D VAS)[d]	757	77.9 (15.2)	2.0 (0.4)	739	78.4 (15.8)	2.5 (0.4)	−0.47 [−1.52; 0.57]; 0.375; -0.05 [-0.15; 0.06]
Health-related quality of life							
FACT-B[e]	770	107.8 (17.7)	-1.5 (0.5)	751	106.4 (18.2)	0.8 (0.5)	-2.34 [-3.60; -1.08]; < 0.001; -0.19 [-0.29; -0.09]
PWB	774	23.5 (4.1)	-0.6 (0.1)	754	23.1 (4.3)	-0.00 (0.1)	−0.55 [−0.87; −0.22]; 0.001; -0.17 [-0.27; -0.07]
SWB	773	22.8 (4.7)	-1.2 (0.1)	754	22.4 (5.0)	-0.9 (0.1)	−0.32 [−0.67; 0.02]; 0.066; -0.09 [-0.19; 0.01]
EWB	774	18.0 (4.1)	0.0 (0.1)	753	18.0 (4.2)	0.1 (0.1)	−0.11 [−0.39; 0.17]; 0.443; -0.04 [-0.14; 0.06]
FWB	773	19.9 (5.2)	0.0 (0.1)	752	19.6 (5.3)	0.6 (0.1)	−0.57 [−0.92; -0.21]; 0.002; -0.16 [-0.26; -0.06]
BCS	771	23.6 (5.8)	0.3 (0.1)	753	23.2 (5.8)	0.9 (0.1)	−0.59 [−0.97; -0.22]; 0.002; -0.16 [-0.26; -0.06]
ESS-19[f] (supplementary information)	772	60.6 (9.3)	-2.9 (0.3)	755	59.6 (9.9)	-1.6 (0.3)	−1.29 [−2.01; -0.57]; 0.001; -0.18 [-0.28; -0.08]

Table 9: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study outcome category outcome	Abemaciclib + endocrine therapy			Endocrine therapy			Abemaciclib + endocrine therapy vs. endocrine therapy
	N	values at baseline mean (SD)	change mean[a] (SE)	N	values at baseline mean (SD)	change mean[a] (SE)	MD [95% CI]; p-value[a]; SMD [95% CI]

a. Mixed-effects model with repeated measures (MMRM) with the variables: value at baseline, treatment, visit, treatment*visit. Although, according to the company, the analysis formally only takes into account all visits at which at least 25% of all patients in both treatment groups have values for the change in score, this does not lead to a loss of data in the present case; no time point is affected. The changes per arm and the effect refer to the entire observation period.
b. Data cut: 01 July 2022.
c. Higher (increasing) values mean fewer symptoms; positive effects indicate an advantage for the intervention (scale range 0 to 52).
d. Higher (increasing) values indicate better health status; positive effects indicate an advantage for the intervention (scale range 0 to 100).
e. Higher (increasing) values indicate better health-related quality of life; positive effects indicate an advantage for the intervention (scale range 0 to 148).
f. Higher (increasing) values indicate better health-related quality of life; positive effects indicate an advantage for the intervention (scale range: 0 to 76).

BCS: Breast Cancer Subscale; CI: confidence interval; ESS: Endocrine Symptom Scale; EWB: emotional well-being; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FWB: functional well-being; MMRM: mixed-effects model with repeated measures; MD: mean difference; N: number of patients at the start of the study It is unclear how many female patients were considered in the effect estimate; PWB: physical well-being; RCT: randomised controlled trial; SD: standard deviation; SE: standard error; SMD: standardised mean difference; SWB: social/family well-being; VAS: visual analogue scale

As described in Section 2.2.1, the risk of bias across outcomes in the MONARCH-E study was assessed as high at study level. On the basis of the available information, at most hints, e.g. of an added benefit, could be derived for all outcomes.

Mortality

Overall survival

The results for the outcome overall survival are not interpretable (for reasons, see Section 2.2.2.1). This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Morbidity

Failure of the curative treatment approach

For the outcome failure of the curative treatment approach, there was a statistically significant effect in favour of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for both recurrence rate and disease-free survival. This results in a hint of an added benefit of abemaciclib in combination with endocrine therapy versus endocrine therapy.

Symptoms, recorded using the FACIT-Fatigue

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcome of symptoms, recorded using the FACIT-Fatigue. However, the 95% confidence interval (CI) of the standardised mean difference is not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effect is relevant. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

No statistically significant difference of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy was shown for the outcome of health status, recorded using the EQ-5D VAS. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life, recorded with the FACT-B

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcome of health-related quality of life, recorded using the FACT-B. However, the 95% CI of the standardised mean difference is not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effect is relevant. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome; an added benefit is therefore not proven.

Side effects

SAEs

A statistically significant difference between treatment groups to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcome SAEs. This

results in a hint of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

Severe AEs (CTCAE ≥ 3)

A statistically significant difference between treatment groups to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcome severe AEs (CTCAE grade ≥3). This results in a hint of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

Discontinuation due to AEs

A statistically significant difference between treatment groups to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcome of discontinuation due to AEs. This results in a hint of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

Specific AEs

Neutropenia (severe AEs), eye disorders (AEs), skin and subcutaneous tissue disorders (AEs), gastrointestinal disorders (severe AEs), diarrhoea (severe AEs), general disorders and administration site conditions (severe AEs), hepatobiliary disorders (severe AEs), examinations (severe AEs), metabolism and nutrition disorders (severe AEs), respiratory, thoracic and mediastinal disorders (severe AEs)

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for each of the outcomes neutropenia (severe AEs), eye disorders (AEs), skin and subcutaneous tissue disorders (AEs), gastrointestinal disorders (severe AEs), diarrhoea (severe AEs), general disorders and administration site conditions (severe AEs), hepatobiliary disorders (severe AEs), examinations (severe AEs), metabolism and nutrition disorders (severe AEs) and respiratory, thoracic and mediastinal disorders (severe AEs). This results in a hint of greater harm from abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for each of these outcomes.

Reproductive system and breast disorders (SOC, severe AEs)

A significant difference in favour of abemaciclib in combination with endocrine therapy was shown for the outcome reproductive system and breast disorders (severe AEs). This results in a hint of lesser harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

2.2.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were to be considered in the benefit assessment:

- age (< 65 years/≥ 65 years)

- severity of the disease (tumour stage IIA versus IIB versus IIIA versus IIIB versus IIIC)

The company did not present any subgroup analyses. This was not appropriate. The data in Module 4A of the dossier [2] provide no indication of any relevant effect modification for the two subgroup characteristics mentioned for the subpopulation presented therein.

2.2.3 Probability and extent of added benefit

Probability and extent of the added benefit for research question 1 (premenopausal women) 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 [15].

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 10).

Determination of the outcome category for the side effects outcomes

It cannot be inferred from the dossier whether the following side effect outcomes are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Discontinuation due to AEs

Information on the severity of the included events is not available for the outcome discontinuation due to AEs. Therefore, the outcome was assigned to the category non-serious/non-severe side effects.

Specific AE outcomes

No information is available on the severity of the events included for the specific AE outcomes eye disorders and skin and subcutaneous tissue disorders. Therefore, the outcome was assigned to the outcome category non-serious/non-severe side effects.

Table 10: Extent of added benefit at outcome level: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Outcome category **outcome**	**Abemaciclib + endocrine therapy vs. endocrine therapy** **median time to event (months) or proportion of events (%) or mean change in the course of the study** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	Results not interpretable	Outcome category: mortality lesser benefit not proven / added benefit not proven
Morbidity		
Failure of the curative treatment approach	17.8% vs. 26.8% RR: 0.67 [0.56; 0.80] p<0.001 probability: hint	Outcome category: serious/severe symptoms / late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: considerable[d]
Disease-free survival	Median: NA vs. NA HR: 0.61 [0.50; 0.75] p<0.001 probability: hint	
Outcomes with shortened observation period		
Morbidity		
Symptoms		
FACIT-Fatigue	-0.7 vs. 0.5 MD: -1.23 [-1.86; -0.60] p<0.001 SMD: -0.20 [-0.30; -0.10][e]	Lesser benefit not proven / added benefit not proven
Health status (EQ-5D VAS)	2.0 vs. 2.5 MWD: -0.47 [-1.52; 0.57]; p=0.375	Lesser benefit not proven / added benefit not proven
Health-related quality of life		
FACT-B (total score)	-1.5 vs. 0.8 MD: -2.34 [-3.60; -1.08] p<0.001 SMD: -0.19 [-0.29; -0.09][e]	Lesser benefit not proven / added benefit not proven

Table 10: Extent of added benefit at outcome level: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Outcome category **outcome**	**Abemaciclib + endocrine therapy vs. endocrine therapy** **median time to event (months) or proportion of events (%) or mean change in the course of the study** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	13.7% vs. 9.0% RR: 1.51 [1.15; 1.98] RR: 0.66 [0.51; 0.87][f] p = 0.003 probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent considerable
Severe AEs	48.7% vs. 16.9% RR: 2.88 [2.44; 3.39] RR: 0.35 [0.29; 0.41][f] p < 0.001 probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5 % greater harm, extent: major
Discontinuation due to AEs	11.7% vs. 0.8% RR: 14.24 [6.66; 30.46] RR: 0.07 [0.03; 0.15][f] p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects $CI_u<0.80$ greater harm, extent: considerable
Neutropenia (PT, severe AEs)	7.6% vs. 0.7% RR: 10.86 [4.73; 24.91] RR: 0.09 [0.04; 0.21][f] p < 0.001 probability: hint	Outcome category: serious/severe side effects $CI_u < 0.75$, risk ≥ 5 % greater harm, extent: major
Eye disorders (SOC, AEs)	14.1% vs. 7.2% RR: 1.97 [1.47; 2.65] RR: 0.51 [0.38; 0.68][f] p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects $CI_u<0.80$ greater harm, extent: considerable
Skin and subcutaneous tissue disorders (SOC, AEs)	40.2% vs. 22.2% RR: 1.81 [1.56; 2.11] RR: 0.55 [0.47; 0.64][f] p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects $CI_u<0.80$ greater harm, extent: considerable

Table 10: Extent of added benefit at outcome level: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Outcome category **outcome**	**Abemaciclib + endocrine therapy vs. endocrine therapy** **median time to event (months) or proportion of events (%) or mean change in the course of the study** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Gastrointestinal disorders (SOC, severe AEs)	7.9% vs. 0.9% RR: 8.39 [4.06; 17.35] RR: 0.12 [0.06; 0.25][f] p < 0.001 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5 % greater harm, extent: major
Diarrhoea (PT, severe AEs)	5.7% vs. 0.4% RR: 16.13 [5.05; 51.53] RR: 0.06 [0.02; 0.20][f] p < 0.001 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5 % greater harm, extent: major
General disorders and administration site conditions (SOC, severe AEs)	2.4% vs. 0.9% RR: 2.59 [1.15; 5.82] RR: 0.39 [0.17; 0.87] p = 0.017 probability: hint	Outcome category: serious/severe side effects 0.75 ≤ CI_u < 0.90 greater harm, extent considerable
Hepatobiliary disorders (SOC, severe AEs)	1.3% vs. 0.4% RR: 3.62 [1.01; 12.93] RR: 0.28 [0.08; 0.99][f] p = 0.035 probability: hint	Outcome category: serious/severe side effects 0.90≤ CI_u <1.00 greater harm, extent: minor
Investigations (SOC, severe AEs)	21.0% vs. 2.5% RR: 8.51 [5.47; 13.24] RR: 0.12 [0.08; 0.18][f] p < 0.001 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5 % greater harm, extent: major
Metabolism and nutrition disorders (SOC, severe AEs)	2.2% vs. 0.8% RR: 2.68 [1.13; 6.34] RR: 0.37 [0.16; 0.88][f] p = 0.020 probability: hint	Outcome category: serious/severe side effects 0.75 ≤ CI_u < 0.90 greater harm, extent considerable
Reproductive system and breast disorders (SOC, severe AEs)	0.8% vs. 2.0% RR: 0.41 [0.17; 0.98] p = 0.039 probability: hint	Outcome category: serious/severe side effects 0.90≤ CI_u <1.00 lesser harm, extent: minor

Table 10: Extent of added benefit at outcome level: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Outcome category **outcome**	**Abemaciclib + endocrine therapy vs. endocrine therapy** **median time to event (months) or proportion of events (%) or mean change in the course of the study** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Respiratory, thoracic and mediastinal disorders (SOC, severe AEs)	1.6% vs. 0.4% RR: 4.61 [1.33; 15.97] RR: 0.22 [0.06; 0.75][f] p = 0.008 probability: hint	Outcome category: serious/severe side effects $0.75 \leq CI_u < 0.90$ greater harm, extent considerable

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. Inadequate subsequent therapy for patients with distant recurrence (see Section 2.2.1).
d. The extent is derived from the result of the recurrence rate.
e. 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.
f. Institute's calculation; reversed direction of effect to enable use of limits to derive the extent of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; HR: hazard ratio; MD: mean difference; NA: not achieved; PT: Preferred Term; RR: relative risk; SMD: standardised mean difference; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

2.2.3.2 Overall conclusion on added benefit

Table 11 summarises the results included in the overall conclusion on the extent of the added benefit.

