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Alpelisib (breast cancer) –

Addendum to Commission A20-81[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BPI-SF	Brief Pain Inventory – Short Form
CTCAE	Common Terminology Criteria for Adverse Events
ECOG-PS	Eastern Cooperative Oncology Group Performance Status
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30
EQ-5D-5L	European-Quality-of-Life-Questionnaire-5-Dimensions-5-Level
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HER 2	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)
NRS	numerical rating scale
PIK3CA	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PT	preferred term
SAE	serious adverse event
SOC	system organ class
VAS	visual analogue scale

1 Background

On 12 January 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct a supplementary assessment for Commission A20-81 (Alpelisib – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter "company") presented results of the SOLAR-1 study, which compared alpelisib in combination with fulvestrant versus placebo + fulvestrant in patients with hormone receptor (HR) positive, human epidermal growth factor receptor 2 (HER2) negative, locally advanced or metastatic breast cancer with phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) mutation. The dossier assessment of alpelisib (A20-81) investigated 4 research questions on the basis of the appropriate comparator therapy (ACT) specified by the G-BA. On the basis of subpopulations of the SOLAR-1 study, conclusions on added benefit can be drawn for 2 research questions (A1, postmenopausal women in first-line therapy, and B1, postmenopausal women in second-line and subsequent-line therapy).

With its comment [3], the company presented further data on the two relevant subpopulations of research questions A1 and B1.

The G-BA commissioned IQWiG to assess the following data presented in the company's comments:

- Data on specific adverse events (AEs)
- Data on symptoms, health-related quality of life (each surveyed using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Cancer-30 [EORTC QLQ-C30], pain (surveyed using Brief Pain Inventory – Short Form [BPI-SF]) and health status (surveyed using the European-Quality-of-Life-Questionnaire-5-Dimensions-5-Level visual analogue scale [EQ-5D-5L VAS]): Responder analyses on time to first deterioration, operationalized using a response criterion of 15% of the range of the scale
- Data on the predefined subgroup analyses for the characteristics of lung and/or liver metastases (yes vs. no) and baseline Eastern Cooperative Oncology Group Performance Status (ECOG-PS) (0 vs. 1)

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

2 Assessment

This addendum is structured as follows: Section 2.1 describes the analyses subsequently submitted by the company. This section also discusses the assessment of the risk of bias on the outcome level since this applies equally to both research questions A1 and B1. The results for the two subpopulations are presented and assessed in Sections 2.2 and 2.3.

2.1 Analyses subsequently submitted by the company

Specific AEs

No usable data on specific AEs were available for the benefit assessment because, for the subpopulations of interest in research questions A1 and B1, the SOLAR-1 study provided only incomplete data on common AEs , severe AEs (operationalized as Common Terminology Criteria for Adverse Events [CTCAE] grade 3 or 4), and serious AEs (SAEs) [1]. The company subsequently submitted the corresponding data together with its comment.

Specific AEs for the benefit assessment are selected, on the one hand, based on the frequency and difference between treatment arms of the events which occurred in the relevant study, taking into account patient relevance. On the other hand, specific AEs which are of particular importance for the clinical picture or the drugs used in the study may be additionally selected.

Risk of bias

The risk of bias of the results on the specific AEs is rated as high, primarily due to potentially informative censoring and different follow-up durations between study arms (see Table 1 and Table 8). For non-serious/non-severe AEs, the risk of bias is additionally rated as high because it was presumably impossible to maintain blinding over the course of the study due to the known AEs of alpelisib, e.g. hyperglycaemia and skin disorders, which occurred in a substantial percentage of patients at an early point of the study (also see dossier assessment [1]). Therefore, at most hints, e.g. of an added benefit, can be derived for all specific AEs.

The high risk of bias notwithstanding, it is possible to derive indications, e.g. of greater harm, for individual outcomes. This is attributable to the fact that the high number of early events and the marked difference between treatment arms did not lower the certainty of results in some cases. Further information is provided in the description of results below.

Morbidity and health-related quality of life

For the dossier assessment, no usable analyses were available on symptoms, health-related quality of life (both EORTC QLQ-C30), pain (Brief Pain Inventory-Short Form [BPI-SF]), and health status (EQ-5D-5L VAS) in the SOLAR-1 subpopulations of interest for answering research questions A1 and B1 [1]. Together with its comment, the company subsequently submitted analyses of time to first deterioration for each of these outcomes. For the EORTC QLQ-C30 scales and for the EQ-5D-5L VAS, the company operationalized deterioration using a response criterion of 15% of the range of the scale (15 points or millimetres for the EORTC QLQ-C30 scales and the EQ-5D-5L VAS). These analyses are adequate.

For the BPI-SF outcomes, the company presents analyses on time to deterioration by 2 points. These analyses are only partially adequate. As explained by the company in the oral hearing on alpelisib, change by 2 points does not represent a predefined response criterion. According to IQWiG General Methods [4], a response criterion should be predefined to cover at least 15% of the range of an instrument's scale in order to reflect with sufficient certainty a change that is perceivable for patients. Alternatively, post hoc analyses can be submitted using exactly 15% of the range of the scale. The BPI-SF assesses "worst pain" using 1 item on a numerical rating scale (NRS). The NRS ranges from 0 to 10 points, with the smallest possible increments on the scale being whole points. It is impossible to represent exactly 15% of the range of the scale, as specified by the methods paper for response criteria defined post hoc. The response criterion of 2 points, as submitted by the company, is therefore the best approximation of 15% and is used for the assessment. However, the responder analyses for the two BPI-SF index scores (pain intensity [items 3–6] and pain interference [items 9a–g]) are disregarded because in the company's post hoc analyses of these two scales, the response criterion does not represent 15% of the range of the scale – in contrast to the outcome of worst pain (BPI-SF item 3). Hence, no usable analyses are available for these two outcomes.

Risk of bias

The risk of bias of the results on morbidity and health-related quality of life is rated as high due to potentially informative censoring and differences in follow-up durations between study arms (see Table 1 and Table 8). In addition, it was presumably impossible to maintain blinding because of the known AEs of alpelisib, e.g. hyperglycaemia and skin toxicity, which occurred in a substantial percentage of patients at an early point in the study. For these outcomes, at most hints, e.g. of an added benefit, can therefore be derived.

Information on patient characteristics and the course of the study

For the dossier assessment, no information was available on the patient characteristics in the relevant subpopulations of research questions A1 and B1. Data on treatment duration and follow-up duration for the individual outcomes were missing as well. The data subsequently submitted by the company on the characteristics and the course of the study are presented in the beginnings of Sections 2.2.1 and 2.3.1 for the respective research question.

2.2 Research question A1: Postmenopausal women, first-line therapy in the advanced stage

2.2.1 Results

Table 1 and Table 2 present patient characteristics and information on the treatment duration and follow-up duration for individual outcomes.

Table 3 and Table 4 summarize the results of the analyses subsequently submitted by the company for the comparison of alpelisib + fulvestrant with placebo + fulvestrant in postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA mutation and disease progression after endocrine monotherapy

administered in a (neo)adjuvant treatment situation. Appendix B.1 presents the Kaplan-Meier curves on the event-time analyses, and Appendix C.1 shows the tables on common AEs.

