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Abemaciclib (breast cancer; adjuvant treatment) –

Addendum to Commission A22-51 (dossier assessment)[1]

Addendum

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Kai Lucaßen
- Erika Baumbach
- Daniela Preukschat
- Anke Schulz

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CI	confidence interval
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
FACT-G	Functional Assessment of Cancer Therapy – General
ESS	Endocrine Symptom Scale
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER2	human epidermal growth factor receptor 2
HR	hormone receptor
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MMRM	mixed-effects model with repeated measures
VAS	visual analogue scale

1 Background

On 6 September 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A22-51 (Abemaciclib – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the analyses of the MONARCH-E study subsequently submitted in the commenting procedure on the EQ-5D visual analogue scale (VAS), Functional Assessment of Cancer Therapy (FACT) – Breast (FACT-B), General (FACT-G), Endocrine Symptoms (FACT-ES 19), Endocrine Symptom Scale (ESS-18) and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue scales, in which follow-up observations for patients with treatment discontinuation were assigned to the corresponding visit, i.e. to a corresponding time window according to occurrence after randomization, taking into account the information provided in the dossier [2].

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

2 Assessment

2.1 Background of the analyses subsequently submitted

The MONARCH-E study, which compares the combination of abemaciclib + endocrine therapy with endocrine therapy, was used for the benefit assessment of abemaciclib in combination with endocrine therapy. The company's dossier contained analyses using a mixed-effects model with repeated measures (MMRM) on progression and change from baseline for the outcomes on symptoms (FACIT-Fatigue), on health status (EQ-5D VAS) and on health-related quality of life (FACT-B, FACT-ES). In these analyses, the company assigned values recorded at different time points after randomization to constructed time points. These time points were referred to as 30-day, 6-month and 12-month follow-up. The actual observation time point for each patient resulted from the individual time point of the end of treatment plus the respective follow-up time (of 30 days, 6 months and 12 months) and not from the time interval from baseline, so that there were no uniform time points of analysis from baseline for all patients. These constructed time points, which were determined relative to the end of treatment, may differ both within a treatment arm and between the treatment arms; the required equality of the time points of analysis between the arms was thus no longer given. Furthermore, no information on the total number of patients included in the MMRM analyses was available in the company's dossier.

In the context of the commenting procedure, the company presented analyses for the scales mentioned in Chapter 1 in which the follow-up observations for patients with premature discontinuation of therapy were assigned to a visit if they could be assigned in a corresponding, undisclosed time window according to the occurrence after randomization [3]. In addition, the company stated at the oral hearing that the numbers of patients with baseline values reported in the results tables corresponded to the total number of patients who contributed data to the MMRM analyses [4].

2.2 Assessment of the relevance of the analyses subsequently submitted

As described in dossier assessment A22-51, the outcomes of symptoms, recorded using the FACIT-Fatigue, health status, recorded using the EQ-5D VAS, and health-related quality of life, recorded using the FACT-B and FACT-ES, are used for the benefit assessment. The FACT-G, as a subscale of the FACT-B or FACT-ES, is presented as supplementary information [5,6].

In addition to the FACT-G, the FACT-ES includes the ESS-19 symptom scale. Instead of the total score, the company only presented the results of the ESS-19 subscale, but referred to it as "FACT-ES 19". Analogous to the specifications for the analysis of the FACT-ES, the total score is relevant to the benefit assessment. The separate consideration of the ESS-19 subscale is not adequate. The ESS-18 subscale, which was also subsequently 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 are therefore

not used for the benefit assessment. The results on ESS-19 and ESS-18 are presented as supplementary information in Appendix A.

2.3 Research question 1: premenopausal women

2.3.1 Risk of bias

For research question 1 (premenopausal women), the risk of bias for the results of the outcomes on symptoms (FACIT-Fatigue), health status (EQ-5D VAS) and health-related quality of life (FACT-B) subsequently submitted is rated as high. This is mainly due to the fact that the lack of blinding of the study can influence the subjective, patient-reported outcomes and that an important proportion of the subpopulation (about 25%) was not included in the analyses.

Summary assessment of certainty of results

Based on the available information, no more than hints can be derived for the outcomes on symptoms (FACIT-Fatigue), health status (EQ-5D VAS) and health-related quality of life (FACT-B).

2.3.2 Results

Table 1 summarizes the results subsequently submitted on the comparison of abemaciclib in combination with endocrine therapy against endocrine therapy in premenopausal patients with node-positive, hormone receptor (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative early breast cancer at high risk of recurrence (research question 1).