Table 11: Positive and negative effects from the assessment of abemaciclib + endocrine therapy in comparison with endocrine therapy (research question 1: premenopausal women)

Positive effects	**Negative effects**
Outcomes with observation over the entire study duration	
Morbidity serious/severe symptoms/late complications ▪ failure of the curative treatment approach: hint of an added benefit – extent: considerable	
Outcomes with shortened observation period	
Serious/severe side effects ▪ reproductive system and breast disorders (severe AEs): hint of lesser harm – extent: minor	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: "considerable" ▪ severe AEs: hint of greater harm – extent: major ▪ neutropenia, gastrointestinal disorders, diarrhoea, examinations (severe AEs each): hint of greater harm – extent: major ▪ general disorders and administration site conditions; metabolism and nutrition disorders; respiratory, thoracic and mediastinal disorders (severe AEs each): hint of greater harm – extent: considerable ▪ hepatobiliary disorders (severe AEs): hint of greater harm – extent: minor
	Non-serious/non-severe side effects ▪ discontinuation due to AEs: hint of greater harm – extent: considerable ▪ eye disorders, skin and subcutaneous tissue disorders: hint of greater harm – extent: considerable
AE: adverse event; SAE: serious adverse event	

Overall, there are both positive and negative effects of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy. On the side of the positive effects, there is a hint of an added benefit with the extent of considerable for the outcome failure of the curative treatment approach. Furthermore, there is a hint of minor added benefit for a specific AE.

The negative effects are related exclusively to outcomes of the category of side effects. There are hints of greater harm from abemaciclib with up to major extents, in particular for the overall rate of SAEs, severe AEs and discontinuations due to AEs as well as for several specific AEs.

Overall, the negative effects therefore call into question the positive ones. Hence, there is no hint of added benefit of abemaciclib in combination with endocrine therapy in comparison

with endocrine therapy alone for premenopausal patients with node-positive, HR-positive, HER2-negative early breast cancer at high risk of recurrence; an added benefit is therefore not proven.

The assessment described above deviates from that by the company, which derived an indication of a major added benefit.

2.3 Research question 2: Postmenopausal women

2.3.1 Study characteristics

A detailed description of the MONARCH-E study can be found in dossier assessment A26-17 [1]. Information on the data cuts, the planned duration of follow-up, the risk of bias across outcomes, and the transferability of the study results to the German health care context can be found in Section 2.2.1.

The company presented analyses of a subpopulation of 2748 postmenopausal patients, 1364 of whom were treated with abemaciclib in combination with endocrine therapy and 1384 with endocrine therapy alone.

Table 12 shows the patient characteristics of the included study.

Table 12: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study characteristic category	Abemaciclib + endocrine therapy N=1364	Endocrine therapy N=1384
MONARCH-E		
Age [years], mean (SD)	59 (9)	59 (9)
Median [min; max]	59 [32; 89]	59 [27; 86]
Sex [F/M], %	100/0	100/0
Family origin, n (%)		
Asian	259 (19[a])	251 (18[a])
White/Caucasian	1028 (75[a])	1047 (76[a])
Other[b]	77 (6)[a]	86 (6)[a]
Region, n (%)		
North America/Europe	739 (54)	747 (54)
Asia	209 (15)	207 (15)
Other	416 (31)	430 (31)
ECOG PS, n (%)		
0	1135 (83)	1111 (80)
1	229 (17)	273 (20)
Primary tumour size by radiology prior to any systemic treatment, n (%)		
< 20 millimeters	385 (28)	377 (27)
≥ 20 to < 50 mm	695 (51)	746 (54)
≥ 50 mm	226 (17)	198 (14)
Missing	58 (4)	63 (5)
Number of positive lymph nodes, n (%)		
0	0 (0)	5 (< 1)
1–3	458 (34)	459 (33)
4–9	581 (43)	589 (43)
≥ 10	325 (24)	331 (24)
Histopathological grading at diagnosis, n (%)		
G1 – well differentiated	94 (7)	105 (8)
G2 – moderately differentiated	653 (48)	662 (48)
G3 – poorly differentiated	562 (41)	551 (40)
Gx – cannot be assessed	52 (4)	62 (5)
missing	3 (< 1)	4 (< 1)
Tumour stage at first diagnosis, n (%)		
Stage IA	0 (0)	0 (0)
Stage IIA	119 (9)	124 (9)

Table 12: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study characteristic category	**Abemaciclib + endocrine therapy N=1364**	**Endocrine therapy N=1384**
Stage IIB	160 (12)	147 (11)
Stage IIIA	524 (38)	536 (39)
Stage IIIB	59 (4)	49 (4)
Stage IIIC	500 (37)	526 (38)
Missing	2 (< 1)	2 (< 1)
Oestrogen receptor status, n (%)		
Positive	1356 (99)	1370 (99)
Negative	6 (< 1)	13 (< 1)
Unknown	1 (< 1)	1 (< 1)
Missing	1 (< 1)	0 (0)
Progesterone receptor status, n (%)		
Positive	1154 (85)	1169 (85)
Negative	170 (13)	179 (13)
Unknown	11 (< 1)	10 (< 1)
Missing	29 (2)	26 (2)
HER2 status at time of first diagnosis, n (%)		
Positive	0 (0)	1 (< 1)
Negative	1364 (100)	1383 (100)
Prior chemotherapy, n (%)		
Adjuvant chemotherapy	841 (62)	846 (61)
Neoadjuvant chemotherapy	449 (33)	454 (33)
No chemotherapy	74 (5)	84 (6)
Endocrine therapy at baseline, n (%)		
Aromatase inhibitors	1222 (90)c	1230 (89)c
Anastrozole	443 (33)	471 (34)
Letrozole	778 (57)	760 (55)
Antioestrogens	142 (10)	154 (11)
Tamoxifen	142 (10)	154 (11)
GnRH analogues	26 (2)	29 (2)
Goserelin	20 (2)	25 (2)
Leuprorelin	4 (< 1)	5 (< 1)
Triptorelin	5 (< 1)	1 (< 1)
Treatment discontinuation, n (%)[d]	278 (20)[a]	232 (17)[a]
Study discontinuation, n (%)[d]	413 (30)[a]	430 (31)[a]

Table 12: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study characteristic category	Abemaciclib + endocrine therapy N=1364	Endocrine therapy N=1384

a. Institute's calculation.
b Other includes Native American/Native Alaskan, Black/African American, Native Hawaiian or Pacific Islander, multiple and missing data.
c. Deviating information in various tables of the company.
d. Common reasons for treatment discontinuation in the intervention arm vs. the comparator arm were the following (percentages refer to randomised patients who received at least one dose of the study medication): AEs (6.7% vs. 0.9%), recurrence (5.9% vs. 9.1%), withdrawal of consent (5.9% vs. 5.5%). The data on the reasons for study discontinuation are incomplete.

AE: adverse event; ECOG PS: Eastern Cooperative Oncology Group Performance Status; F: female; GnRH: gonadotropin-releasing hormone; HER2: human epidermal growth factor receptor -2; M: male; n: number of patients in the category; N: number of randomised patients; RCT: randomised controlled trial; SD: standard deviation

The demographic and clinical characteristics of the patients in both treatment arms are comparable.

The median age of the subpopulation of postmenopausal patients in the MONARCH-E study analysed by the company was 59 years at study entry. About 80% of the patients had tumour stage III (A to C) at first diagnosis. The proportion of patients pretreated with adjuvant chemotherapy was approx. 60%, whilst approximately 33% had previously received neoadjuvant chemotherapy.

At the time of the relevant data cut (15 July 2025), the number of patients who discontinued treatment was similar between the study arms (approx. 20% in the intervention arm versus approx. 17% in the comparator arm). The most common reasons for treatment discontinuation were AEs (6.7% vs. 0.9%), recurrences (5.9% vs. 9.1%) and withdrawal of consent (5.9% vs. 5.5%). The number of study discontinuations was nearly balanced between the study arms (30% vs. 31%). Data regarding the reasons for the study discontinuation are still incomplete.

Information on the course of the study

Table 13 shows the median treatment duration of the patients and the median observation period for individual outcomes of the MONARCH-E study.

Table 13: Information on the course of the study – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women)

Study **duration of the study phase** **outcome category /** **outcome**	**Abemaciclib + endocrine therapy N=1364**	**Endocrine therapy N=1384**
MONARCH-E		
Duration of treatment[a] with abemaciclib [months]	N = 1363	
Median [Q1; Q3]	23.6 [10.5; 23.8][b]	–
Duration of treatmenta with endocrine therapy [months]	N=1358	N = 1385
Median [Q1; Q3]	N D[c]	N D[c]
Observation period [months]		
Overall survival[a, d]		
Median [Q1; Q3]	77.3 [72.5; 83.3]	77.6 [72.5; 83.3]
Morbidity		
Failure of the curative treatment approach[a]		
Median [Q1; Q3]	77.1 [72.5; 83.2]	77.4 [72.5; 83.2]
Symptoms (FACIT-Fatigue)e		
Median [Q1; Q3]	8.3 [6.4; 8.5][b]	8.3 [6.9; 8.5][b]
Health status (EQ-5D VAS)[e]		
Median [Q1; Q3]	8.3 [6.8; 8.5][b]	8.3 [6.9; 8.5][b]
Health-related quality of life[e]		
FACT-B		
Median [Q1; Q3]	8.3 [6.8; 8.5][b]	8.3 [7.0; 8.5][b]
FACT-ES		
Median [Q1; Q3]	8.3 [6.9; 8.5][b]	8.3 [7.0; 8.5][b]
Side effects[a, f]		
Median [Q1; Q3]	5.7 [5.6; 5.7][b]	5.7 [5.6; 5.7][b]

a. The information refers to the data cut from 15 July 2025.
b. Institute's conversion from weeks to months.
c. Conclusive information on the median treatment duration is not available. However, the data subsequently submitted show that 1016 (84%) of the patients in the intervention arm and 976 (81%) of the patients in the comparator arm received endocrine therapy for ≥ 5 years.
d. The observation period is calculated using a Kaplan-Meier curve in which deceased patients were censored at the time of death, while non-deceased patients were categorised as an event at the end of the observation period.
e. The information refers to the data cut from 01 July 2022.
f. SAEs related to the treatment were followed up for up to 5 years after the start of the study. Data on the observation period of SAEs are not available.

FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; N: number of analysed patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomised controlled trial; SAE: serious adverse event; VAS: visual analogue scale

Patients in the intervention arm of the MONARCH-E study were treated with abemaciclib for approximately 2 years. No data are available on the treatment duration with the endocrine therapy for either study arm (see Section 2.1).

In both study arms, the observation period until the data cut of 15 July 2025 is approximately 77 months for both the outcomes overall survival and failure of the curative treatment approach.

The median observation periods for the outcomes symptoms, health-related quality of life (FACT-B, FACT-ES), symptoms (FACIT-Fatigue) and health status (EQ-5D VAS) are shortened compared to the outcome overall survival. The median follow-up durations between the study arms are comparable for these outcomes.

For the outcome category side effects, the median observation periods are balanced between the study arms (approx. 6 months in each case), but are also significantly shorter than for the outcome overall survival.

Information on subsequent therapies

Table 14 shows the subsequent therapies patients received after discontinuing the study medication.

Table 14: Information on subsequent antineoplastic therapies (≥ 5% of the patients in ≥ 1 treatment arm) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women)

Study drug class drug	Patients with subsequent therapy, n (%)	
	abemaciclib + endocrine therapy N=1364	endocrine therapy N=1384
MONARCH-E		
Surgery	31 (2.3)	48 (3.5)
Radiotherapy	46 (3.4)	73 (5.3)
First subsequent systemic therapy	1243 (91.1)	1279 (92.4)
Endocrine therapy[a]	1210 (97.3)	1238 (96.8)
Letrozole	660 (53.1)	619 (48.4)
Anastrozole	380 (30.6)	382 (29.9)
Tamoxifen	120 (9.7)	144 (11.3)
Any subsequent systemic therapy	1243 (91.1)	1279 (92.4)
Endocrine therapy[a]	1216 (97.8)	1248 (97.6)
Letrozole	695 (55.9)	653 (51.1)
Anastrozole	399 (32.1)	414 (32.4)
Tamoxifen	150 (12.1)	176 (13.8)
Fulvestrant	89 (7.2)	165 (12.9)
Exemestane	69 (5.6)	99 (7.7)
Chemotherapy[a]	112 (9)	156 (12.2)
Capecitabine	49 (3.9)	75 (5.9)
Targeted therapy[a]	101 (8.1)	201 (15.7)
Palbociclib	31 (2.5)	84 (6.6)
Abemaciclib	11 (< 1)	67 (5.2)

a. Percentages for the drug classes and the drugs listed below: Institute's calculation, based on the number of patients with any subsequent systemic therapy.

n: number of patients with subsequent therapy; N: number of analysed patients; RCT: randomised controlled trial

In the MONARCH-E study, subsequent antineoplastic therapies were permitted without restrictions in both study arms. The proportion of postmenopausal patients who received at least one subsequent systemic therapy was approx. 91% and 92% in both study arms, and was thus notably higher than the proportion of patients with recurrence (approx. 22% and approx. 29%, see also Table 17). 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. Accordingly, the most common subsequent therapies were endocrine therapies.

According to the S3 Guideline [5], surgery and, if necessary, radiotherapy or systemic treatment (endocrine therapy or chemotherapy) are indicated if local recurrence occurs. Postmenopausal women with distant recurrences are recommended to have endocrine-based therapy with a cyclin-dependent kinase (CDK) 4/6 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. 61% or 69% of patients with recurrence, see Table 17). In the comparator arm, however, only about half of the patients with distant recurrence received a CDK-4/6 inhibitor as subsequent therapy. This had already been the subject of critical discussion by the parties submitting the comments during the oral hearing [3,4].

This has consequences regarding the interpretability of the results of the outcome overall survival. For further explanations, see Sections 2.2.2.1 and 2.2.2.2.

2.3.2 Results on added benefit

2.3.2.1 Outcomes included

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

- Mortality
  - overall survival
- Morbidity
  - failure of the curative treatment approach
  - symptoms, recorded using the FACIT-Fatigue
  - health status, recorded with the EQ-5D VAS
- Health-related quality of life
  - recorded using the FACT-B and the FACT-ES
- Side effects
  - SAEs
  - severe AEs (CTCAE grade ≥ 3)
  - discontinuation due to AEs
  - diarrhoea, PT (severe AEs [CTCAE grade ≥ 3])
  - neutropenia, PT (severe AEs [CTCAE grade ≥ 3])
  - other specific AEs, if any

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

Table 15 shows for which outc omes data were available in the included study.