Table 1: Information on the course of the study – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage)

Study **Duration of the study phase** **Outcome category**	**Alpelisib + fulvestrant** **N = 88**	**Placebo + fulvestrant** **N = 89**
SOLAR-1 (3rd data cut-off: 23/04/2020)		
Treatment duration [months]		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Follow-up duration [months]		
Overall survival		
Median [min; max]	34.4 [0.5; 51.1]	30.5 [0.5; 53.4]
Mean (SD)	29.5 (14.8)	27.6 (15.6)
Symptoms and health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	7.9 [−0.5; 47.0]	5.5 [−0.3; 52.5]
Mean (SD)	13.9 (13.5)	10.8 (12.1)
Pain (BPI-SF)		
Median [min; max]	7.8 [−0.5; 47.0]	5.5 [−0.4; 52.5]
Mean (SD)	13.4 (13.3)	10.5 (12.2)
Health status (EQ-5D-5L VAS)		
Median [min; max]	6.4 [−0.5; 44.2]	3.7 [−0.9; 52.5]
Mean (SD)	11.5 (13.5)	9.4 (12.2)
AEs		
Median [min; max]	8.9 [0.6; 47.5]	6.6 [1.0; 52.5]
Mean (SD)	15.6 (14.3)	12.4 (12.6)

BPI-SF: Brief Pain Inventory – Short Form; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L: European Quality of Life-5 Dimensions-5-Level; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; VAS: visual analogue scale

Table 2: Characterization of the study population – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Study Characteristic Category	**Alpelisib + fulvestrant N[a] = 88**	**Placebo + fulvestrant N[a] = 89**
SOLAR-1		
Age [years], mean (SD)	64 (10)	65 (9)
Sex [f/m], n (%)	87 (99) / 1 (1)	89 (100) / 0 (0)
Family origin, n (%)		
White	59 (67)	57 (64)
Asian	20 (23)	20 (23)
Black or African American	0 (0)	1 (1)
American Indian or Alaska Native	1 (1)	2 (2)
Other	3 (3)	5 (6)
Unknown	5 (6)	4 (5)
ECOG-PS, n (%)		
0	59 (67[b])	63 (71[b])
1	28 (32[b])	26 (29[b])
Missing	1 (1)[b]	0 (0)[b]
Disease stage at study inclusion, n (%)		
Stage III	1 (1)	3 (3)
Stage IV	87 (99)	86 (97)
Disease duration: period from initial diagnosis to randomization [months], median [min; max]	68.1 [13.7; 200.9]	57.0 [7.8; 235.1]
Localization of metastases, n (%)		
Bone	65 (74)	57 (64)
Bone only	21 (24)	22 (25)
Visceral	49 (56)	53 (60)
Lung	28 (32)	34 (38)
Liver	26 (30)	32 (36)
Other visceral	3 (3)	1 (1)
Lymph nodes	30 (34)	30 (34)
Skin	2 (2)	0 (0)
Breast	0 (0)	1 (1)
CNS	0 (0)	1 (1)
Other	14 (16)	7 (8)
No	0 (0)	0 (0)

Table 2: Characterization of the study population – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Study **Characteristic** **Category**	**Alpelisib + fulvestrant** **N[a] = 88**	**Placebo + fulvestrant** **N[a] = 89**
Type of most recent therapy, n (%)		
Chemotherapy	0 (0)	1 (1)
Endocrine therapy	55 (63)	57 (64)
Radiotherapy	30 (34)	28 (32)
Surgery	5 (6)	6 (7)
Other	1 (1)	0 (0)
Prior endocrine therapies, n (%)		
Aromatase inhibitor	88 (100)	88 (99)
Letrozole	41 (47)	42 (47)
Anastrozole	40 (46)	43 (48)
Exemestane	14 (16)	11 (12)
Antioestrogens	20 (23)	23 (26)
Tamoxifen	20 (23)	23 (26)
Sensitivity to endocrine therapy, n (%)		
Primary resistant[c]	11 (13)	14 (16)
Secondary resistant[d]	57 (65)	56 (63)
Sensitive[e]	20 (23)	19 (21)
Treatment discontinuation[f], n (%)	74 (84)	83 (93)
Study discontinuation, n (%)	ND	ND

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line, provided the deviation is relevant.
b. IQWiG calculations.
c. Recurrence < 24 months in the adjuvant setting or disease progression < 6 months in the advanced stage, each during endocrine therapy.
d. Recurrence ≥ 24 months in the adjuvant setting or disease progression ≥ 6 months in the advanced stage, each during endocrine therapy, or recurrence < 12 months after termination of endocrine therapy in the adjuvant setting.
e. Recurrence ≥ 12 months in the adjuvant setting or disease progression ≥ 12 months in the advanced stage, each after termination of endocrine therapy.
f. Discontinuation of combination therapy, alpelisib or placebo and fulvestrant.

CNS: central nervous system; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; f: female; max: maximum; min: minimum; m: male; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

Table 3: Results (morbidity, health-related quality of life) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Study Outcome category Outcome	Alpelisib + fulvestrant N	Alpelisib + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Placebo + fulvestrant N	Placebo + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Alpelisib + fulvestrant vs. placebo + fulvestrant HR [95% CI]; p-value[a]
SOLAR-1 (3rd data cut-off: 23/04/2020)					
Morbidity					
EORTC QLQ-C30 – symptom scales[b]					
Fatigue	88	15.4 [3.9; 33.1] 41 (46.6)	89	16.6 [11.0; NR] 29 (32.6)	1.33 [0.82; 2.15]; 0.264
Nausea and vomiting	88	9.2 [4.2; NR] 38 (43.2)	89	NR [19.6; NR] 17 (19.1)	2.44 [1.37; 4.35]; 0.002
Pain	88	14.7 [7.5; 27.6] 37 (42.0)	89	7.5 [3.7; 14.7] 38 (42.7)	0.80 [0.50; 1.26]; 0.332
Dyspnoea	88	16.6 [7.4; NR] 35 (39.8)	89	19.4 [5.7; NR] 29 (32.6)	1.04 [0.63; 1.70]; 0.879
Insomnia	88	22.1 [11.0; 34.4] 36 (40.9)	89	22.1 [7.5; NR] 29 (32.6)	0.96 [0.58; 1.58]; 0.883
Decreased appetite	88	4.2 [3.7; 9.3] 48 (54.5)	89	22.1 [9.2; NR] 28 (31.5)	2.01 [1.25; 3.22]; 0.003
Constipation	88	NR [22.1; NR] 21 (23.9)	89	NR [5.6; NR] 26 (29.2)	0.62 [0.35; 1.11]; 0.102
Diarrhoea	88	7.4 [3.7; 11.1] 43 (48.9)	89	NR [NR; NR] 14 (15.7)	3.96 [2.13; 7.35]; < 0.001
Worst pain (BPI-SF)[c]	88	13.1 [7.4; 30.4] 39 (44.3)	89	11.2 [5.6; 25.3] 35 (39.3)	0.91 [0.57; 1.45]; 0.700
Pain intensity (BPI-SF)				No usable data	
Pain interference (BPI-SF)				No usable data	
Health status (EQ-5D-5L VAS)[b]	88	22.1 [5.6; NR] 36 (40.9)	89	22.3 [9.2; NR] 28 (31.5)	1.24 [0.75: 2.04]; 0.418
Health-related quality of life					
EORTC QLQ-C30 – global health status and functioning scales[b]					
Global health status	88	9.2 [3.9; 22.2] 44 (50.0)	89	7.5 [5.6; 24.9] 34 (38.2)	1.07 [0.68; 1.68]; 0.786
Physical functioning	88	NR [33.1; NR] 19 (21.6)	89	NR [19.3; NR] 21 (23.6)	0.78 [0.42; 1.45]; 0.434
Role functioning	88	11.0 [5.6; 20.4] 40 (45.5)	89	13.1 [5.6; 24.8] 38 (42.7)	1.00 [0.63; 1.56]; 0.972