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

Study Outcome category Outcome	Abemaciclib + endocrine therapy			Endocrine therapy			Abemaciclib + endocrine therapy vs. endocrine therapy
	N[a]	Values at baseline mean (SD)	Change mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change mean[b] (SE)	Difference Δ [95% CI]; p-value; SMD [95% CI]
MONARCH-E							
Morbidity							
Symptoms (FACIT-Fatigue)[c]	476	40.35 (9.18)	−0.86 (0.28)	467	40.33 (8.84)	0.75 (0.28)	−1.60 [−2.39; −0.82]; < 0.001; −0.26 [−0.39; −0.13]
Health status (EQ-5D VAS)[d]	478	77.47 (15.05)	1.92 (0.47)	471	78.50 (15.39)	2.51 (0.48)	−0.59 [−1.91; 0.73]; 0.380
Health-related quality of life							
FACT-B (total score)[e]	489	106.47 (17.11)	−1.53 (0.54)	477	105.86 (17.26)	1.13 (0.55)	−2.67 [−4.18; −1.15]; < 0.001; −0.22 [−0.35; −0.10]
FACT-G (total score)[f]	490	83.37 (13.41)	−1.70 (0.44)	477	82.84 (13.77)	0.32 (0.44)	−2.02 [−3.24; −0.80]; 0.001; −0.21 [−0.33; −0.08]

a. Those in the premenopausal patient population without a switch to unapproved endocrine therapy (553 vs. 535) for whom usable data were available at baseline and at least one further documentation time.
b. MMRM: The change in score from baseline is modelled. Independent variables are: 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. Higher (increasing) values indicate improved 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. Result is composed of the FACT-G and the BCS subscale. Higher (increasing) values indicate better quality of life; positive effects indicate an advantage for the intervention (scale range 0 to 148). No analyses of the BCS subscale are available.
f. Result is composed of the FACT-G subscales (EWB, FWB, PWB, SWB). Higher (increasing) values indicate better quality of life; positive effects indicate an advantage for the intervention (scale range 0 to 108). No analyses of the subscales are available.

BCS: Breast Cancer Subscale; CI: confidence interval; EWB: emotional wellbeing; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-G: Functional Assessment of Cancer Therapy – General; FWB: functional wellbeing; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; PWB: physical wellbeing; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; SWB: social/family wellbeing

Morbidity

Symptoms (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 standardized 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 (FACT-B)

A 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 standardized 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.

2.3.2.1 Subgroups and other effect modifiers

There are no subgroup analyses for the results subsequently submitted.

2.3.3 Probability and extent of added benefit

2.3.3.1 Assessment of added benefit at outcome level

As there is no hint of an added benefit or of lesser benefit from the analyses subsequently submitted, the extent of the added benefit at outcome level is not presented in table form. In each case, the added benefit is not proven.

2.3.3.2 Overall conclusion on added benefit

Table 2 summarizes the results included in the overall conclusion on the extent of added benefit.

Table 2: 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
Serious/severe symptoms/late complications ▪ Recurrence: hint of an added benefit – extent: "considerable"	
	Serious/severe side effects ▪ SAEs: indication of greater harm – extent: "minor" ▪ Severe AEs: indication of greater harm – extent: "major" ▫ Neutropenia, diarrhoea, blood and lymphatic system disorders (in each case severe AEs): indication of greater harm – extent: "major" ▫ Hepatic events (severe AEs): indication of greater harm – extent "considerable"
	Non-serious/non-severe side effects ▪ Discontinuation due to AEs: hint of greater harm – extent: "considerable" ▪ General disorders and administration site conditions, eye disorders, respiratory, thoracic and mediastinal disorders, gastrointestinal disorders, skin and subcutaneous tissue disorders (in each case AEs): hint of greater harm – extent: "considerable"
AE: adverse event	

The overall conclusion on the added benefit for research question 1 (premenopausal women) from dossier assessment A22-51 does not change due to the analyses on patient-reported outcomes subsequently submitted. Usable data are now available for the patient-reported outcomes on symptoms, health status and health-related quality of life; there are no relevant positive or negative effects.

2.4 Research question 2: postmenopausal women

2.4.1 Risk of bias

For research question 2 (postmenopausal women), the risk of bias for the results of the outcomes on symptoms (FACIT-Fatigue), health status (EQ-5D VAS) and health-related quality of life (FACT-B) subsequently submitted is rated as high. This is mainly due to the fact that the lack of blinding of the study can influence the subjective, patient-reported outcomes and that an important proportion of the subpopulation (about 20%) was not included in the analyses.

Summary assessment of certainty of results

Based on the available information, no more than hints can be derived for the outcomes on symptoms (FACIT-Fatigue), health status (EQ-5D VAS) and health-related quality of life (FACT-B).

2.4.2 Results

Table 3 summarizes the results subsequently submitted on 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).