Table 15: Matrix of outcomes – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women)

Study	Outcomes											
	Overall survival	Failure of the curative treatment approach[a]	Symptoms (FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-B)	Health-related quality of life (FACT-ES)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Diarrhoea (PT, severe AEs[b])	Neutropenia (PT, severe AEs[b])	Further specific AEs[d]
MONARCH-E	No[f]	Yes	Yes	Yes	Yes	No[e]	Yes	Yes	Yes	Yes	Yes	Yes

a. Presented based on the recurrence rate and disease-free survival, includes the events of local breast cancer recurrence, regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, second primary carcinoma (no breast cancer), and death without recurrence.
b. Severe AEs are operationalised as CTCAE grade ≥3.
c. Discontinuation of at least one of the drugs used.
d. The following events (MedDRa coding) were considered: skin and subcutaneous tissue disorders (SOC, AE), vascular disorders (SOC, SAE); blood and lymphatic system disorders (SOC, severe AEs), eye disorders (SOC, severe AEs), gastrointestinal disorders (SOC, severe AEs), general disorders and administration site conditions (SOC, severe AEs), infections and infestations (SOC, severe AEs), examinations (SOC, severe AEs), metabolism and nutrition disorders
(SOC, severe AEs), musculoskeletal and connective tissue disorders (SOC, severe AEs), renal and urinary disorders (SOC, severe AEs), respiratory, thoracic and mediastinal disorders (SOC, severe AEs). In the analyses submitted by the company, the PTs were not assigned to the relevant SOCs and were therefore not taken into account
e. No usable data available (for explanation see running text below, Section 2.3.2.1).
f. Data cannot be interpreted (see the following running text and Section 2.2.2.1)

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term, RCT: randomised controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

Detailed information on the outcomes included in the assessment can be found in Section 2.2.2.1. The limitations described there – in particular, the lack of interpretability of the outcome overall survival and the biasing aspects of the outcome failure of the curative treatment approach – also apply to research question 2.

2.3.2.2 Risk of bias

Table 16 describes the risk of bias for the results of the relevant outcomes.

Table 16: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women)

Study	Study level	Outcomes												
		Overall survival	Failure of the curative treatment approach[a]	Symptoms (FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life (FACT-B)	Health-related quality of life (FACT-ES)	SAEs	Severe AEs[b]	Discontinuation due to AEs[c]	Neutropenia (PT, severe AEs[b])	Diarrhoea (PT, severe AEs[b])	Further specific AEs[d]
MONARCH-E	H	-[e, k]	H[e, f]	H[e, f, g]	H[e, f, g]	H[e, f, g]	-[h]	H[e]	H[e, i]	H[e, f]	H[e, i]	H[e, i]	H[e, j]

a. Presented based on the recurrence rate and disease-free survival, includes the events: local breast cancer recurrence, regional invasive breast cancer recurrence, distant recurrence, contralateral invasive breast cancer, second primary carcinoma (no breast cancer), and death.
b. Severe AEs are operationalised as CTCAE grade ≥3.
c. Discontinuation of at least one of the drugs used.
d. The following events (MedDRa coding) were considered: skin and subcutaneous tissue disorders (SOC, AE), vascular disorders (SOC, SAE); blood and lymphatic system disorders (SOC, severe AEs), eye disorders (SOC, severe AEs), gastrointestinal disorders (SOC, severe AEs), general disorders and administration site conditions (SOC, severe AEs), infections and infestations (SOC, severe AEs), examinations (SOC, severe AEs), metabolism and nutrition disorders (SOC, severe AEs), musculoskeletal and connective tissue disorders (SOC, severe AEs), renal and urinary disorders (SOC, severe AEs), respiratory, thoracic and mediastinal disorders (SOC, severe AEs).
e. High risk of bias across outcomes.
f. Lack of blinding in subjective recording of outcomes.
g. Large proportion of patients not considered in the analysis (> 10%); decrease in the return of questionnaires in the course of the study, and lack of blinding in subjective recording of outcomes.
h. No usable data available (see Section 2.2.2.1).
i. Incomplete observations for potentially informative reasons.
j. Except for vascular diseases (SOC, SAE): incomplete observations for potentially informative reasons. For non-severe/non-serious AEs, additionally lack of blinding in subjective recording of outcomes.
k. Data not interpretable (see Section 2.2.2.1).

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; MedDRA: Medical Dictionary for Regulatory Activities; PT: Preferred Term, RCT: randomised controlled trial; SAE: serious adverse event; SOC: System Organ Class; VAS: visual analogue scale

As with the subpopulation of premenopausal women, there was a high risk of bias for the results on all outcomes, as there was already a high risk of bias across outcomes (see Section

2.2.1 on the risk of bias at study level). Detailed information on the risk of bias in the results for the outcome failure of the curative treatment approach, for the patient-reported outcomes in the categories symptoms, health status and health-related quality of life, and for the outcomes in the side effects category can be found in Section 2.2.2.2.

2.3.2.3 Results

Table 17 and Table 18 summarise the results of the comparison of abemaciclib in combination with endocrine therapy against endocrine therapy in postmenopausal patients with node-positive, HR-positive, HER2-negative early breast cancer at high risk of recurrence (research question 2). Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The Kaplan-Meier curves for the time-to-event analyses of the outcomes in the MONARCH-E study are shown in Appendix A.1.2 and Appendix A.2.2 of the full dossier assessment. Results on common AEs can be found in Appendix B.2 of the full dossier assessment.

Table 17: Results (mortality, morbidity. side effects, dichotomous) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study outcome category outcome	Abemaciclib + endocrine therapy		Endocrine therapy		Abemaciclib + endocrine therapy vs. endocrine therapy
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
MONARCH-E[b]					
Mortality					
Supplementary information					
Overall survival	*1364*	*185 (13.6)* *median time to event NA*	*1384*	*220 (15.9)* *median time to event NA*	*HR: 0.87 [0.71; 1.06];* *< 0.155[c]*
Morbidity					
Failure of the curative treatment approach					
Recurrence rate[d]	1364	303 (22.2)	1384	398 (28.8)	0.77 [0.68; 0.88]; <0.001
Local breast cancer recurrence	1364	23 (1.7)	1384	35 (2.5)	–
Regional invasive breast cancer recurrence	1364	22 (1.6)	1384	23 (1.7)	–
Distant recurrence	1364	185 (13.6)	1384	276 (19.9)	–
Contralateral invasive breast cancer	1364	6 (< 1)	1384	9 (< 1)	–
Second primary cancer (non-breast cancer)	1364	32 (2.3)	1384	35 (2.5)	–
Death	1364	43 (3.2)	1384	26 (1.9)	–
Disease-free survival[e]	1364	303 (22.2) Median time to event NA	1384	398 (28.8) Median time to event NA	HR: 0.76 [0.66; 0.89]; < 0.001[c]
Side effects					
AEs (supplementary information)	1363	1339 (98.2)	1385	1237 (89.3)	–
SAEs	1363	233 (17.1)	1385	141 (10.2)	1.68 [1.38; 2.04]; <0.001
Severe AEs[f]	1363	694 (50.9)	1385	254 (18.3)	2.78 [2.46; 3.14]; <0.001
Discontinuation due to AEs	1363	317 (23.3)	1385	18 (1.3)	17.9 [11.2; 28.6]; <0.001

Table 17: Results (mortality, morbidity. side effects, dichotomous) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study outcome category outcome	Abemaciclib + endocrine therapy		Endocrine therapy		Abemaciclib + endocrine therapy vs. endocrine therapy
	N	patients with event n (%)	N	patients with event n (%)	RR [95% CI]; p-value[a]
Skin and subcutaneous tissue disorders (SOC, AEs)	1363	546 (40.1)	1385	327 (23.6)	1.70 [1.51; 1.90]; < 0.001
Vascular diseases (SOC, SAEs)	1363	22 (1.6)	1385	6 (0.4)	3.73 [1.52; 9.16]; 0.002
Blood and lymphatic system disorders (SOC, severe AEs[f])	1363	215 (15.8)	1385	16 (1.2)	13.65 [8.26; 22.57]; < 0.001
Neutropenia (PT, severe AEs[f])	1363	143 (10.5)	1385	4 (< 1)	36.33 [13.49; 97.84]; <0.001
Eye disorders (SOC, severe AEs[f])	1363	15 (1.1)	1385	6 (0.4)	2.54 [0.99; 6.53]; 0.047
Gastrointestinal disorders (SOC, severe AEs[f])	1363	159 (11.7)	1385	21 (1.5)	7.69 [4.91; 12.05]; < 0.001
Diarrhoea (PT, severe AEs[f])	1363	133 (9.8)	1385	2 (< 1)	67.57 [16.76; 272.46]; <0.001
General disorders and administration site conditions (SOC, severe AEs[f])	1363	60 (4.4)	1385	9 (0.6)	6.77 [3.38; 13.60]; < 0.001
Infections and infestations (SOC, severe AEs[f])	1363	77 (5.6)	1385	39 (2.8)	2.01 [1.37; 2.93]; < 0.001
Investigations (SOC, severe AEs[f])	1363	256 (18.8)	1385	33 (2.4)	7.88 [5.53; 11.24]; < 0.001
Metabolism and nutrition disorders (SOC, severe AEs[f])	1363	69 (5.1)	1385	26 (1.9)	2.70 [1.73; 4.21]; < 0.001
Musculoskeletal and connective tissue disorders (SOC, severe AEs[f])	1363	17 (1.2)	1385	38 (2.7)	0.45 [0.26; 0.80]; 0.005
Renal and urinary disorders (SOC, severe AEs[d])	1363	15 (1.1)	1385	4 (0.3)	3.81 [1.27; 11.45]; 0.010

Table 17: Results (mortality, morbidity. side effects, dichotomous) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study **outcome category** **outcome**	**Abemaciclib + endocrine therapy**		**Endocrine therapy**		**Abemaciclib + endocrine therapy vs. endocrine therapy**
	N	**patients with event n (%)**	**N**	**patients with event n (%)**	**RR [95% CI]; p-value[a]**
Respiratory, thoracic and mediastinal disorders (SOC, severe AEs)	1363	27 (2.0)	1385	11 (0.8)	2.49 [1.24; 5.01]; 0.008

a. Institute's calculation, unconditional exact test (CSZ method according to [14]).
b. Data cut: 15 July 2025.
c. p-value: log-rank test. No information on the model; presumably unstratified Cox proportional hazards model.
d. The individual components are presented in the lines below. The sum of the individual components is greater than the number of events used to calculate the recurrence rate. Therefore, the individual components presumably include all events, rather than just the qualifying ones.
e. For individual components, see failure of the curative treatment approach.
f. Operationalised as CTCAE grade ≥3.

AE: adverse event; CI: confidence interval; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; n: number of patients with (at least one) event; N: number of analysed patients; NA: not achieved; PT: Preferred Term; RCT: randomised controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class

Table 18: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (multipage table)

Study outcome category outcome	Abemaciclib + endocrine therapy			Endocrine therapy			Abemaciclib + endocrine therapy vs. endocrine therapy
	N[a]	values at baseline mean (SD)	change mean[a] (SE)	N[a]	values at baseline mean (SD)	change mean[b] (SE)	MD [95% CI]; p-value[b]; SMD [95% CI]
MONARCH-E[c]							
Morbidity							
Symptoms (FACIT-Fatigue)[d]	1144	39.9 (9.6)	-1.0 (0.2)	1169	39.3 (9.7)	0.3 (0.2)	−1.34 [−1.85; −0.84]; < 0.001; -0.22 [-0.3; -0.13]
Health status (EQ-5D VAS)[e]	1159	77.7 (16.6)	-0.1 (0.3)	1188	78.0 (15.2)	1.2 (0.3)	−1.26 [−2.1; −0.43]; 0.003; -0.12 [-0.2; -0.04]
Health-related quality of life							
FACT-B[f]	1173	108.0 (18.4)	-1.9 (0.4)	1209	107.4 (18.0)	-0.2 (0.4)	−1.71 [−2.68; −0.74]; < 0.001; -0.14 [-0.22; -0.06]
PWB	1178	23.3 (4.3)	-0.7 (0.1)	1211	22.9 (4.4)	-0.1 (0.1)	−0.66 [−0.91; −0.41]; < 0.001; -0.21 [-0.29; -0.13]
SWB	1177	22.6 (5.2)	-0.8 (0.1)	1211	22.7 (5.1)	-0.8 (0.1)	−0.05 [−0.34; 0.23]; 0.710; -0.02 [-0.10; 0.07]
EWB	1176	18.5 (4.0)	0.0 (0.1)	1210	18.5 (4.1)	0.0 (0.1)	−0.02 [−0.23; 0.19]; 0.838; -0.01 [-0.09; 0.07]
FWB	1176	19.7 (5.7)	-0.6 (0.1)	1210	19.5 (5.7)	0.0 (0.1)	−0.58 [−0.88; −0.29]; < 0.001; -0.16 [-0.24; -0.08]
BCS	1176	23.9 (5.6)	0.3 (0.1)	1210	23.7 (5.7)	0.6 (0.1)	−0.32 [−0.6; −0.03]; 0.031; -0.09 [-0.17; -0.01]
ESS-19[g] (supplementary information)	1176	63.5 (8.8)	-2.3 (0.2)	1208	62.8 (9.0)	-1.5 (0.2)	−0.81 [−1.30; −0.32]; 0.001; -0.13 [-0.21; -0.05]

Table 18: Results (morbidity, health-related quality of life, continuous) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (multipage table)

Study outcome category outcome	Abemaciclib + endocrine therapy			Endocrine therapy			Abemaciclib + endocrine therapy vs. endocrine therapy
	N[a]	values at baseline mean (SD)	change mean[a] (SE)	N[a]	values at baseline mean (SD)	change mean[b] (SE)	MD [95% CI]; p-value[b]; SMD [95% CI]
a. It is unclear how many patients were included in the effect estimate. a. MMRM with the variables: value at baseline, treatment, visit, treatment*visit. Although, according to the company, the analysis formally only takes into account all visits at which at least 25% of all patients in both treatment groups have values for the change in score, this does not lead to a loss of data in the present case; no time point is affected. The changes per arm and the effect refer to the entire observation period. c. Data cut: 01 July 2022. d. Higher (increasing) values indicate improved symptoms; positive effects indicate an advantage for the intervention (scale range 0 to 52). e. Higher (increasing) values indicate better health status; positive effects indicate an advantage for the intervention (scale range 0 to 100). f. Higher (increasing) values indicate better health-related quality of life; positive effects indicate an advantage for the intervention (scale range: 0 to 148). g. Higher (increasing) values indicate better health-related quality of life; positive effects indicate an advantage for the intervention (scale range: 0 to 76). BCS: Breast Cancer Subscale; CI: confidence interval; ESS: Endocrine Symptom Scale; EWB: emotional well-being; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FWB: functional well-being; MMRM: mixed-effects model with repeated measures; MD: mean difference; N: number of patients at the start of the study; PWB: physical well-being; RCT: randomised controlled trial; SD: standard deviation; SE: standard error; SMD: standardised mean difference; SWB: social/family well-being; VAS: visual analogue scale						

As described in Section 2.2.1, the risk of bias across outcomes in the MONARCH-E study was assessed as high at study level. On the basis of the available information, at most hints, e.g. of an added benefit, could be derived for all outcomes.