Table 3: Results (morbidity, health-related quality of life) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Study **Outcome category** **Outcome**	**Alpelisib + fulvestrant**		**Placebo + fulvestrant**		**Alpelisib + fulvestrant vs. placebo + fulvestrant**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
Emotional functioning	88	11.1 [5.6; 33.1] 36 (40.9)	89	26.9 [9.3; NR] 26 (29.2)	1.30 [0.78; 2.18]; 0.315
Cognitive functioning	88	5.6 [3.8; 27.6] 45 (51.1)	89	12.9 [3.7; 19.6] 36 (40.4)	1.10 [0.70; 1.71]; 0.672
Social functioning	88	5.6 [3.7; 19.3] 47 (53.4)	89	16.5 [7.4; NR] 27 (30.3)	1.89 [1.17; 3.05]; 0.009

a. HR and CI: Cox proportional hazards model; p-value: log-rank test; each stratified by prior therapy with a CDK 4/6 inhibitor (yes vs. no) and by the presence of liver and/or lung metastases (yes vs. no).
b. Time to first deterioration by 15 points (EORTC QLQ-C30) or 15 mm (EQ-5D-5L VAS).
c. Time to first deterioration by 2 points.

BPI-SF: Brief Pain Inventory – Short Form; CDK: cyclin-dependent kinase; CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L: European Quality of Life 5-Dimensions 5-Level; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NR: not reached; RCT: randomized controlled trial; VAS: visual analogue scale

Table 4: Results (AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Study Outcome category Outcome	Alpelisib + fulvestrant		Placebo + fulvestrant		Alpelisib + fulvestrant vs. placebo + fulvestrant
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
SOLAR-1 (3rd data cut-off: 23/04/2020)					
AEs					
Hyperglycaemia (SMQ, severe AEs[b])	88	NR [NR; NR] 36 (40.9)	89	NR [NR; NR] 1 (1.1)	45.00 [6.17; 328.46]; < 0.001
Skin rash (CMQ, severe AEs[b])	88	NR [NR; NR] 21 (23.9)	89	NR [NR; NR] 0 (0)	NC; < 0.001
Change in sense of taste (PT, AEs)	88	NR [NR; NR] 15 (17.0)	89	NR [NR; NR] 3 (3.4)	5.14 [1.49; 17.78]; 0.004
Alopecia (PT, AEs)	88	NR [NR; NR] 20 (22.7)	89	NR [NR; NR] 4 (4.6)	4.65 [1.58; 13.63]; 0.002
Gastrointestinal disorders (SOC, AEs)	88	0.4 [0.3; 0.7] 76 (86.4)	89	13.2 [5.7; 32.2] 40 (44.9)	3.17 [2.14; 4.71]; < 0.001
Mucosal inflammation (PT, AEs)	88	NR [NR; NR] 14 (15.9)	89	NR [NR; NR] 2 (2.2)	7.61 [1.73; 33.53]; 0.002
Peripheral oedema (PT, AEs)	88	NR [NR; NR] 12 (13.6)	89	NR [NR; NR] 1 (1.1)	10.96 [1.42; 84.80]; 0.004
Diarrhoea (PT, severe AEs[b]):	88	NR [NR; NR] 8 (9.1)	89	NR [NR; NR] 0 (0)	NC; 0.007
Increased gamma glutamyltransferase (PT, severe AEs[b]):	88	NR [NR; NR] 1 (1.1)	89	NR [NR; NR] 6 (6.7)	0.16 [0.02; 1.30] 0.048
Hypertension (PT, severe AEs[b])	88	NR [0.9; NR] 7 (8.0)	89	NR [NR; NR] 1 (1.1)	7.14 [0.88; 58.22]; 0.032
Weight decreased (PT, severe AEs[b]):	88	NR [NR; NR] 5 (5.7)	89	NR [NR; NR] 0 (0)	NC; 0.032
Metabolic and nutritional disorders (SOC, severe AEs[b])	88	22.3 [4.2; NR] 42 (47.7)	89	NR [NR; NR] 7 (7.9)	7.61 [3.41; 16.98]; < 0.001

a. HR and CI: Cox proportional hazards model; p-value: log-rank test; each stratified by prior therapy with a CDK 4/6 inhibitor (yes vs. no) and by the presence of liver and/or lung metastases (yes vs. no).
b. Operationalized as CTCAE grade 3 or 4.

AE: adverse event; CDK: cyclin-dependent kinase; CMQ: Customized MedDRA Query; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; CI: confidence interval; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: standardized MedDRA query; SOC: system organ class

Morbidity

Symptom scales of the EORTC QLQ-C30

Regarding the symptoms surveyed by means of the EORTC QLQ-C30, no statistically significant difference between treatment groups was found for either pain, dyspnoea, insomnia, or constipation. Consequently, for each of these outcomes, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven for these outcomes.

For the outcome of fatigue, there is likewise no statistically significant difference between treatment groups, but an effect modification by the characteristic of age was found (see Section 2.2.1.1). Overall, this results in no hint of added benefit regarding the outcome of fatigue in patients < 65 years of age; an added benefit is therefore not proven for these patients. For patients ≥ 65 years of age, there is a hint of lesser benefit of alpelisib + fulvestrant in comparison with fulvestrant.

For each of the outcomes of nausea and vomiting, decreased appetite, and diarrhoea, there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant. For each of these outcomes, this results in a hint of lesser benefit of alpelisib + fulvestrant in comparison with fulvestrant.

Pain (BPI-SF)

For worst pain, surveyed using the BPI-SF (item 3), no statistically significant difference was found between treatment groups. Hence, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant for this outcome; an added benefit is therefore not proven.

No usable data are available for the “pain intensity” and “pain interference” scales, which were also surveyed using the BPI-SF. Consequently, there is no hint of added benefit for these scales either; an added benefit is therefore not proven.

Health status (EQ-5D-5L VAS)

For health status, as documented using the EQ-5D-5L VAS, no statistically significant difference between treatment groups was found. Hence, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant for this outcome; an added benefit is therefore not proven.

Health-related quality of life

Global health status and the functioning scales surveyed with EORTC QLQ-C30

For global health status and the physical, role, emotional, and cognitive functioning scales of the EORTC QLQ-C30, no statistically significant differences between treatment groups were found. Consequently, for each of these outcomes, there is no hint of added benefit of alpelisib +

fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven for these outcomes.