Table 3: Results (morbidity, health-related quality of life) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women)

Study Outcome category Outcome	Abemaciclib + endocrine therapy			Endocrine therapy			Abemaciclib + endocrine therapy vs. endocrine therapy
	N[a]	Values at baseline mean (SD)	Change mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change mean[b] (SE)	Difference Δ [95% CI]; p-value; SMD [95% CI]
MONARCH-E							
Morbidity							
Symptoms (FACIT-Fatigue)[c]	1075	40.22 (9.39)	−1.16 (0.19)	1077	39.54 (9.58)	0.47 (0.19)	−1.63 [−2.16; −1.10]; < 0.001; −0.26 [−0.34; −0.17]
Health status (EQ-5D VAS)[d]	1090	78.16 (16.34)	−0.21 (0.31)	1092	78.53 (14.92)	1.25 (0.31)	−1.46 [−2.33; −0.59]; 0.001; −0.14 [−0.23; −0.06]
Health-related quality of life							
FACT-B (total score)[e]	1105	108.31 (18.20)	−2.08 (0.37)	1110	107.72 (17.91)	−0.10 (0.37)	−1.98 [−3.00; −0.96]; < 0.001; −0.16 [−0.25; −0.08]
FACT-G (total score)[f]	1107	84.38 (14.38)	−2.29 (0.30)	1110	83.96 (14.16)	−0.75 (0.29)	−1.54 [−2.35; −0.72]; < 0.001; −0.16 [−0.24; −0.07]

a. Those in the postmenopausal patient population without a switch to unapproved endocrine therapy (1284 vs. 1264) for whom usable data were available at baseline and at least one further documentation time.
b. MMRM: The change in score from baseline is modelled. Independent variables are: 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. Higher (increasing) values indicate improved 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. Result is composed of the FACT-G and the BCS subscale. Higher (increasing) values indicate better quality of life; positive values indicate an advantage for the intervention (scale range 0 to 148). No analyses of the BCS subscale were available.
f. Result is composed of the FACT-G subscales (EWB, FWB, PWB, SWB). Higher (increasing) values indicate better quality of life; positive effects indicate an advantage for the intervention (scale range 0 to 108). No analyses of the subscales were available.

BCS: Breast Cancer Subscale; CI: confidence interval; EWB: emotional wellbeing; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy – Fatigue; FACT-B: Functional Assessment of Cancer Therapy – Breast; FACT-G: Functional Assessment of Cancer Therapy – General; FWB: functional wellbeing; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; PWB: physical wellbeing; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference; SWB: social/family wellbeing

Morbidity

Symptoms (FACIT-Fatigue) and health status (EQ-5D VAS)

A statistically significant difference to the disadvantage of abemaciclib in combination with endocrine therapy was shown for each of the outcomes of symptoms, recorded using the FACIT-Fatigue, and health status, recorded using the EQ-5D VAS. In each case, however, the 95% CI of the standardized 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. In each case, 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 (FACT-B)

A 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 standardized 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.

2.4.2.1 Subgroups and other effect modifiers

There are no subgroup analyses for the results subsequently submitted.

2.4.3 Probability and extent of added benefit

2.4.3.1 Assessment of added benefit at outcome level

As there is no hint of an added benefit or of lesser benefit from the analyses subsequently submitted, the extent of the added benefit at outcome level is not presented in table form. In each case, the added benefit is not proven.

2.4.3.2 Overall conclusion on added benefit

Table 4 summarizes the results included in the overall conclusion on the extent of added benefit.

Table 4: 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**
Serious/severe symptoms/late complications ▪ Recurrence: hint of an added benefit – extent: "minor"	
	Serious/severe side effects ▪ SAEs: indication of greater harm – extent "considerable" ▫ ILD/pneumonitis (SAEs): indication of greater harm – extent: "minor" ▪ Severe AEs: indication of greater harm – extent: "major" ▫ Neutropenia, diarrhoea, blood and lymphatic system disorders (in each case severe AEs): indication of greater harm – extent: "major" ▫ Hypokalaemia, fatigue, hepatic events (severe AEs): indication of greater harm – extent "considerable" ▫ Venous thromboembolism (severe AEs): - Age ≥ 65: indication of greater harm – extent: "minor"
Non-serious/non-severe side effects ▪ Arthralgia (PT, AEs): hint of an added benefit – extent: "considerable"	Non-serious/non-severe side effects ▪ Discontinuation due to AEs: hint of greater harm – extent: "considerable" ▪ Alopecia, dizziness, eye disorders, gastrointestinal disorders (in each case PT, AEs): hint of greater harm – extent: "considerable"
AE: adverse event; ILD: interstitial lung disease; PT: Preferred Term; SAE: serious adverse event	

The overall conclusion on the added benefit for research question 2 (postmenopausal women) from dossier assessment A22-51 does not change due to the analyses on patient-reported outcomes subsequently submitted. Usable data are now available for the patient-reported outcomes on symptoms, health status and health-related quality of life; there are no relevant positive or negative effects.