Mortality

The results for the outcome overall survival are not interpretable (for reasons, see Section 2.2.2.1). This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Morbidity

Failure of the curative treatment approach

For the outcome failure of the curative treatment approach, there was a statistically significant effect in favour of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for both recurrence rate and disease-free survival. This

results in a hint of an added benefit of abemaciclib in combination with endocrine therapy versus endocrine therapy.

Symptoms, recorded using the FACIT-Fatigue

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcome of symptoms, recorded using the FACIT-Fatigue. However, the 95% CI of the standardised mean difference is not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effect is relevant. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Health status (EQ-5D VAS)

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcome health status, recorded using the EQ-5D VAS. However, the 95% CI of the standardised mean difference is not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effect is relevant. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy; an added benefit is therefore not proven.

Health-related quality of life

Health-related quality of life, recorded with the FACT-B

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcome of health-related quality of life, recorded using the FACT-B. However, the 95% CI of the standardised mean difference is not fully outside the irrelevance range of −0.2 to 0.2. It can therefore not be inferred that the observed effect is relevant. This results in no hint of an added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome; an added benefit is therefore not proven.

Side effects

SAEs

A statistically significant difference between treatment groups to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcome SAEs. This results in a hint of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

Severe AEs (CTCAE ≥ 3)

A statistically significant difference between treatment groups to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcome severe AEs

(CTCAE grade ≥3). This results in a hint of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

Discontinuation due to AEs

A statistically significant difference between treatment groups to the disadvantage of abemaciclib in combination with endocrine therapy was shown for the outcome of discontinuation due to AEs. This results in a hint of greater harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

Specific AEs

Skin and subcutaneous tissue disorders (AEs), vascular disorders (SAEs); blood and lymphatic system disorders (severe AEs), neutropenia (severe AEs), eye disorders (severe AEs), gastrointestinal disorders (severe AEs), diarrhoea (severe AEs), general disorders and administration site conditions (severe AEs), infections and infestations (severe AEs), examinations (severe AEs), metabolism and nutrition disorders (severe AEs), renal and urinary disorders (severe AEs), respiratory, thoracic and mediastinal disorders (severe AEs)

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for each of the outcomes skin and subcutaneous tissue disorders (AEs), vascular disorders (SAEs); blood and lymphatic system disorders (severe AEs), neutropenia (severe AEs), eye disorders (severe AEs), gastrointestinal disorders (severe AEs), diarrhoea (severe AEs), general disorders and administration site conditions (severe AEs), infections and infestations (severe AEs), examinations (severe AEs), metabolism and nutrition disorders (severe AEs), renal and urinary disorders (severe AEs), respiratory, thoracic and mediastinal disorders (severe AEs). This results in a hint of greater harm from abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for each of these outcomes.

Musculoskeletal and connective tissue disorders (severe AEs)

A significant difference in favour of abemaciclib in combination with endocrine therapy was shown for the outcome musculoskeletal and connective tissue disorders (severe AEs). This results in a hint of lesser harm of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for this outcome.

2.3.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were to be considered in the benefit assessment:

- age (< 65 years/≥ 65 years)
- severity of the disease (tumour stage IIA versus IIB versus IIIA versus IIIB versus IIIC)

The company did not present any subgroup analyses. This was not appropriate. The data in Module 4A of the dossier [2] provide no indication of any relevant effect modification for the two subgroup characteristics mentioned for the subpopulation presented therein.

2.3.3 Probability and extent of added benefit

Probability and extent of the added benefit for research question 2 (postmenopausal women) 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 [15].

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.

2.3.3.1 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 2.3.2.3 (see Table 19).

Determination of the outcome category for the side effects outcomes

It cannot be inferred from the dossier whether the following side effect outcomes are serious/severe or non-serious/non-severe. Reasoning is provided for the classification of these outcomes.

Discontinuation due to AEs

Information on the severity of the included events is not available for the outcome discontinuation due to AEs. Therefore, the outcome was assigned to the category non-serious/non-severe side effects.

Specific AE outcomes

No information is available on the severity of the events included for the specific AE outcome skin and subcutaneous tissue disorders. Therefore, these outcomes are assigned to the outcome category of non-serious/non-severe side effects.

Table 19: Extent of added benefit at outcome level: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Outcome category **outcome**	**Abemaciclib + endocrine therapy vs. endocrine therapy** **median time to event (months) or proportion of events (%) or mean change in the course of the study** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Outcomes with observation over the entire study duration		
Mortality		
Overall survival	Results not interpretable	Lesser benefit not proven / added benefit not proven
Morbidity		
Failure of the curative treatment approach	22.2% vs. 28.8% RR: 0.77 [0.68; 0.88] p<0.001 probability: hint	Outcome category: serious/severe symptoms / late complications $0.75 \leq CI_u < 0.90$ added benefit, extent: considerable[c]
Disease-free survival	Median: NA vs. NA HR: 0.76 [0.66; 0.89] p<0.001 probability: hint	
Outcomes with shortened observation period		
Morbidity		
Symptoms		
FACIT-Fatigue	-1.0 vs. 0.3 MWD: -1.34 [-1.85; -0.84] p<0.001 SMD: -0.22 [-0.3; -0.13][d]	Lesser benefit not proven / added benefit not proven
Health status (EQ-5D VAS)	-0.1 vs. 1.2 MWD: -1.26 [-2.1; -0.43] p=0.003 SMD: -0.12 [-0.2; -0.04][d]	Lesser benefit not proven / added benefit not proven
Health-related quality of life		
FACT-B (total score)	-1.9 vs. -0.2 MWD: -1.71 [-2.68; -0.74] p<0.001 SMD: −0.14 [−0.22; −0.06][d]	Lesser benefit not proven / added benefit not proven

Table 19: Extent of added benefit at outcome level: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Outcome category **outcome**	**Abemaciclib + endocrine therapy vs. endocrine therapy** **median time to event (months) or proportion of events (%) or mean change in the course of the study** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Side effects		
SAEs	17.1% vs. 10.2% RR: 1.68 [1.38; 2.04] RR: 0.60 [0.49; 0.72][e] p < 0.001 probability: hint	Outcome category: serious/severe side effects CI_u<0.75, risk ≥5% greater harm, extent: major
Severe AEs	50.9% vs. 18.3% RR: 2.78 [2.46; 3.14] RR: 0.36 [0.32; 0.41][e] p < 0.001 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5 % greater harm, extent: major
Discontinuation due to AEs	23.3% vs. 1.3% RR: 17.9 [11.2; 28.6] RR: 0.06 [0.03; 0.09][e] p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_u<0.80 greater harm, extent: considerable
Skin and subcutaneous tissue disorders (SOC, AE), vascular disorders (SOC, AE)	40.1% vs. 23.6% RR: 1.70 [1.51; 1.90] RR: 0.59 [0.53; 0.66][e] p < 0.001 probability: hint	Outcome category: non-serious/non-severe side effects CI_u<0.80 greater harm, extent: considerable
Vascular diseases (SOC, SAEs)	1.6% vs. 0.4% RR: 3.73 [1.52; 9.16] RR: 0.27 [0.11; 0.66][e] p = 0.002 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk < 5% greater harm, extent: considerable
Blood and lymphatic system disorders (SOC, severe AEs)	15.8% vs. 1.2% RR: 13.65 [8.26; 22.57] RR: 0.07 [0.04; 0.12]e p < 0.001 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5 % greater harm, extent: major

Table 19: Extent of added benefit at outcome level: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Outcome category **outcome**	**Abemaciclib + endocrine therapy vs. endocrine therapy** **median time to event (months) or proportion of events (%) or mean change in the course of the study** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Neutropenia (PT, severe AEs[f])	10.5% vs. < 1% RR: 36.33 [13.49; 97.84] RR: 0.03 [0.01; 0.07]e p < 0.001 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5 % greater harm, extent: major
Eye disorders (SOC, severe AEs)	1.1% vs. 0.4% RR: 2.54 [0.99; 6.53] RR: 0.39 [0.15; 1.01][e] p = 0.047 probability: hint	Outcome category: serious/severe side effects 1 < CI_u; p < 0.05[f] greater harm, extent: minor
Gastrointestinal disorders (SOC, severe AEs)	11.7% vs. 1.5% RR: 7.69 [4.91; 12.05] RR: 0.13 [0.08; 0.20][e] p < 0.001 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5 % greater harm, extent: major
Diarrhoea (PT, severe AEs)	9.8% vs. < 1% RR: 67.57 [16.76; 272.46] RR: 0.01 [0.004; 0.06][e] p < 0.001 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5 % greater harm, extent: major
General disorders and administration site conditions (SOC, severe AEs)	4.4% vs. 0.6% RR: 6.77 [3.38; 13.60] RR: 0.15 [0.07; 0.30][e] p < 0.001 probability: hint	Outcome category: serious/severe side effects CI_u<0.75, risk < 5% greater harm, extent: considerable
Infections and infestations (SOC, severe AEs)	5.6% vs. 2.8% RR: 2.01 [1.37; 2.93] RR: 0.50 [0.34; 0.73][e] p < 0.001 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5 % greater harm, extent: major
Investigations (SOC, severe AEs)	18.8% vs. 2.4% RR: 7.88 [5.53; 11.24] RR: 0.13 [0.09; 0.18][e] p < 0.001 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5 % greater harm, extent: major

Table 19: Extent of added benefit at outcome level: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Outcome category **outcome**	**Abemaciclib + endocrine therapy vs. endocrine therapy** **median time to event (months) or proportion of events (%) or mean change in the course of the study** **effect estimation [95% CI];** **p-value** **probability**[a]	**Derivation of extent**[b]
Metabolism and nutrition disorders (SOC, severe AEs)	5.1% vs. 1.9% RR: 2.70 [1.73; 4.21] RR: 0.37 [0.24; 0.58][e] p < 0.001 probability: hint	Outcome category: serious/severe side effects CI_u < 0.75, risk ≥ 5 % greater harm, extent: major
Musculoskeletal and connective tissue disorders (SOC, severe AEs)	1.2% vs. 2.7% RR: 0.45 [0.26; 0.80] p = 0.005 probability: hint	Outcome category: serious/severe side effects 0.75≤ CI_u <0.90 lesser harm, extent: considerable
Renal and urinary disorders (SOC, severe AEs[d])	1.1% vs. 0.3% RR: 3.81 [1.27; 11.45] RR: 0.26 [0.09; 0.79][e] p = 0.010 probability: hint	Outcome category: serious/severe side effects 0.75≤ CI_u <0.90 greater harm, extent: considerable
Respiratory, thoracic and mediastinal disorders (SOC, severe AEs)	2.0% vs. 0.8% RR: 2.49 [1.24; 5.01] RR: 0.40 [0.20; 0.81][e] p = 0.008 probability: hint	Outcome category: serious/severe side effects 0.75≤ CI_u <0.90 greater harm, extent: considerable

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, the effect size is estimated using different limits based on the upper limit of the confidence interval (CI_u).
c. The extent is derived from the result of the recurrence rate.
d. 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.
e. Institute's calculation; inverse direction of effect to enable use of limits to derive the extent of the added benefit.
f. Discrepancy between CI and p-value. The result of the statistical test (p-value) is decisive for the derivation of the added benefit.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; HR: hazard ratio; MD: mean difference; NA: not achieved; PT: Preferred Term; RR: relative risk; SMD: standardised mean difference; SAE: serious adverse event; SOC: system organ class; VAS: visual analogue scale

2.3.3.2 Overall conclusion on added benefit

Table 20 summarises the results included in the overall conclusion on the extent of the added benefit.

Table 20: Positive and negative effects from the assessment of abemaciclib + endocrine therapy in comparison with endocrine therapy (research question 2: postmenopausal women)

Positive effects	Negative effects
Outcomes with observation over the entire study duration	
Morbidity serious/severe symptoms/late complications ▫ failure of the curative treatment approach: hint of an added benefit – extent: considerable	
Outcomes with shortened observation period	
Serious/severe side effects musculoskeletal and connective tissue disorders (severe AEs): hint of lesser harm – extent: considerable	Serious/severe side effects ▪ SAEs: hint of greater harm – extent: major ▪ severe AEs: hint of greater harm – extent: major ▪ blood and lymphatic system disorders, neutropenia, gastrointestinal disorders, diarrhoea, infections and infestations, examinations, metabolism and nutrition disorders (severe AEs each): hint of greater harm – extent: major ▪ general disorders and administration site conditions; renal and urinary disorders; respiratory, thoracic and mediastinal disorders (severe AEs each), vascular disorders (SAEs): hint of greater harm – extent: considerable ▪ eye disorders (severe AEs): hint of greater harm – extent: minor
	Non-serious/non-severe side effects ▪ discontinuation due to AEs: hint of greater harm – extent: considerable ▪ skin and subcutaneous tissue disorders: hint of greater harm – extent: considerable
AE: adverse event; SAE: serious adverse event	

Overall, there are both positive and negative effects of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy. On the side of the positive effects, there is a hint of an added benefit with the extent of considerable for the outcome failure of the curative treatment approach. Furthermore, there is a hint of considerable added benefit for a specific AE.