For social functioning, there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant. For this outcome, this results in a hint of lesser benefit of alpelisib + fulvestrant in comparison with fulvestrant.

AEs

Severe hyperglycaemia (Standardized MedDRA Query [SMQ], CTCAE grade 3 or 4)

For the outcome of severe hyperglycaemia, there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant. Despite a high risk of bias of results, this outcome is associated with a high certainty of results due to the effect size observed already early in the study (see Kaplan-Meier curves in Appendix 1.1.1). For this outcome, there is therefore an indication of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

Severe skin rash (Customized MedDRA Query [SMQ], CTCAE grade 3 or 4)

For the outcome of severe skin rash, there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant. For this outcome, there is therefore a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

Further specific AEs to the disadvantage of alpelisib + fulvestrant

Dysgeusia (preferred term [PT], AEs)

For the outcome of dysgeusia (PT, AEs), there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant. For this outcome, there is therefore a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

Alopecia (PT, AEs)

For the outcome of alopecia (PT, AEs), there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant. For this outcome, there is therefore a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

Gastrointestinal disorders (SOC, AEs), diarrhoea (PT, severe AEs)

For each of the outcomes of gastrointestinal disorders (SOC, AEs) and diarrhoea (PT, severe AEs), there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant. For each of these outcomes, there is therefore a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

Mucosal inflammation (PT, AEs), peripheral oedema (PT, AEs)

For each of the outcomes of mucosal inflammation (PT, AEs) and peripheral oedema (PT, AEs), a statistically significant difference to the disadvantage of alpelisib + fulvestrant is found. For each of these outcomes, there is therefore a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

Hypertension (PT, severe AEs)

For the outcome of hypertension (PT, severe AEs), there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant. For this outcome, there is therefore a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

Weight decreased (PT, severe AEs)

For the outcome of weight decreased (PT, severe AEs), there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant. For this outcome, there is therefore a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

Metabolic and nutritional disorders (SOC, severe AEs)

For the outcome of metabolic and nutritional disorders (SOC, severe AEs), there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant. Despite a high risk of bias of results, this outcome is associated with a high certainty of results due to the effect size observed already early in the study (see Kaplan-Meier curves in Appendix 1.1.1). For this outcome, there is therefore an indication of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

Further specific AEs in favour of alpelisib + fulvestrant

Increased gamma glutamyltransferase (PT, severe AEs)

For the outcome of increased gamma glutamyltransferase (PT, severe AEs), there is a statistically significant difference in favour of alpelisib + fulvestrant. For this outcome, there is therefore a hint of lesser harm from alpelisib + fulvestrant in comparison with fulvestrant.

2.2.1.1 Subgroups and other effect modifiers

For the dossier assessment, no subgroup analyses of the SOLAR-1 study subpopulations of interest to answer research questions A1 and B1 were available. With its comment, the company subsequently submitted corresponding subgroup analyses.

The present assessment accounts for the following potential effect modifiers:

- Age (< 65 / ≥ 65 years)
- Lung and/or liver metastasis (yes/no)
- Visceral metastasis (yes/no)

Furthermore, the G-BA commissioned IQWiG with assessing the effect modifier ECOG-PS (0/1). As already described in the dossier assessment, a comparison between ECOG-PS 0 and ECOG-PS 1 is unsuitable for distinguishing between varying degrees of disease severity. The results on the relevant effect modifiers for ECOG-PS are shown in Appendix A.

Only results showing an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup

results are presented only if there is a statistically significant and relevant effect in at least one subgroup.

Table 5: Subgroups (mortality, morbidity, AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Study **Outcome**	**Alpelisib + fulvestrant**		**Placebo + fulvestrant**		**Alpelisib + fulvestrant vs. placebo + fulvestrant**	
Characteristic **Subgroup**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI][a]**	**p-value[a]**
SOLAR-1 (3rd data cut-off: 23/04/2020)						
Overall survival						
Lung and/or liver metastasis						
Yes	44	40.6 [30.23; NR] 21 (47.7)	47	22.2 [17.68; 29.27] 35 (74.5)	0.52 [0.30; 0.91]	0.020
No	44	41.9 [31.87; NR] 20 (45.5)	42	NR [41.30; NR] 14 (33.3)	1.49 [0.74; 3.01]	0.256
Total					Interaction[b]:	0.025
Visceral metastases						
Yes	49	40.6 [30.23; NR] 24 (49.0)	53	23.4 [18.60; 30.82] 36 (67.9)	0.60 [0.36; 1.02]	0.06
No	39	48.6 [31.87; NR] 17 (43.6)	36	46.7 [41.30; NR] 13 (36.1)	1.30 [0.62; 2.73]	0.48
Total					Interaction[b]:	0.123
Morbidity						
EORTC QLQ-C30 – symptom scales[c]						
Fatigue						
Age						
< 65 years	47	22.1 [4.2; NR] 19 (40.4)	46	11.0 [5.5; NR] 18 (39.1)	0.76 [0.39; 1.47]	0.409
≥ 65 years	41	5.6 [2.8; 19.4] 22 (53.7)	43	24.8 [14.8; NR] 11 (25.6)	2.56 [1.20; 5.43]	0.013
Total					Interaction[b]:	0.011

Table 5: Subgroups (mortality, morbidity, AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Study Outcome	Alpelisib + fulvestrant		Placebo + fulvestrant		Alpelisib + fulvestrant vs. placebo + fulvestrant	
Characteristic Subgroup	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]	p-value[a]
AEs						
Gastrointestinal disorders (SOC, AEs)						
Lung and/or liver metastasis						
Yes	44	0.3 [0.2; 0.6] 41 (93.2)	47	20.2 [8.0; NR] 17 (36.2)	4.96 [2.77; 8.89]	< 0.001
No	44	0.5 [0.3; 1.6] 35 (79.5)	42	6.0 [1.0; 32.2] 23 (54.8)	2.08 [1.22; 3.54]	0.006
Total					Interaction[b]:	0.036
Visceral metastases						
Yes	49	0.3 [0.2; 0.5] 45 (91.8)	53	NR [8.0; NR] 19 (35.8)	4.81 [2.77; 8.35]	< 0.001
No	39	0.5 [0.3; 1.6] 31 (79.5)	36	6.0 [1.0; 21.2] 21 (58.3)	1.87 [1.07; 3.27]	0.024
Total					Interaction[b]	0.015

a. HR and CI: Cox proportional hazards model; p-value: log-rank test; each stratified by prior therapy with a CDK 4/6 inhibitor (yes vs. no) and by the presence of liver and/or lung metastases (yes vs. no).
b. The p-value for the interaction term "treatment*subgroup characteristic" in a Cox proportional hazards model.
c. Time to first deterioration by 15 points.

AE: adverse event; CDK: cyclin-dependent kinase; CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NR: not reached; RCT: randomized controlled trial; SOC: system organ class

Mortality

Overall survival

For the outcome of overall survival, there is an effect modification by the characteristic of lung and/or liver metastases (yes/no). For the second examined characteristic on severity (visceral metastases [yes/no]), which was slightly broader, a similar result was found, but without reaching statistical significance.