2.5 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 A22-51.

The following Table 5 shows the result of the benefit assessment of abemaciclib under consideration of dossier assessment A22-51 and the present addendum.

Table 5: Abemaciclib in combination with endocrine therapy – probability and extent of added benefit

Research question	Subindication	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	▪ tamoxifen (possibly in addition to suppression of the ovarian function)	▪ Hint of minor added benefit
2	Postmenopausal women	▪ anastrozole or ▪ letrozole or ▪ possibly tamoxifen if aromatase inhibitors are unsuitable or ▪ anastrozole or ▪ exemestane ▪ in sequence after tamoxifen	▪ Added benefit not proven
3	Men	▪ tamoxifen	▪ Added benefit not proven

a. Presented is the respective ACT specified by the GBA.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HER2: human epidermal growth factor receptor 2; HR: hormone receptor

The G-BA decides on the added benefit.

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

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Appendix A – Supplementary presentation of results on health-related quality of life

Table 6: Results (health-related quality of life, supplementary presentation) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 1: premenopausal women)

Study Outcome category Outcome	Abemaciclib + endocrine therapy			Endocrine therapy			Abemaciclib + endocrine therapy vs. endocrine therapy
	N[a]	Values at baseline mean (SD)	Change mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change mean[b] (SE)	Difference Δ [95% CI]; p-value; SMD [95% CI]
MONARCH-E							
Health-related quality of life							
ESS-19[c]	491	60.32 (9.59)	−3.07 (0.32)	478	59.84 (9.76)	−1.59 (0.32)	−1.47 [−2.37; −0.58]; 0.001; −0.21 [−0.33; −0.08]
ESS-18[d]	491	57.65 (8.95)	−3.09 (0.30)	478	57.20 (9.01)	−1.63 (0.31)	−1.46 [−2.31; −0.62]; < 0.001; −0.22 [−0.34; −0.09]

a. Those in the premenopausal patient population without a switch to unapproved endocrine therapy (553 vs. 535) for whom usable data were available at baseline and at least one further documentation time.
b. MMRM: The change in score from baseline is modelled. Independent variables are: 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. Referred to by the company as "FACT-ES 19". Higher (increasing) values indicate better quality of life; positive values indicate an advantage for the intervention (scale range 0 to 76).
d. Analysis of the ESS-19 questionnaire shortened by the last question, which was additionally presented by the company.

CI: confidence interval; ESS: Endocrine Symptom Scale; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; MMRM: mixed effect model with repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference

Table 7: Results (health-related quality of life, supplementary presentation) – RCT, direct comparison: abemaciclib + endocrine therapy vs. endocrine therapy (research question 2: postmenopausal women)

Study Outcome category	Abemaciclib + endocrine therapy			Endocrine therapy			Abemaciclib + endocrine therapy vs. endocrine therapy
Outcome	N[a]	Values at baseline mean (SD)	Change mean[b] (SE)	N[a]	Values at baseline mean (SD)	Change mean[b] (SE)	Difference Δ [95% CI]; p-value; SMD [95% CI]
MONARCH-E							
Health-related quality of life							
ESS-19[c]	1107	63.70 (8.67)	−2.27 (0.19)	1109	63.09 (8.87)	−1.39 (0.18)	−0.88 [−1.40; −0.37]; < 0.001; −0.14 [−0.23; −0.06]
ESS-18[d]	1107	61.07 (7.98)	−2.10 (0.17)	1109	60.58 (8.20)	−1.14 (0.17)	−0.97 [−1.44; −0.49]; < 0.001; −0.17 [−0.25; −0.09]

a. Those in the postmenopausal patient population without a switch to unapproved endocrine therapy (1284 vs. 1264) for whom usable data were available at baseline and at least one further documentation time.
b. MMRM: The change in score from baseline is modelled. Independent variables are: 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. Referred to by the company as "FACT-ES 19". Higher (increasing) values indicate better quality of life; positive values indicate an advantage for the intervention (scale range 0 to 76).
d. Analysis of the ESS-19 questionnaire shortened by the last question, which was additionally presented by the company.

CI: confidence interval; ESS: Endocrine Symptom Scale; FACT-ES: Functional Assessment of Cancer Therapy – Endocrine Symptoms; MMRM: mixed effect model with repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SMD: standardized mean difference