The negative effects are related exclusively to outcomes of the category of side effects. There are hints of greater harm from abemaciclib with up to major extents, in particular for the

overall rate of SAEs, severe AEs and discontinuations due to AEs as well as for several specific AEs.

Overall, the negative effects therefore call into question the positive ones. Hence, there is no hint of added benefit of abemaciclib in combination with endocrine therapy in comparison with endocrine therapy for postmenopausal patients with node-positive, HR-positive, HER2-negative early breast cancer at high risk of recurrence; an added benefit is therefore not proven.

The assessment described above differs from that of the company, which derived an indication of considerable added benefit.

3 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of abemaciclib from dossier assessment A26-17.

The following Table 21 shows the result of the benefit assessment of abemaciclib, taking into account dossier assessment A26-17 and this addendum.

Table 21: Abemaciclib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adjuvant treatment of patients with HR-positive, HER2-negative, node-positive early breast cancer at high risk of recurrence			
1	Premenopausal women[b, c, d]	▪ Tamoxifen (accompanied by ovarian function suppression, as appropriate) or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline breast cancer-associated gene [BRCA]1/2 mutations) or ▪ an aromatase inhibitor (anastrozole, letrozole or exemestane) in combination with ovarian function suppression (exemestane only in combination with triptorelin) or ▪ ribociclib in combination with an aromatase inhibitor	Added benefit not proven
2	Postmenopausal women[b, c, e]	▪ An aromatase inhibitor (anastrozole or letrozole) alone; possibly tamoxifen if aromatase inhibitors are unsuitable or ▪ an aromatase inhibitor (anastrozole or exemestane) in sequence after tamoxifen or ▪ olaparib as monotherapy or in combination with endocrine therapy (only for patients with germline breast cancer-associated gene [BRCA]1/2 mutations) or ▪ ribociclib in combination with an aromatase inhibitor	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. According to the Summary of product characteristics (SmPC), the aromatase inhibitor should be combined with an LH-RH agonist in pre- or perimenopausal women.
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.

ACT: appropriate comparator therapy; BRCA: breast cancer-associated gene; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor; LHRH: luteinizing hormone-releasing hormone

The G-BA decides on the added benefit.

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Appendix A Graphic display of the event time analyses presented in the benefit assessment (Kaplan-Meier curves)

A.1 Mortality (presented as supplementary information)

A.1.1 Research question 1: Premenopausal women

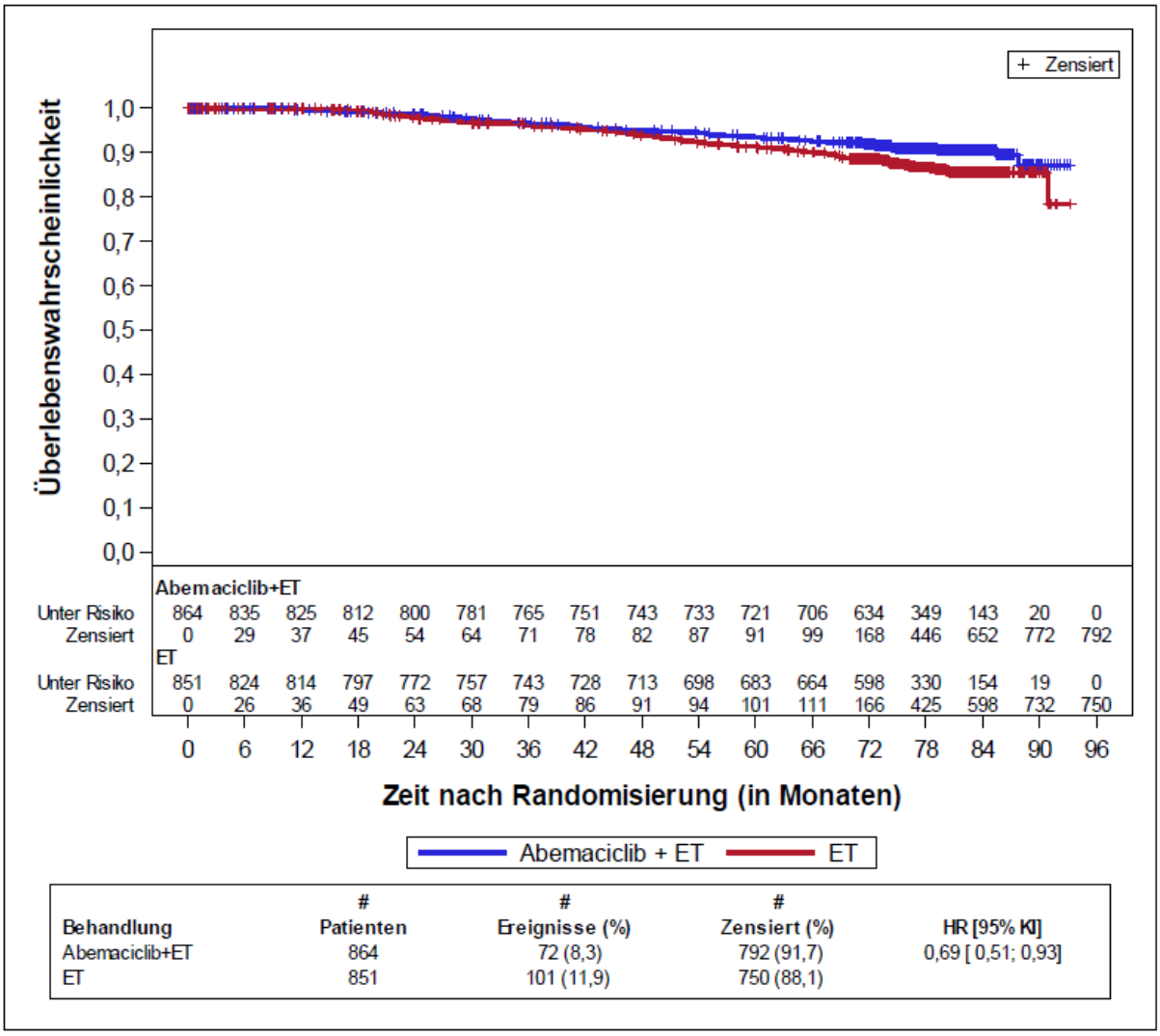


Figure 1: Kaplan-Meier curve, outcome overall survival, research question 1 (presented as supplementary information)

A.1.2 Research question 2: Postmenopausal women

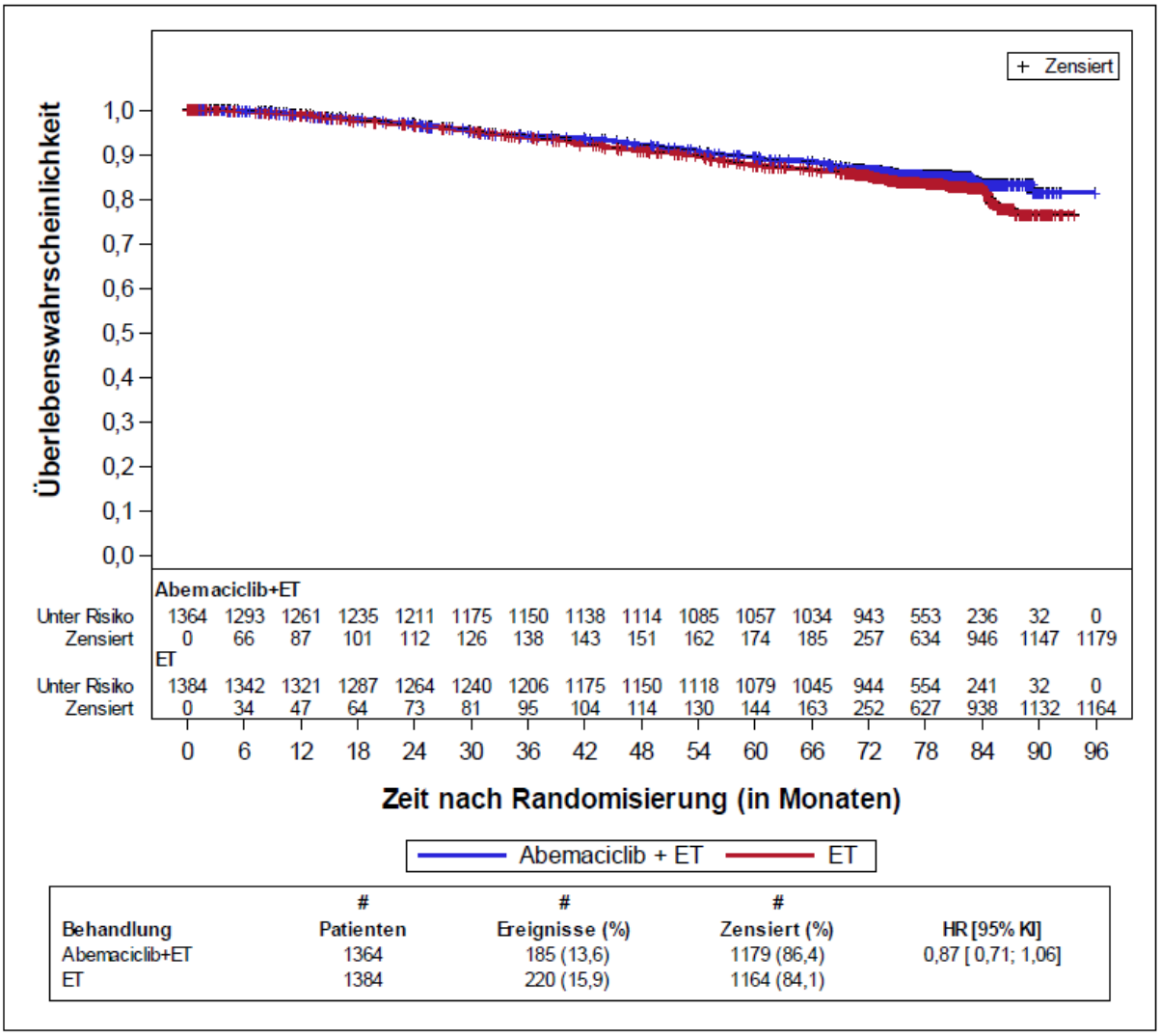
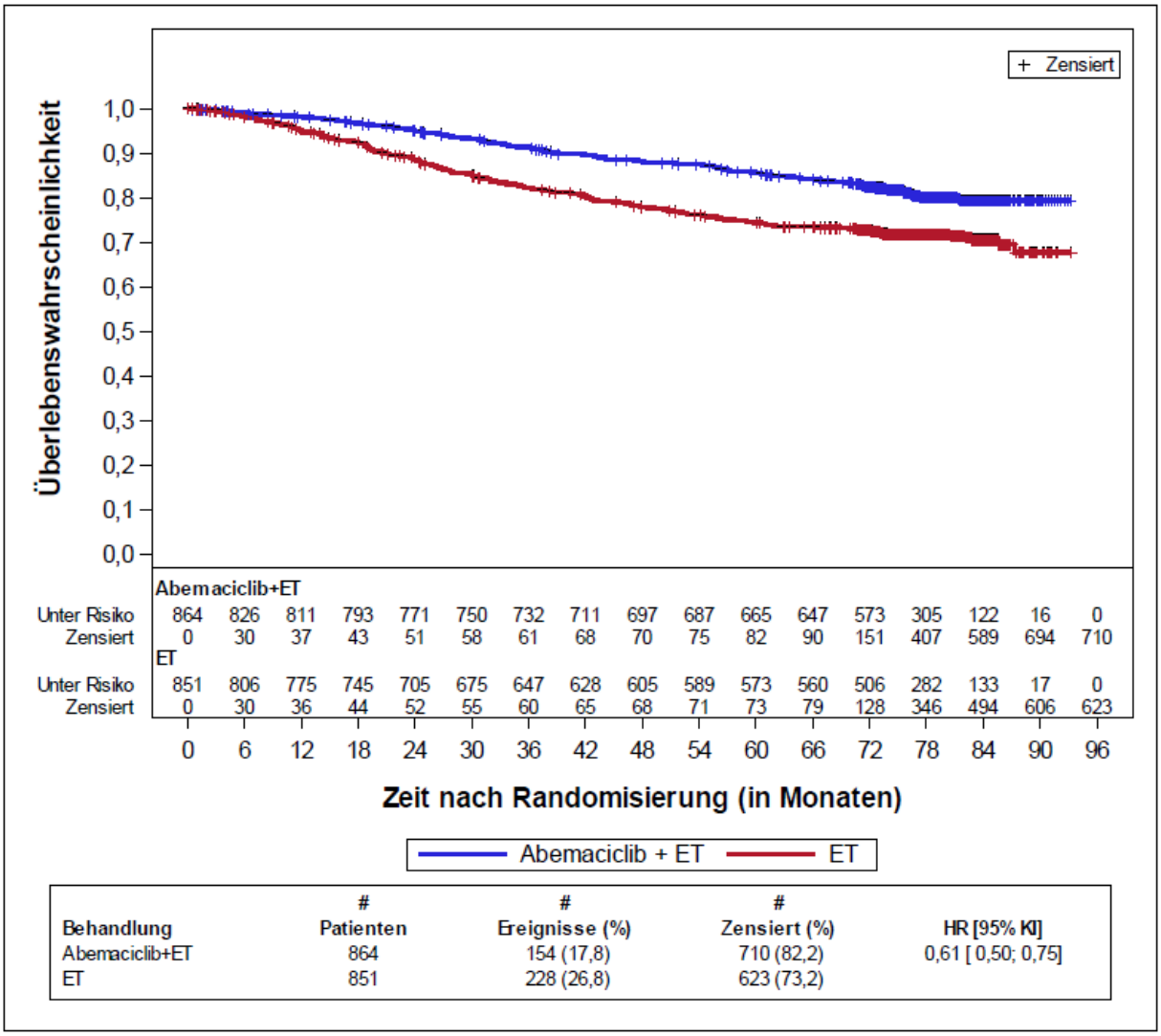