In the present situation, it is unclear whether to prefer the characteristic "lung and/or liver metastases" or "visceral metastases". Both effect modifiers were predefined and are generally

suitable for representing the severity of disease. The two characteristics lead to different results regarding effect modification. Furthermore, inexplicable discrepancies were found with regard to the number of patients in the subgroups. According to the data on patient characteristics which were subsequently submitted with the company's comments, at most 4 patients had visceral metastases other than lung and/or liver metastasis (also see Table 2); however, according to the differences in subgroup sizes between the two characteristics, it should be 11 patients. For these reasons, the effect modification observed for the characteristic of lung and/or liver metastasis is disregarded, and the result of the entire subpopulation A1 is used for deriving any added benefit (see dossier assessment A20-81 [1]).

Morbidity

Fatigue (EORTC QLQ-C30)

For the outcome of fatigue, there is an effect modification by the characteristic of age (< 65 years / ≥ 65 years). No statistically significant difference between treatment groups was found for patients < 65 years of age. For patients < 65 years of age, this results in no hint of added benefit; an added benefit is therefore not proven for these patients. For patients ≥ 65 years of age, there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant. For these patients, this results in a hint of lesser benefit of alpelisib + fulvestrant in comparison with fulvestrant.

AEs

Gastrointestinal disorders (SOC, AEs)

For the outcome of gastrointestinal disorders, there are effect modifications by the characteristic of lung and/or liver metastases (yes/no) and visceral metastasis (yes/no). However, the results differ between the two effect modifiers: For the subgroup of lung and/or liver metastasis (no), there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant in comparison with fulvestrant. For the subgroup of visceral metastasis (no), there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant. However, the extent of the effect is at most marginal. As was done for the outcome of overall survival, the subgroup results are disregarded in light of the differences and discrepancies regarding the numbers of patients in subgroups, and the result of the entire subpopulation A1 is used for deriving any added benefit.

2.2.2 Extent and probability of added benefit

Hereinbelow, the probability and extent of added benefit on the outcome level is derived for the morbidity and health-related quality of life outcomes and specific AEs. The various outcome categories and the effect sizes have been taken into account. The methods used for this purpose are explained in the IQWiG General Methods [4]. The probability and extent of the further outcomes of the SOLAR-1 study are available in the dossier assessment [1].

The approach for deriving an overall conclusion on added benefit by aggregating the conclusions derived on the outcome level from the dossier assessment and the addendum is a proposal by IQWiG. The G-BA decides on the added benefit.

Assessment of added benefit at outcome level

On the basis of the results presented in Section 2.2.1, the extent of the respective added benefit at outcome level was estimated (see Table 6).

Determination of the outcome category for the outcomes of symptoms and AEs

Not for all outcomes examined in the present benefit assessment does the dossier permit inferences as to whether they were serious/severe or non-serious/non-severe. A rationale for the classification of these outcomes is provided below.

EORTC QLQ-C30 (symptom scales)

Module 4 of the dossier provides no information suitable for categorizing the severity of the outcomes of fatigue, nausea and vomiting, decreased appetite, and diarrhoea. Therefore, these outcomes are allocated to the outcome category of non-serious/non-severe symptoms / late complications.

Table 6: Extent of added benefit at outcome level: RCT, direct comparison: alpelisib + fulvestrant vs. fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Outcome category **Outcome** **Subgroup**	**Alpelisib + fulvestrant vs. fulvestrant** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Morbidity		
EORTC QLQ-C30 – symptom scales		
Fatigue		
Age		
< 65 years	22.1 vs. 11.0 months HR: 0.76 [0.39; 1.47] p = 0.409	Lesser/added benefit not proven
≥ 65 years	5.6 vs. 24.8 months HR: 2.56 [1.20; 5.43] HR: 0.39 [0.18; 0.83][c] p = 0.013 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Lesser benefit; extent: minor
Nausea and vomiting	9.2 month vs. NR HR: 2.44 [1.37; 4.35] HR: 0.41 [0.23; 0.73][c] p = 0.002 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.80$ Lesser benefit; extent: considerable
Pain	14.7 vs. 7.5 months HR: 0.80 [0.50; 1.26] p = 0.332	Lesser/added benefit not proven
Dyspnoea	16.6 vs. 19.4 months HR: 1.04 [0.63; 1.70]; p = 0.879	Lesser/added benefit not proven
Insomnia	22.1 vs. 22.1 months HR: 0.96 [0.58; 1.58]; p = 0.883	Lesser/added benefit not proven
Decreased appetite	4.2 vs. 22.1 months HR: 2.01 [1.25; 3.22] HR: 0.50 [0.31; 0.80][c] p = 0.003 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Lesser benefit; extent: minor
Constipation	NR vs. NR HR: 0.62 [0.35; 1.11]; p = 0.102	Lesser/added benefit not proven

Table 6: Extent of added benefit at outcome level: RCT, direct comparison: alpelisib + fulvestrant vs. fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Outcome category **Outcome** **Subgroup**	**Alpelisib + fulvestrant vs. fulvestrant** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Diarrhoea	7.4 vs. NR HR: 3.96 [2.13; 7.35] HR: 0.25 [0.14; 0.47][c] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.80$ Lesser benefit; extent: considerable
Worst pain (BPI-SF item 3)	13.1 vs. 11.2 months HR: 0.91 [0.57; 1.45]; p = 0.700	Lesser/added benefit not proven
Pain intensity (BPI-SF)	No usable data	Lesser/added benefit not proven
Pain interference (BPI-SF)	No usable data	Lesser/added benefit not proven
Health status (EQ-5D-5L VAS)	22.1 vs. 22.3 months HR: 1.24 [0.75: 2.04]; p = 0.418	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 – global health status and functioning scales		
Global health status	9.2 vs. 7.5 months HR: 1.07 [0.68; 1.68]; p = 0.786	Lesser/added benefit not proven
Physical functioning	NR vs. NR HR: 0.78 [0.42; 1.45] p = 0.434	Lesser/added benefit not proven
Role functioning	11.0 vs. 13.1 months HR: 1.00 [0.63; 1.56]; p = 0.972	Lesser/added benefit not proven
Emotional functioning	11.1 vs. 26.9 months HR: 1.30 [0.78; 2.18]; p = 0.315	Lesser/added benefit not proven
Cognitive functioning	5.6 vs. 12.9 months HR: 1.10 [0.70; 1.71]; p = 0.672	Lesser/added benefit not proven
Social functioning	5.6 vs. 16.5 months HR: 1.89 [1.17; 3.05] HR: 0.53 [0.33; 0.85][c] p = 0.009 Probability: hint	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Lesser benefit; extent: considerable

Table 6: Extent of added benefit at outcome level: RCT, direct comparison: alpelisib + fulvestrant vs. fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Outcome category **Outcome** **Subgroup**	**Alpelisib + fulvestrant vs. fulvestrant** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
AEs		
Hyperglycaemia (SMQ, severe AEs[d])	NR vs. NR HR: 45.00 [6.17; 328.46] HR: 0.02 [0.003; 0.16][c] p < 0.001 Probability: indication[e]	Outcome category: serious/severe AEs $CI_u < 0.75$, risk ≥ 5% Greater harm; extent: major
Skin rash (CMQ, severe AEs[d])	NR vs. NR HR: NC; p < 0.001 Probability: hint	Outcome category: serious/severe AEs Greater harm; extent: non-quantifiable
Dysgeusia (PT, AEs)	NR vs. NR HR: 5.14 [1.49; 17.78] HR: 0.19 [0.06; 0.67][c] p = 0.004 Probability: hint	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ Greater harm; extent: considerable
Alopecia (PT, AEs)	NR vs. NR HR: 4.65 [1.58; 13.63] HR: 0.22 [0.07; 0.63][c] p = 0.002 Probability: hint	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ Greater harm; extent: considerable
Gastrointestinal disorders (SOC, AEs)	0.4 vs. 13.2 months HR: 3.17 [2.14; 4.71] HR: 0.32 [0.2; 0.47][c] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ Greater harm; extent: considerable
Mucosal inflammation (PT, AEs)	NR vs. NR HR: 7.61 [1.73; 33.53] HR: 0.13 [0.03; 0.58][c] p = 0.002 Probability: hint	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ Greater harm; extent: considerable
Peripheral oedema (PT, AEs)	NR vs. NR HR: 10.96 [1.42; 84.80] HR: 0.09 [0.01; 0.70][c] p = 0.004 Probability: hint	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ Greater harm; extent: considerable

Table 6: Extent of added benefit at outcome level: RCT, direct comparison: alpelisib + fulvestrant vs. fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Outcome category **Outcome** **Subgroup**	**Alpelisib + fulvestrant vs. fulvestrant** **Median time to event (months)** **Effect estimation [95% CI];** **p-value** **Probability[a]**	**Derivation of extent[b]**
Diarrhoea (PT, severe AEs[d])	NR vs. NR HR: NC; p = 0.007 Probability: hint	Outcome category: serious/severe AEs Greater harm; extent: non-quantifiable
Increased gamma glutamyltransferase (PT, severe AEs[d])	NR vs. NR HR: 0.16 [0.02; 1.30]; p = 0.048 Probability: hint	Outcome category: serious/severe AEs Lesser harm; extent: non-quantifiable[f]
Hypertension (PT, severe AEs[d])	NR vs. NR HR: 7.14 [0.88; 58.22] HR: 0.14 [0.02; 1.14][c] p = 0.032 Probability: hint	Outcome category: serious/severe AEs Greater harm; extent: non-quantifiable[f]
Weight decreased (PT, severe AEs[d])	NR vs. NR HR: NC; p = 0.032 Probability: hint	Outcome category: serious/severe AEs Greater harm; extent: non-quantifiable
Metabolic and nutritional disorders (SOC, severe AEs[d])	22.3 vs. NR HR: 7.61 [3.41; 16.98] HR: 0.13 [0.06; 0.29][c] p < 0.001 Probability: Indication[e]	Outcome category: serious/severe AEs $CI_u < 0.75$, risk ≥ 5% Greater harm; extent: major

a. Probability is stated if a statistically significant and relevant effect is present.
b. Estimations of effect size are made depending on the outcome category, with different limits according to the upper confidence limit (CI_u).
c. IQWiG calculation, reversed direction of effect to enable use of limits to derive the extent of added benefit.
d. Operationalized as CTCAE grade 3 or 4.
e. The certainty of results is deemed high since the observation of an effect of this size cannot be explained solely by different follow-up durations and incomplete follow-up for potentially informative reasons.
f. Discrepancy between p-value (log rank test) and CI (Cox proportional hazards model) due to different calculation methods; derived using p-value.

AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; CI: confidence interval; CI_u: upper limit of CI; CMQ: Customized MedDRA Query; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L: European Quality of Life 5-Dimensions 5-Level; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; NC: not calculable; NR: not reached; PT: preferred term; RCT: randomized controlled trial; SMQ: standardized MedDRA query; SOC: system organ class; VAS: visual analogue scale

Overall conclusion on added benefit

Table 7 summarizes the results of the dossier assessment [1] and the addendum which are used to draw the overall conclusion on the extent of added benefit for research question A1.

Table 7: Favourable and unfavourable effects from the assessment of alpelisib in combination with fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage)

Favourable effects	**Unfavourable effects**[a]
–	Non-serious/non-severe symptoms / late complications ▪ Fatigue ▫ Age (≥ 65 years): hint of lesser benefit – extent: minor ▪ Nausea and vomiting; diarrhoea: hint of lesser harm – extent: considerable ▪ Decreased appetite: hint of lesser benefit – extent: minor
–	Health-related quality of life ▪ Social functioning: hint of lesser harm – extent: considerable
Serious/severe AEs ▪ Increased gamma glutamyltransferase: hint of lesser harm – extent: non-quantifiable	Serious/severe AEs ▪ **SAEs: hint of greater harm – extent: minor** ▪ **Severe AEs: indication of greater harm – extent: major** Including ▫ hyperglycaemia, metabolic and nutritional disorders: each indication of greater harm – extent: major ▫ Skin rash, diarrhoea, hypertension, weight decreased: each hint of greater harm – extent: non-quantifiable
–	Non-serious/non-severe AEs ▪ **Discontinuation due to AEs: hint of greater harm – extent: considerable** ▪ Dysgeusia, alopecia, gastrointestinal disorders, mucosal inflammation, peripheral oedema: each hint of greater harm – extent: considerable
a. Results shown in bold were already included in the dossier assessment's overall conclusion on added benefit. AE: adverse event; SAE: serious adverse event	

When including the data subsequently submitted in the commenting procedure, exclusively unfavourable effects of alpelisib in combination with fulvestrant are found for the outcomes of morbidity and of health-related quality of life. For the subsequently submitted data on specific AEs, all but one effect of alpelisib in combination with fulvestrant were unfavourable, some with the probability of indication.

In summary, for postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA mutation and progression of disease following endocrine monotherapy in the (neo)adjuvant treatment situation, there is an indication of lesser benefit of alpelisib plus fulvestrant in comparison with fulvestrant.

2.3 Research question B1: Postmenopausal women, second-line and subsequent-line therapy in the advanced stage

2.3.1 Results

Table 8 and Table 9 present patient characteristics and information on the treatment duration and follow-up duration for individual outcomes.

Table 10 and Table 11 summarize the results of the analyses subsequently submitted by the company for the comparison of alpelisib + fulvestrant with placebo + fulvestrant in postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA mutation and disease progression after endocrine monotherapy administered in a locally advanced or metastatic stage. Where necessary, calculations conducted by IQWiG are provided in addition to the data from the company's dossier. Appendix B.2 contains the Kaplan-Meier curves on the event-time analyses, and Appendix C.2 presents the tables on common AEs.