Figure 2: Kaplan-Meier curve, outcome overall survival, research question 2 (presented as supplementary information)

A.2 Morbidity

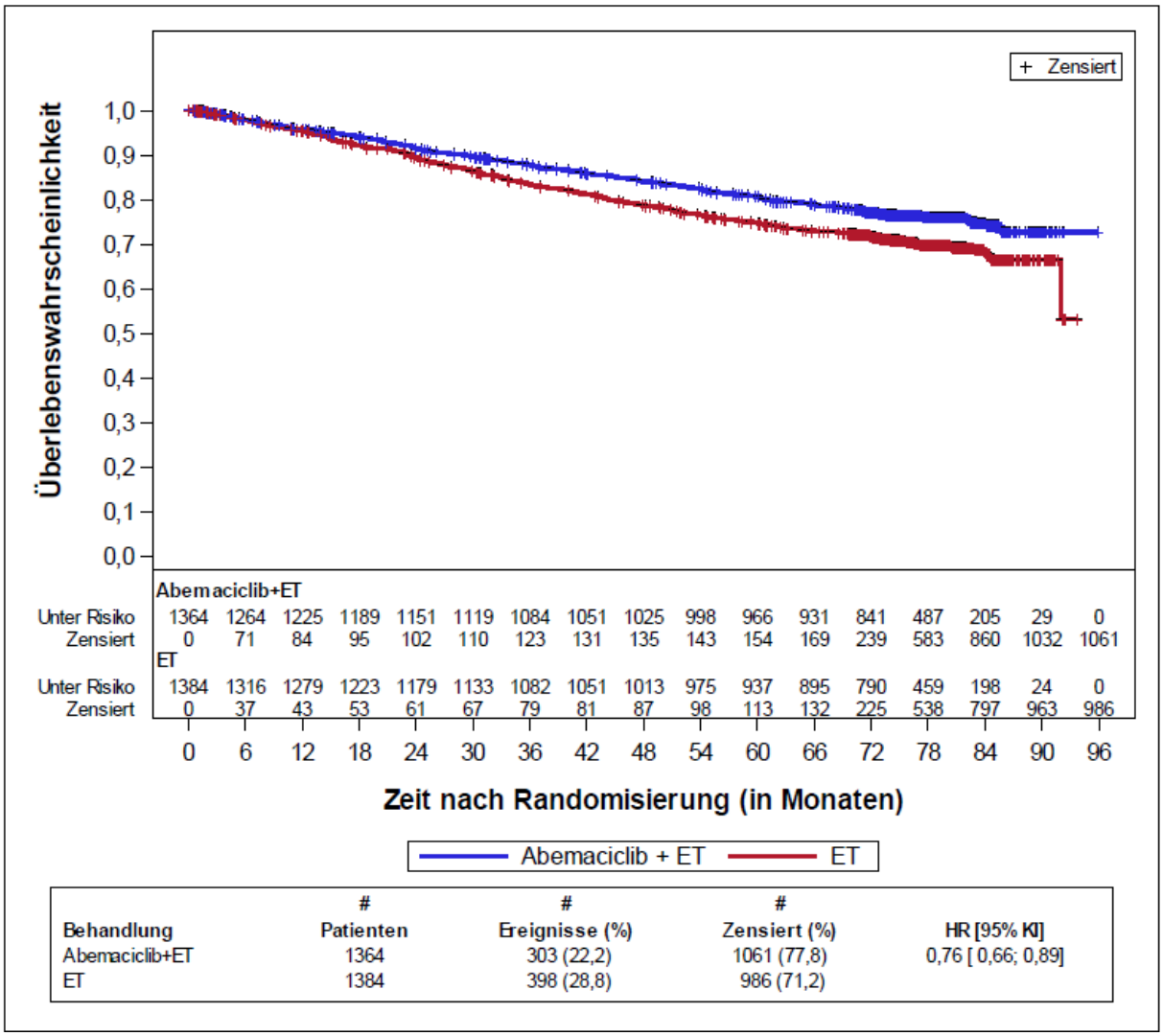
A.2.1 Research question 1: Premenopausal women



Behandlung	# Patienten	# Ereignisse (%)	# Zensiert (%)	HR [95% KI]
Abemaciclib+ET	864	154 (17,8)	710 (82,2)	0,61 [0,50; 0,75]
ET	851	228 (26,8)	623 (73,2)	

Figure 3: Kaplan-Meier curve, outcome disease-free survival, research question 1

A.2.2 Research question 2: Postmenopausal women



Behandlung	# Patienten	# Ereignisse (%)	# Zensiert (%)	HR [95% KI]
Abemaciclib+ET	1364	303 (22,2)	1061 (77,8)	0,76 [0,66; 0,89]
ET	1384	398 (28,8)	986 (71,2)	

Figure 4: Kaplan-Meier curve, outcome disease-free survival, research question 2

Appendix B Results on side effects

For AEs, SAEs and severe AEs (CTCAE grade ≥ 3), the following tables present the proportion of events for System Organ Classes (SOCs) and Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA), each on the basis of the following criteria:

- AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- Severe AEs (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, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

B.1 Research question 1: Premenopausal women

Table 22: Common AEsa – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	abemaciclib + endocrine therapy N=863	endocrine therapy N=852
MONARCH-E		
Overall AE rate	848 (98.3)	756 (88.7)
Blood and lymphatic system disorders	319 (37.0)	93 (10.9)
Cardiac disorders	41 (4.8)	25 (2.9)
Ear and labyrinth disorders	44 (5.1)	40 (4.7)
Endocrine disorders	19 (2.2)	29 (3.4)
Eye disorders	122 (14.1)	61 (7.2)
Gastrointestinal disorders	784 (90.8)	288 (33.8)
General disorders and administration site conditions	485 (56.2)	292 (34.3)
Hepatobiliary disorders	49 (5.7)	29 (3.4)
Immune system disorders	19 (2.2)	19 (2.2)
Infections and infestations	487 (56.4)	357 (41.9)
Injury, poisoning and procedural complications	140 (16.2)	119 (14.0)
Investigations	454 (52.6)	189 (22.2)
Metabolism and nutrition disorders	201 (23.3)	108 (12.7)
Musculoskeletal and connective tissue disorders	430 (49.8)	486 (57.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	21 (2.4)	26 (3.1)
Nervous system disorders	325 (37.7)	265 (31.1)
Psychiatric disorders	201 (23.3)	192 (22.5)
Renal and urinary disorders	68 (7.9)	41 (4.8)
Reproductive system and breast disorders	171 (19.8)	192 (22.5)
Respiratory, thoracic and mediastinal disorders	256 (29.7)	142 (16.7)
Skin and subcutaneous tissue disorders	347 (40.2)	189 (22.2)
Surgical and medical procedures	54 (6.3)	58 (6.8)
Vascular disorders	316 (36.6)	324 (38.0)
Abdominal discomfort	11 (1.3)	6 (0.7)
Abdominal distension	26 (3.0)	11 (1.3)
Abdominal pain	241 (27.9)	49 (5.8)
Abdominal pain upper	113 (13.1)	29 (3.4)

Table 22: Common AEsa – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	abemaciclib + endocrine therapy N=863	endocrine therapy N=852
Alanine aminotransferase increased	100 (11.6)	48 (5.6)
Alopecia	89 (10.3)	17 (2.0)
Anaemia	177 (20.5)	36 (4.2)
Anxiety	41 (4.8)	48 (5.6)
Arthralgia	212 (24.6)	293 (34.4)
Aspartate aminotransferase increased	105 (12.2)	41 (4.8)
Asthenia	88 (10.2)	38 (4.5)
Axillary pain	15 (1.7)	10 (1.2)
Back pain	102 (11.8)	109 (12.8)
Blood alkaline phosphatase increased	29 (3.4)	13 (1.5)
Blood cholesterol increased	20 (2.3)	19 (2.2)
Blood creatinine increased	83 (9.6)	4 (0.5)
Blood lactate dehydrogenase increased	11 (1.3)	3 (0.4)
Bone pain	17 (2.0)	25 (2.9)
Breast oedema	10 (1.2)	1 (0.1)
Breast pain	41 (4.8)	41 (4.8)
Breast reconstruction	12 (1.4)	13 (1.5)
Bronchitis	8 (0.9)	10 (1.2)
COVID-19	13 (1.5)	6 (0.7)
Cellulitis	26 (3.0)	11 (1.3)
Chest discomfort	14 (1.6)	7 (0.8)
Chest pain	15 (1.7)	13 (1.5)
Chills	22 (2.5)	2 (0.2)
Conjunctivitis	17 (2.0)	6 (0.7)
Constipation	113 (13.1)	59 (6.9)
Contusion	15 (1.7)	15 (1.8)
Cough	111 (12.9)	53 (6.2)
Cystitis	26 (3.0)	12 (1.4)
Decreased appetite	81 (9.4)	15 (1.8)
Dental caries	4 (0.5)	11 (1.3)
Depressed mood	11 (1.3)	12 (1.4)
Depression	44 (5.1)	35 (4.1)
Diarrhoea	720 (83.4)	57 (6.7)
Dizziness	87 (10.1)	58 (6.8)

Table 22: Common AEsa – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	abemaciclib + endocrine therapy N=863	endocrine therapy N=852
Dry eye	29 (3.4)	16 (1.9)
Dry mouth	21 (2.4)	6 (0.7)
Dry skin	44 (5.1)	22 (2.6)
Dysgeusia	24 (2.8)	1 (0.1)
Dyspareunia	10 (1.2)	7 (0.8)
Dyspepsia	77 (8.9)	25 (2.9)
Dyspnoea	50 (5.8)	22 (2.6)
Dysuria	15 (1.7)	14 (1.6)
Eczema	7 (0.8)	18 (2.1)
Endometrial hyperplasia	5 (0.6)	11 (1.3)
Epistaxis	12 (1.4)	3 (0.4)
Erythema	17 (2.0)	5 (0.6)
Fall	13 (1.5)	5 (0.6)
Fatigue	243 (28.2)	112 (13.1)
Flatulence	19 (2.2)	2 (0.2)
Gamma-glutamyltransferase increased	34 (3.9)	12 (1.4)
Gastritis	25 (2.9)	10 (1.2)
Gastroenteritis	20 (2.3)	8 (0.9)
Gastrooesophageal reflux disease	27 (3.1)	17 (2.0)
Haemorrhoids	34 (3.9)	13 (1.5)
Headache	182 (21.1)	150 (17.6)
Hepatic steatosis	20 (2.3)	15 (1.8)
Herpes zoster	9 (1.0)	15 (1.8)
Hot flush	157 (18.2)	215 (25.2)
Hypercalcaemia	11 (1.3)	7 (0.8)
Hyperglycaemia	12 (1.4)	18 (2.1)
Hypertension	51 (5.9)	43 (5.0)
Hypertriglyceridaemia	32 (3.7)	15 (1.8)
Hyperuricaemia	12 (1.4)	2 (0.2)
Hypokalaemia	28 (3.2)	7 (0.8)
Hypothyroidism	13 (1.5)	17 (2.0)
Influenza	48 (5.6)	41 (4.8)
Influenza like illness	70 (8.1)	45 (5.3)
Insomnia	92 (10.7)	92 (10.8)

Table 22: Common AEsa – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	abemaciclib + endocrine therapy N=863	endocrine therapy N=852
Irritability[d]	6 (0.7)	12 (1.4)
Lacrimation increased	42 (4.9)	2 (0.2)
Leukopenia	93 (10.8)	19 (2.2)
Libido decreased	13 (1.5)	11 (1.3)
Lymphocyte count decreased	86 (10.0)	27 (3.2)
Lymphoedema	120 (13.9)	89 (10.4)
Lymphopenia	36 (4.2)	17 (2.0)
Malaise	31 (3.6)	12 (1.4)
Mastitis	13 (1.5)	15 (1.8)
Memory impairment	10 (1.2)	13 (1.5)
Migraine	8 (0.9)	10 (1.2)
Mouth ulceration	16 (1.9)	1 (0.1)
Mucosal inflammation	21 (2.4)	9 (1.1)
Muscle spasms	57 (6.6)	38 (4.5)
Musculoskeletal chest pain	27 (3.1)	24 (2.8)
Musculoskeletal pain	8 (0.9)	14 (1.6)
Musculoskeletal stiffness	11 (1.3)	9 (1.1)
Myalgia	68 (7.9)	55 (6.5)
Nail disorder	18 (2.1)	2 (0.2)
Nasal congestion	13 (1.5)	11 (1.3)
Nasopharyngitis	108 (12.5)	73 (8.6)
Nausea	243 (28.2)	78 (9.2)
Neck pain	23 (2.7)	16 (1.9)
Neuropathy peripheral	19 (2.2)	15 (1.8)
Neutropenia	174 (20.2)	30 (3.5)
Neutrophil count decreased	237 (27.5)	46 (5.4)
Night sweats	13 (1.5)	9 (1.1)
Non-cardiac chest pain	11 (1.3)	8 (0.9)
Oedema	14 (1.6)	3 (0.4)
Oedema peripheral	63 (7.3)	44 (5.2)
Onychoclasis	21 (2.4)	5 (0.6)
Oral herpes	10 (1.2)	4 (0.5)
Oropharyngeal pain	48 (5.6)	29 (3.4)
Osteopenia	14 (1.6)	9 (1.1)

Table 22: Common AEsa – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	abemaciclib + endocrine therapy N=863	endocrine therapy N=852
Osteoporosis	19 (2.2)	29 (3.4)
Pain	25 (2.9)	18 (2.1)
Pain in extremity	88 (10.2)	93 (10.9)
Palpitations	15 (1.7)	2 (0.2)
Paraesthesia	12 (1.4)	19 (2.2)
Peripheral sensory neuropathy	17 (2.0)	16 (1.9)
Peripheral swelling	16 (1.9)	16 (1.9)
Pharyngitis	10 (1.2)	12 (1.4)
Platelet count decreased	62 (7.2)	12 (1.4)
Pneumonia	23 (2.7)	12 (1.4)
Pneumonitis	17 (2.0)	3 (0.4)
Procedural pain	30 (3.5)	23 (2.7)
Productive cough	16 (1.9)	6 (0.7)
Pruritus	80 (9.3)	40 (4.7)
Pyrexia	95 (11.0)	47 (5.5)
Radiation pneumonitis	12 (1.4)	9 (1.1)
Rash	71 (8.2)	38 (4.5)
Rash maculo-papular	14 (1.6)	7 (0.8)
Rectal haemorrhage	14 (1.6)	2 (0.2)
Rhinitis allergic	18 (2.1)	15 (1.8)
Rhinorrhoea	14 (1.6)	7 (0.8)
Seasonal allergy	12 (1.4)	7 (0.8)
Sinusitis	34 (3.9)	13 (1.5)
Skin infection	14 (1.6)	9 (1.1)
Spinal pain	6 (0.7)	10 (1.2)
Stomatitis	64 (7.4)	13 (1.5)
Taste disorder	11 (1.3)	2 (0.2)
Thrombocytopenia	31 (3.6)	10 (1.2)
Tinnitus	5 (0.6)	12 (1.4)
Toothache	28 (3.2)	15 (1.8)
Upper respiratory tract infection	103 (11.9)	81 (9.5)
Urinary tract infection	76 (8.8)	42 (4.9)
Urticaria	12 (1.4)	6 (0.7)
Vaginal discharge	13 (1.5)	27 (3.2)

Table 22: Common AEsa – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**abemaciclib + endocrine therapy N=863**	**endocrine therapy N=852**
Vaginal haemorrhage	16 (1.9)	16 (1.9)
Vaginal infection	17 (2.0)	14 (1.6)
Vertigo	25 (2.9)	13 (1.5)
Viral infection	14 (1.6)	9 (1.1)
Vision blurred	14 (1.6)	10 (1.2)
Vitamin D deficiency	11 (1.3)	18 (2.1)
Vomiting	147 (17.0)	37 (4.3)
Vulvovaginal dryness	54 (6.3)	52 (6.1)
Vulvovaginal pruritus	11 (1.3)	9 (1.1)
Weight decreased	24 (2.8)	13 (1.5)
Weight increased	22 (2.5)	21 (2.5)
White blood cell count decreased	239 (27.7)	59 (6.9)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 28.0; SOC and PT notation taken without adaptation from the comments provided by the company.

AE: adverse event; COVID-19: coronavirus disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomised controlled trial; SOC: System Organ Class

Table 23: Common SAEsa – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women)

Study	**Patients with event n (%)**	
SOC[b, c]	**abemaciclib + endocrine therapy N=863**	**endocrine therapy N=852**
MONARCH-E		
Overall SAE rate	118 (13.7)	77 (9.0)
Gastrointestinal disorders	11 (1.3)	2 (0.2)
General disorders and administration site conditions	10 (1.2)	4 (0.5)
Hepatobiliary disorders	10 (1.2)	1 (0.1)
Infections and infestations	39 (4.5)	26 (3.1)
Injury, poisoning and procedural complications	10 (1.2)	8 (0.9)
Reproductive system and breast disorders	8 (0.9)	13 (1.5)
Respiratory, thoracic and mediastinal disorders	12 (1.4)	3 (0.4)

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 28.0; SOC notation taken without adaptation from the comments provided by the company.
c. For SAEs, no MedDRA PTs met the criterion for presentation.

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

Table 24: Common severe AEsa (CTCAE grade ≥3) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	abemaciclib + endocrine therapy N=863	endocrine therapy N=852
MONARCH-E		
Overall rate of severe AEs (CTCAE grade ≥3)	420 (48.7)	144 (16.9)
Blood and lymphatic system disorders	97 (11.2)	15 (1.8)
Gastrointestinal disorders	68 (7.9)	8 (0.9)
General disorders and administration site conditions	21 (2.4)	8 (0.9)
Hepatobiliary disorders	11 (1.3)	3 (0.4)
Infections and infestations	40 (4.6)	26 (3.1)
Injury, poisoning and procedural complications	10 (1.2)	6 (0.7)
Investigations	181 (21.0)	21 (2.5)
Metabolism and nutrition disorders	19 (2.2)	7 (0.8)
Musculoskeletal and connective tissue disorders	7 (0.8)	12 (1.4)
Nervous system disorders	12 (1.4)	10 (1.2)
Reproductive system and breast disorders	7 (0.8)	17 (2.0)
Respiratory, thoracic and mediastinal disorders	14 (1.6)	3 (0.4)
Surgical and medical procedures	12 (1.4)	11 (1.3)
Vascular disorders	14 (1.6)	17 (2.0)
Abdominal pain	10 (1.2)	1 (0.1)
Alanine aminotransferase increased	23 (2.7)	7 (0.8)
Aspartate aminotransferase increased	18 (2.1)	6 (0.7)
Diarrhoea	49 (5.7)	3 (0.4)
Fatigue	11 (1.3)	0 (0)
Gamma-glutamyltransferase increased	13 (1.5)	1 (0.1)
Hypertension	10 (1.2)	11 (1.3)
Hypertriglyceridaemia	11 (1.3)	3 (0.4)
Leukopenia	22 (2.5)	0 (0)
Lymphocyte count decreased	38 (4.4)	2 (0.2)
Lymphopenia	12 (1.4)	3 (0.4)
Neutropenia	66 (7.6)	6 (0.7)
Neutrophil count decreased	96 (11.1)	8 (0.9)
White blood cell count decreased	74 (8.6)	6 (0.7)

Table 24: Common severe AEsa (CTCAE grade ≥3) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women) multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	abemaciclib + endocrine therapy N=863	endocrine therapy N=852

a. Events that occurred in ≥ 10 patients in at least one study arm.
b. MedDRA version 28.0; SOC and PT notation taken without adaptation from the comments provided by the company.

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: randomised controlled trial; SOC: System Organ Class

Table 25: Discontinuation due to AEsa – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women)

Study	Patients with event n (%)	
SOC[b] PT[b]	abemaciclib + endocrine therapy N=863	endocrine therapy N=852
MONARCH-E		
Overall rate of discontinuations due to AEs	101 (11.7)	7 (0.8)
Gastrointestinal disorders	38 (4.4)	0 (0)
Diarrhoea	28 (3.2)	0 (0)
Abdominal pain	3 (0.3)	0 (0)
Nausea	2 (0.2)	0 (0)
Investigations	12 (1.4)	0 (0)
Alanine aminotransferase increased	5 (0.6)	0 (0)
Aspartate aminotransferase increased	3 (0.3)	0 (0)
Blood creatinine increased	2 (0.2)	0 (0)
Gamma-glutamyltransferase increased	2 (0.2)	0 (0)
Blood and lymphatic system disorders	12 (1.4)	0 (0)
Neutropenia	7 (0.8)	0 (0)
Leukopenia	3 (0.3)	0 (0)
General disorders and administration site conditions	8 (0.9)	0 (0)
Fatigue	6 (0.7)	0 (0)
Respiratory, thoracic and mediastinal disorders	7 (0.8)	0 (0)
Interstitial lung disease	2 (0.2)	0 (0)
Pneumonitis	2 (0.2)	0 (0)
Pulmonary embolism	2 (0.2)	0 (0)
Infections and infestations	5 (0.6)	1 (0.1)
Psychiatric disorders	5 (0.6)	2 (0.2)
Anxiety	2 (0.2)	0 (0)
Depression	2 (0.2)	1 (0.1)
Skin and subcutaneous tissue disorders	4 (0.5)	0 (0)
Nervous system disorders	3 (0.3)	1 (0.1)
Cerebral venous thrombosis	2 (0.2)	0 (0)
Vascular disorders	2 (0.2)	2 (0.2)

a. Events that occurred in ≥ 2 patients in at least one study arm.
b. MedDRA version 28.0; SOC and PT notation taken without adaptation from the comments provided by the company.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomised controlled trial; SOC: System Organ Class

B.2 Research question 2: Postmenopausal women

Table 26: Common AEsa – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	abemaciclib + endocrine therapy N=1363	endocrine therapy N=1385
MONARCH-E		
Overall AE rate	1339 (98.2)	1237 (89.3)
Blood and lymphatic system disorders	621 (45.6)	122 (8.8)
Cardiac disorders	99 (7.3)	68 (4.9)
Ear and labyrinth disorders	57 (4.2)	64 (4.6)
Endocrine disorders	26 (1.9)	35 (2.5)
Eye disorders	214 (15.7)	76 (5.5)
Gastrointestinal disorders	1215 (89.1)	481 (34.7)
General disorders and administration site conditions	770 (56.5)	480 (34.7)
Hepatobiliary disorders	65 (4.8)	61 (4.4)
Immune system disorders	31 (2.3)	34 (2.5)
Infections and infestations	657 (48.2)	523 (37.8)
Injury, poisoning and procedural complications	242 (17.8)	216 (15.6)
Investigations	662 (48.6)	314 (22.7)
Metabolism and nutrition disorders	386 (28.3)	236 (17.0)
Musculoskeletal and connective tissue disorders	688 (50.5)	854 (61.7)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	42 (3.1)	42 (3.0)
Nervous system disorders	546 (40.1)	410 (29.6)
Psychiatric disorders	231 (16.9)	260 (18.8)
Renal and urinary disorders	113 (8.3)	78 (5.6)
Reproductive system and breast disorders	142 (10.4)	197 (14.2)
Respiratory, thoracic and mediastinal disorders	409 (30.0)	286 (20.6)
Skin and subcutaneous tissue disorders	546 (40.1)	327 (23.6)
Surgical and medical procedures	78 (5.7)	87 (6.3)
Vascular disorders	436 (32.0)	441 (31.8)
Abdominal discomfort	21 (1.5)	7 (0.5)
Abdominal distension	38 (2.8)	15 (1.1)
Abdominal pain	335 (24.6)	75 (5.4)
Abdominal pain upper	130 (9.5)	51 (3.7)
Alanine aminotransferase increased	168 (12.3)	79 (5.7)
Alopecia	159 (11.7)	43 (3.1)
Anaemia	348 (25.5)	51 (3.7)

Table 26: Common AEsa – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**abemaciclib + endocrine therapy N=1363**	**endocrine therapy N=1385**
Anxiety	43 (3.2)	64 (4.6)
Arthralgia	384 (28.2)	585 (42.2)
Arthritis	12 (0.9)	25 (1.8)
Aspartate aminotransferase increased	157 (11.5)	73 (5.3)
Asthenia	155 (11.4)	80 (5.8)
Axillary pain	24 (1.8)	23 (1.7)
Back pain	125 (9.2)	169 (12.2)
Blood alkaline phosphatase increased	65 (4.8)	42 (3.0)
Blood bilirubin increased	18 (1.3)	10 (0.7)
Blood cholesterol increased	16 (1.2)	27 (1.9)
Blood creatinine increased	162 (11.9)	19 (1.4)
Bone pain	41 (3.0)	58 (4.2)
Breast pain	48 (3.5)	67 (4.8)
Bronchitis	26 (1.9)	33 (2.4)
COVID-19	38 (2.8)	10 (0.7)
Cataract	28 (2.1)	11 (0.8)
Cellulitis	31 (2.3)	21 (1.5)
Chest pain	30 (2.2)	29 (2.1)
Chills	20 (1.5)	14 (1.0)
Conjunctivitis	22 (1.6)	13 (0.9)
Constipation	166 (12.2)	83 (6.0)
Contusion	21 (1.5)	19 (1.4)
Cough	206 (15.1)	126 (9.1)
Cystitis	38 (2.8)	35 (2.5)
Decreased appetite	175 (12.8)	47 (3.4)
Deep vein thrombosis	31 (2.3)	5 (0.4)
Dehydration	26 (1.9)	5 (0.4)
Depression	60 (4.4)	58 (4.2)
Dermatitis	20 (1.5)	8 (0.6)
Diarrhoea	1126 (82.6)	133 (9.6)
Dizziness	148 (10.9)	99 (7.1)
Dry eye	41 (3.0)	12 (0.9)
Dry mouth	55 (4.0)	21 (1.5)
Dry skin	54 (4.0)	29 (2.1)