Table 8: Information on the course of the study – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in advanced stage)

Study **Duration of the study phase** **Outcome category**	**Alpelisib + fulvestrant** **N = 79**	**Placebo + fulvestrant** **N = 82**
SOLAR-1 (3rd data cut-off: 23/04/2020)		
Treatment duration [months]		
Median [min; max]	ND	ND
Mean (SD)	ND	ND
Follow-up duration [months]		
Overall survival		
Median [min; max]	31.6 [0.4; 52.3]	26.6 [0.9; 53.3]
Mean (SD)	27.6 (14.6)	25.5 (14.2)
Symptoms and health-related quality of life (EORTC QLQ-C30)		
Median [min; max]	7.3 [−0.5; 47.0]	3.7 [−0.7; 35.9]
Mean (SD)	12.0 (12.0)	8.1 (8.9)
Pain (BPI-SF)		
Median [min; max]	6.2 [−0.6; 47.0]	3.7 [−0.7; 35.9]
Mean (SD)	11.4 (12.0)	7.3 (8.9)
Health status (EQ-5D-5L VAS)		
Median [min; max]	5.6 [−0.6; 47.0]	3.6 [−0.8; 33.4]
Mean (SD)	10.5 (12.2)	6.3 (7.8)
AEs		
Median [min; max]	8.8 [0.4; 51.4]	5.6 [1.7; 37.7]
Mean (SD)	13.2 (12.4)	9.6 (8.8)

BPI-SF: Brief Pain Inventory – Short Form; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L: European Quality of Life-5 Dimensions-5-Level; max: maximum; min: minimum; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard error; VAS: visual analogue scale

Table 9: Characterization of the study population – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage) (multi-page table)

Study **Characteristic** **Category**	**Alpelisib + fulvestrant** **N[a] = 79**	**Placebo + fulvestrant** **N[a] = 82**
SOLAR-1		
Age [years], mean (SD)	62 (11)	63 (11)
Sex [f/m], n (%)	79 (100) / 0 (0)	82 (100) / 0 (0)
Family origin, n (%)		
White	57 (72)	52 (63)
Asian	14 (18)	20 (24)
Black or African American	0 (0)	1 (1)
American Indian or Alaska Native	0 (0)	0 (0)
Other	5 (6)	5 (6)
Unknown	3 (4)	4 (5)
ECOG-PS, n (%)		
0	51 (65[b])	49 (60[b])
1	28 (35[b])	32 (39[b])
Missing	0 (0)[b]	1 (1)[b]
Disease stage at study inclusion, n (%)		
Stage III	0 (0)	4 (5)
Stage IV	79 (100)	78 (95)
Disease duration: period from initial diagnosis to randomization [months], median [min; max]	62.8 [5.3; 336.5]	67.1 [7.5; 399.8]
Localization of metastases, n (%)		
Bone	65 (82)	63 (77)
Bone only	20 (25)	12 (15)
Visceral	43 (54)	47 (57)
Lung	28 (35)	34 (42)
Liver	23 (29)	22 (27)
Other visceral	0 (0)	0 (0)
Lymph nodes	25 (32)	35 (43)
Skin	2 (3)	6 (7)
Breast	1 (1)	2 (2)
CNS	0 (0)	1 (1)
Other	11 (14)	11 (13)
None	0 (0)	1 (1)

Table 9: Characterization of the study population – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage) (multi-page table)

Study **Characteristic** **Category**	**Alpelisib + fulvestrant** **N[a] = 79**	**Placebo + fulvestrant** **N[a] = 82**
Type of most recent therapy, n (%)		
Endocrine therapy	58 (73)	57 (70)
Targeted therapy	5 (6)	4 (5)
Radiotherapy	15 (19)	15 (18)
Surgery	4 (5)	8 (10)
Other	1 (1)	1 (1)
Prior endocrine therapies, n (%)		
Aromatase inhibitor	74 (94)	79 (96)
Letrozole	55 (70)	52 (63)
Anastrozole	14 (18)	21 (26)
Exemestane	6 (8)	8 (10)
Antioestrogens	6 (8)	6 (7)
Tamoxifen	4 (5)	6 (7)
Fulvestrant	1 (1)	0 (0)
Other	1 (1)	0 (0)
Sensitivity to endocrine therapy, n (%)		
Primary resistant[c]	11 (14)	8 (10)
Secondary resistant[d]	61 (77)	70 (85)
Sensitive[e]	ND	ND
Treatment discontinuation[f], n (%)	72 (91)	80 (98)
Study discontinuation, n (%)	ND	ND

a. Number of randomized patients. Values which are based on different patient numbers are marked in the corresponding line, provided the deviation is relevant.
b. IQWiG calculations.
c. Recurrence < 24 months in the adjuvant setting or disease progression < 6 months in the advanced stage, each during endocrine therapy.
d. Recurrence ≥ 24 months in the adjuvant setting or disease progression ≥ 6 months in the advanced stage, each during endocrine therapy, or recurrence < 12 months after termination of endocrine therapy in the adjuvant setting.
e. Recurrence ≥ 12 months in the adjuvant setting or disease progression ≥ 12 months in the advanced stage, each after termination of endocrine therapy.
f. Discontinuation of combination therapy, alpelisib or placebo and fulvestrant.

CNS: central nervous system; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; f: female; m: male; max: maximum; min: minimum; n: number of patients in the category; N: number of randomized (or included) patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation

Table 10: Results (morbidity, health-related quality of life) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage) (multi-page table)

Study Outcome category Outcome	Alpelisib + fulvestrant N	Median time to event in months [95% CI] Patients with event n (%)	Placebo + fulvestrant N	Median time to event in months [95% CI] Patients with event n (%)	Alpelisib + fulvestrant vs. placebo + fulvestrant HR [95% CI]; p-value[a]
SOLAR-1 (3rd data cut-off: 23/04/2020)					
Morbidity					
EORTC QLQ-C30 – symptom scales[b]					
Fatigue	79	7.4 [5.6; 16.6] 35 (44.3)	82	NR [11.1; NR] 21 (25.6)	1.71 [0.98; 2.96]; 0.054
Nausea and vomiting	79	7.4 [4.7; 11.2] 40 (50.6)	82	12.9 [9.2; NR] 23 (28.0)	1.89 [1.12; 3.18]; 0.016
Pain	79	9.2 [5.5; 12.9] 37 (46.8)	82	6.5 [3.7; 14.7] 35 (42.7)	0.79 [0.49; 1.28]; 0.330
Dyspnoea	79	22.6 [12.9; NR] 19 (24.1)	82	9.2 [3.8; 13.0] 33 (40.2)	0.39 [0.22; 0.70]; 0.001
Insomnia	79	6.5 [3.7; 11.1] 38 (48.1)	82	NR [5.6; NR] 25 (30.5)	1.39 [0.83; 2.33]; 0.203
Decreased appetite	79	4.0 [1.9; 19.4] 39 (49.4)	82	13.9 [7.4; 22.1] 28 (34.1)	1.67 [1.02; 2.73]; 0.045
Constipation	79	28.6 [11.0; NR] 21 (26.6)	82	9.3 [7.4; 19.9] 29 (35.4)	0.61 [0.34; 1.08]; 0.092
Diarrhoea	79	5.6 [3.7; 9.2] 40 (50.6)	82	NR [14.8; NR] 16 (19.5)	2.86 [1.59; 5.12]; < 0.001
Worst pain (BPI-SF)[c]	79	12.9 [7.4; 28.6] 29 (36.7)	82	9.2 [3.9; 14.8] 32 (39.0)	0.63 [0.37; 1.07]; 0.089
Pain intensity (BPI-SF)				No usable data	
Pain interference (BPI-SF)				No usable data	
Health status (EQ-5D-5L VAS)[b]	79	14.3 [5.7; NR] 28 (35.4)	82	22.1 [9.4; NR] 22 (26.8)	1.06 [0.60; 1.89]; 0.839
Health-related quality of life					
EORTC QLQ-C30 – global health status and functioning scales[b]					
Global health status	79	5.6 [3.7; 11.1] 40 (50.6)	82	9.2 [4.2; NR] 27 (32.9)	1.43 [0.87; 2.34]; 0.145
Physical functioning	79	NR [28.6; NR] 19 (24.1)	82	NR [11.1; NR] 17 (20.7)	1.01 [0.51; 1.98]; 0.990
Role functioning	79	5.6 [2.0; 9.3] 37 (46.8)	82	5.6 [3.7; 11.4] 38 (46.3)	1.07 [0.68; 1.69]; 0.827