Table 26: Common AEsa – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**abemaciclib + endocrine therapy N=1363**	**endocrine therapy N=1385**
Dysgeusia	63 (4.6)	6 (0.4)
Dyspepsia	100 (7.3)	39 (2.8)
Dyspnoea	101 (7.4)	62 (4.5)
Exertional dyspnoea	14 (1.0)	10 (0.7)
Dysuria	26 (1.9)	15 (1.1)
Eczema	14 (1.0)	16 (1.2)
Epistaxis	24 (1.8)	3 (0.2)
Erythema	17 (1.2)	17 (1.2)
Fall	48 (3.5)	34 (2.5)
Fatigue	426 (31.3)	181 (13.1)
Flatulence	44 (3.2)	9 (0.6)
Gamma-glutamyltransferase increased	45 (3.3)	17 (1.2)
Gastritis	33 (2.4)	25 (1.8)
Gastroenteritis	22 (1.6)	15 (1.1)
Gastrointestinal pain	17 (1.2)	1 (0.1)
Gastrooesophageal reflux disease	45 (3.3)	30 (2.2)
Haemorrhoids	32 (2.3)	15 (1.1)
Headache	243 (17.8)	175 (12.6)
Hepatic steatosis	24 (1.8)	22 (1.6)
Herpes zoster	25 (1.8)	27 (1.9)
Hot flush	171 (12.5)	261 (18.8)
Hypercalcaemia	27 (2.0)	19 (1.4)
Hypercholesterolaemia	15 (1.1)	26 (1.9)
Hyperglycaemia	20 (1.5)	33 (2.4)
Hyperhidrosis	19 (1.4)	28 (2.0)
Hyperkalaemia	14 (1.0)	10 (0.7)
Hypertension	62 (4.5)	84 (6.1)
Hypertriglyceridaemia	27 (2.0)	29 (2.1)
Hyperuricaemia	20 (1.5)	10 (0.7)
Hypoalbuminaemia	16 (1.2)	8 (0.6)
Hypokalaemia	62 (4.5)	17 (1.2)
Hyponatraemia	20 (1.5)	10 (0.7)
Hypotension	26 (1.9)	9 (0.6)
Hypothyroidism	17 (1.2)	22 (1.6)

Table 26: Common AEsa – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	abemaciclib + endocrine therapy N=1363	endocrine therapy N=1385
Influenza	50 (3.7)	49 (3.5)
Influenza like illness	61 (4.5)	48 (3.5)
Insomnia	108 (7.9)	117 (8.4)
Joint stiffness	15 (1.1)	36 (2.6)
Lacrimation increased	80 (5.9)	6 (0.4)
Leukopenia	197 (14.5)	25 (1.8)
Lymphocyte count decreased	119 (8.7)	28 (2.0)
Lymphoedema	165 (12.1)	122 (8.8)
Lymphopenia	71 (5.2)	12 (0.9)
Malaise	36 (2.6)	14 (1.0)
Mastitis	12 (0.9)	20 (1.4)
Memory impairment	21 (1.5)	13 (0.9)
Mouth ulceration	14 (1.0)	3 (0.2)
Mucosal inflammation	42 (3.1)	11 (0.8)
Muscle spasms	80 (5.9)	67 (4.8)
Muscular weakness	21 (1.5)	10 (0.7)
Musculoskeletal chest pain	41 (3.0)	36 (2.6)
Musculoskeletal pain	13 (1.0)	16 (1.2)
Musculoskeletal stiffness	18 (1.3)	22 (1.6)
Myalgia	84 (6.2)	99 (7.1)
Nail disorder	25 (1.8)	2 (0.1)
Nasal congestion	21 (1.5)	15 (1.1)
Nasopharyngitis	113 (8.3)	96 (6.9)
Nausea	419 (30.7)	119 (8.6)
Neck pain	28 (2.1)	36 (2.6)
Neuropathy peripheral	42 (3.1)	46 (3.3)
Neutropenia	311 (22.8)	31 (2.2)
Neutrophil count decreased	298 (21.9)	25 (1.8)
Night sweats	11 (0.8)	18 (1.3)
Non-cardiac chest pain	14 (1.0)	13 (0.9)
Oedema	18 (1.3)	10 (0.7)
Oedema peripheral	102 (7.5)	63 (4.5)
Onychoclasis	23 (1.7)	3 (0.2)
Oral herpes	18 (1.3)	7 (0.5)

Table 26: Common AEsa – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**abemaciclib + endocrine therapy N=1363**	**endocrine therapy N=1385**
Oropharyngeal pain	53 (3.9)	39 (2.8)
Osteoarthritis	17 (1.2)	29 (2.1)
Osteopenia	25 (1.8)	29 (2.1)
Osteoporosis	31 (2.3)	50 (3.6)
Pain	32 (2.3)	34 (2.5)
Pain in extremity	139 (10.2)	160 (11.6)
Palpitations	32 (2.3)	15 (1.1)
Paraesthesia	38 (2.8)	39 (2.8)
Paronychia	15 (1.1)	4 (0.3)
Peripheral sensory neuropathy	17 (1.2)	14 (1.0)
Peripheral swelling	32 (2.3)	25 (1.8)
Pharyngitis	10 (0.7)	15 (1.1)
Platelet count decreased	121 (8.9)	9 (0.6)
Pneumonia	34 (2.5)	20 (1.4)
Pneumonitis	21 (1.5)	4 (0.3)
Procedural pain	40 (2.9)	30 (2.2)
Productive cough	22 (1.6)	16 (1.2)
Pruritus	117 (8.6)	63 (4.5)
Pyrexia	109 (8.0)	56 (4.0)
Rash	125 (9.2)	44 (3.2)
Rash maculo-papular	22 (1.6)	5 (0.4)
respiratory tract infection	16 (1.2)	10 (0.7)
Rhinitis allergic	24 (1.8)	26 (1.9)
Sciatica	13 (1.0)	17 (1.2)
Seroma	20 (1.5)	7 (0.5)
Sinusitis	33 (2.4)	36 (2.6)
Skin infection	13 (1.0)	16 (1.2)
Stomatitis	70 (5.1)	12 (0.9)
Superficial vein thrombosis	14 (1.0)	1 (0.1)
Syncope	15 (1.1)	11 (0.8)
Taste disorder	23 (1.7)	2 (0.1)
Tendonitis	12 (0.9)	22 (1.6)
Thrombocytopenia	90 (6.6)	9 (0.6)
Tooth extraction	10 (0.7)	14 (1.0)

Table 26: Common AEsa – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	abemaciclib + endocrine therapy N=1363	endocrine therapy N=1385
Toothache	19 (1.4)	20 (1.4)
Tremor	18 (1.3)	8 (0.6)
Trigger finger	14 (1.0)	19 (1.4)
Upper respiratory tract infection	116 (8.5)	102 (7.4)
Urinary incontinence	7 (0.5)	14 (1.0)
Urinary tract infection	130 (9.5)	79 (5.7)
Vaginal haemorrhage	5 (0.4)	14 (1.0)
Vertigo	41 (3.0)	30 (2.2)
Viral infection	15 (1.1)	2 (0.1)
Vision blurred	33 (2.4)	14 (1.0)
Vitamin B12 deficiency	16 (1.2)	4 (0.3)
Vitamin D deficiency	17 (1.2)	16 (1.2)
Vomiting	245 (18.0)	68 (4.9)
Vulvovaginal dryness	32 (2.3)	44 (3.2)
Weight decreased	60 (4.4)	20 (1.4)
Weight increased	25 (1.8)	37 (2.7)
White blood cell count decreased	304 (22.3)	55 (4.0)

a. Events that occurred in ≥ 1% of patients in at least one study arm.
b. MedDRA version 28.0; SOC and PT notation taken without adaptation from the comments provided by the company.

AE: adverse event; COVID-19: coronavirus disease 2019; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomised controlled trial; SOC: System Organ Class

Table 27: Common SAEsa – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**abemaciclib + endocrine therapy N=1363**	**endocrine therapy N=1385**
MONARCH-E		
Overall SAE rate	233 (17.1)	141 (10.2)
Blood and lymphatic system disorders	14 (1.0)	2 (0.1)
Cardiac disorders	18 (1.3)	9 (0.6)
Gastrointestinal disorders	33 (2.4)	15 (1.1)
Infections and infestations	76 (5.6)	38 (2.7)
Injury, poisoning and procedural complications	21 (1.5)	19 (1.4)
Nervous system disorders	17 (1.2)	15 (1.1)
Respiratory, thoracic and mediastinal disorders	20 (1.5)	8 (0.6)
Vascular disorders	22 (1.6)	6 (0.4)
Deep vein thrombosis	15 (1.1)	2 (0.1)
Pneumonia	15 (1.1)	8 (0.6)

a. Events which occurred in ≥ 1% of patients in at least 1 study arm.
b. MedDRA version 28.0; SOC and PT notation taken without adaptation from the comments provided by the company.

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

Table 28: Common severe AEsa (CTCAE grade ≥3) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study	Patients with event n (%)	
SOC[b] PT[b]	abemaciclib + endocrine therapy N=1363	endocrine therapy N=1385
MONARCH-E		
Overall rate of severe AEs (CTCAE grade ≥3)	694 (50.9)	254 (18.3)
Blood and lymphatic system disorders	215 (15.8)	16 (1.2)
Cardiac disorders	15 (1.1)	12 (0.9)
Eye disorders	15 (1.1)	6 (0.4)
Gastrointestinal disorders	159 (11.7)	21 (1.5)
General disorders and administration site conditions	60 (4.4)	9 (0.6)
Infections and infestations	77 (5.6)	39 (2.8)
Injury, poisoning and procedural complications	19 (1.4)	22 (1.6)
Investigations	256 (18.8)	33 (2.4)
Metabolism and nutrition disorders	69 (5.1)	26 (1.9)
Musculoskeletal and connective tissue disorders	17 (1.2)	38 (2.7)
Nervous system disorders	29 (2.1)	21 (1.5)
Renal and urinary disorders	15 (1.1)	4 (0.3)
Respiratory, thoracic and mediastinal disorders	27 (2.0)	11 (0.8)
Surgical and medical procedures	15 (1.1)	14 (1.0)
Vascular disorders	34 (2.5)	37 (2.7)
Alanine aminotransferase increased	36 (2.6)	9 (0.6)
Anaemia	39 (2.9)	6 (0.4)
Arthralgia	5 (0.4)	20 (1.4)
Aspartate aminotransferase increased	23 (1.7)	5 (0.4)
Diarrhoea	133 (9.8)	2 (0.1)
Fatigue	36 (2.6)	3 (0.2)
Gamma-glutamyltransferase increased	21 (1.5)	5 (0.4)
Hypertension	17 (1.2)	26 (1.9)
Hypokalaemia	20 (1.5)	4 (0.3)
Leukopenia	49 (3.6)	2 (0.1)
Lymphocyte count decreased	47 (3.4)	5 (0.4)
Lymphopenia	22 (1.6)	3 (0.2)
Neutropenia	143 (10.5)	4 (0.3)
Neutrophil count decreased	132 (9.7)	4 (0.3)
White blood cell count decreased	101 (7.4)	3 (0.2)

Table 28: Common severe AEsa (CTCAE grade ≥3) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**abemaciclib + endocrine therapy N=1363**	**endocrine therapy N=1385**
a. Events that occurred in ≥ 1% of patients in at least one study arm. b. MedDRA version 28.0; SOC and PT notation taken without adaptation from the comments provided by the company. 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: randomised controlled trial; SOC: System Organ Class		

Table 29: Discontinuation due to AEsa – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**abemaciclib + endocrine therapy** **N = 1363**	**endocrine therapy** **N = 1385**
MONARCH-E		
Overall rate of discontinuations due to AEs	317 (23.3)	18 (1.3)
Gastrointestinal disorders	135 (9.9)	0 (0)
Diarrhoea	96 (7.0)	0 (0)
Abdominal pain	15 (1.1)	0 (0)
Nausea	8 (0.6)	0 (0)
Vomiting	4 (0.3)	0 (0)
Constipation	2 (0.1)	0 (0)
Dyspepsia	2 (0.1)	0 (0)
Gastritis	2 (0.1)	0 (0)
General disorders and administration site conditions	43 (3.2)	1 (0.1)
Fatigue	38 (2.8)	0 (0)
Oedema peripheral	2 (0.1)	0 (0)
Investigations	24 (1.8)	0 (0)
Alanine aminotransferase increased	10 (0.7)	0 (0)
Blood creatinine increased	7 (0.5)	0 (0)
Gamma-glutamyltransferase increased	4 (0.3)	0 (0)
Aspartate aminotransferase increased	2 (0.1)	0 (0)
Blood and lymphatic system disorders	23 (1.7)	0 (0)
Neutropenia	12 (0.9)	0 (0)
Leukopenia	5 (0.4)	0 (0)
Thrombocytopenia	2 (0.1)	0 (0)
Respiratory, thoracic and mediastinal disorders	17 (1.2)	2 (0.1)
Pneumonitis	8 (0.6)	0 (0)
Cough	2 (0.1)	0 (0)
Infections and infestations	16 (1.2)	4 (0.3)
Gastroenteritis	2 (0.1)	0 (0)
Pneumonia	2 (0.1)	0 (0)
Urinary tract infection	2 (0.1)	0 (0)
Skin and subcutaneous tissue disorders	10 (0.7)	0 (0)
Alopecia	3 (0.2)	0 (0)
Rash	2 (0.1)	0 (0)
Vascular disorders	10 (0.7)	1 (0.1)

Table 29: Discontinuation due to AEsa – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women) (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**abemaciclib + endocrine therapy N = 1363**	**endocrine therapy N = 1385**
Deep vein thrombosis	6 (0.4)	0 (0)
Psychiatric disorders	9 (0.7)	2 (0.1)
Depression	3 (0.2)	1 (0.1)
Insomnia	2 (0.1)	0 (0)
Nervous system disorders	8 (0.6)	3 (0.2)
Neuropathy	2 (0.1)	0 (0)
Cardiac disorders	7 (0.5)	0 (0)
Cardiac failure	2 (0.1)	0 (0)
Hepatobiliary disorders	4 (0.3)	0 (0)
Hepatic cirrhosis	2 (0.1)	0 (0)
Musculoskeletal and connective tissue disorders	4 (0.3)	5 (0.4)
Pain in extremity	2 (0.1)	0 (0)
Arthralgia	1 (0.1)	5 (0.4)
Metabolism and nutrition disorders	3 (0.2)	0 (0)
Decreased appetite	2 (0.1)	0 (0)
Eye disorders	2 (0.1)	0 (0)
Injury, poisoning and procedural complications	2 (0.1)	0 (0)

a. Events that occurred in ≥ 2 patients in at least one study arm.
b. MedDRA version 28.0; SOC and PT notation taken without adaptation from the comments provided by the company.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; PT: Preferred Term; RCT: randomised controlled trial; SOC: System Organ Class