Table 10: Results (morbidity, health-related quality of life) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage) (multi-page table)

Study **Outcome category** **Outcome**	**Alpelisib + fulvestrant**		**Placebo + fulvestrant**		**Alpelisib + fulvestrant vs. placebo + fulvestrant**
	N	**Median time to event in months [95% CI]** **Patients with event n (%)**	**N**	**Median time to event in months [95% CI]** **Patients with event n (%)**	**HR [95% CI]; p-value[a]**
Emotional functioning	79	12.8 [5.5; NR] 29 (36.7)	82	11.1 [7.5; 17.1] 27 (32.9)	1.01 [0.60; 1.71]; 0.965
Cognitive functioning	79	7.4 [5.6; 14.8] 33 (41.8)	82	11.1 [3.7; NR] 30 (36.6)	1.21 [0.73; 2.00]; 0.450
Social functioning	79	4.7 [3.7; 12.9] 38 (48.1)	82	14.8 [7.4; 22.1] 26 (31.7)	1.77 [1.07; 2.92]; 0.027

a. HR and CI: Cox proportional hazards model; p-value: log-rank test; each stratified by prior therapy with a CDK 4/6 inhibitor (yes vs. no) and by the presence of liver and/or lung metastases (yes vs. no).
b. Time to first deterioration by 15 points.
c. Time to first deterioration by 2 points.

BPI-SF: Brief Pain Inventory – Short Form; CDK: cyclin-dependent kinase; CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L: European Quality of Life 5-Dimensions 5-Level; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NR: not reached; RCT: randomized controlled trial; VAS: visual analogue scale

Table 11: Results (AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage) (multi-page table)

Study Outcome category Outcome	Alpelisib + fulvestrant N	Alpelisib + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Placebo + fulvestrant N	Placebo + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Alpelisib + fulvestrant vs. placebo + fulvestrant HR [95% CI]; p-value[a]
SOLAR-1 (3rd data cut-off: 23/04/2020)					
AEs					
Hyperglycaemia (SMQ, severe AEs[b])	79	NR [NR; NR] 28 (35.4)	81	NR [NR; NR] 0 (0)	NC; < 0.001
Skin rash (CMQ, severe AEs[b])	79	NR [NR; NR] 19 (24.1)	81	NR [NR; NR] 0 (0)	NC; < 0.001
Alopecia (PT, AEs)	79	NR [NR; NR] 16 (20.3)	81	NR [NR; NR] 1 (1.2)	17.39 [2.30; 131.33]; < 0.001
Pruritus (PT, AEs)	79	NR [18.9; NR] 18 (22.8)	81	NR [NR; NR] 3 (3.7)	6.09 [1.78; 20.85]; 0.001
Gastrointestinal disorders (SOC, AEs)	79	0.3 [0.2; 0.4] 69 (87.3)	81	5.4 [2.3; 17.8] 44 (54.3)	3.30 [2.20; 4.97]; < 0.001
Mucosal inflammation (PT, AEs)	79	NR [31.0; NR] 14 (17.7)	81	NR [NR; NR] 2 (2.5)	7.61 [1.73; 33.55]; 0.002
Weight decreased (PT, AEs)	79	NR [NR; NR] 23 (29.1)	81	NR [NR; NR] 0 (0)	NC; < 0.001
Stomatitis (PT, SAEs)	79	NR [NR; NR] 4 (5.1)	81	NR [NR; NR] 0 (0)	NC; 0.048
Musculoskeletal and connective tissue disorders (SOCs, SAEs)	79	NR [39.5; NR] 6 (7.6)	81	NR [NR; NR] 0 (0)	NC; 0.033
Diarrhoea (PT, severe AEs[b])	79	NR [NR; NR] 5 (6.3)	81	NR [NR; NR] 0 (0)	NC; 0.029
General disorders and administration site conditions (SOC, severe AEs[b])	79	NR [NR; NR] 6 (6.3)	81	NR [NR; NR] 0 (0)	NC; 0.014
Investigations (SOC, severe AEs[b])	79	NR [NR; NR] 26 (32.9)	81	NR [NR; NR] 11 (13.6)	2.50 [1.23; 5.08]; 0.009
Hypokalemia (PT, severe AEs[b])	79	NR [NR; NR] 5 (6.3)	81	NR [NR; NR] 0 (0)	NC; 0.032

a. HR and CI: Cox proportional hazards model; p-value: log-rank test; each stratified by prior therapy with a CDK 4/6 inhibitor (yes vs. no) and by the presence of liver and/or lung metastases (yes vs. no).
b. Operationalized as CTCAE grade 3 or 4.

Table 11: Results (AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage) (multi-page table)

Study Outcome category Outcome	Alpelisib + fulvestrant		Placebo + fulvestrant		Alpelisib + fulvestrant vs. placebo + fulvestrant
	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI]; p-value[a]
AE: adverse event; CDK: cyclin-dependent kinase; CI: confidence interval; CMQ: Customized MedDRA Query; CTCAE: Common Terminology Criteria for Adverse Events; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least 1) event; N: number of analysed patients; NC: not calculable; NR: not reached; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: standardized MedDRA query; SOC: system organ class					

Morbidity

Symptom scales of the EORTC QLQ-C30

Regarding the symptoms surveyed using the EORTC QLQ-C30, no statistically significant difference between treatment groups was found for either fatigue, pain, insomnia, or constipation. Consequently, for each of these outcomes, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven for these outcomes.

For both of the outcomes “nausea and vomiting” and “diarrhoea”, a statistically significant difference was found to the disadvantage of alpelisib + fulvestrant. Hence, there is a hint of lesser benefit of alpelisib + fulvestrant in comparison with fulvestrant.

Likewise, for the outcome of decreased appetite, there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant. However, the extent of this effect is at most marginal (see Section 2.3.1.1). Consequently, for this outcome, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven for this outcome.

For the outcome of dyspnoea, a statistically significant difference was found in favour of alpelisib + fulvestrant. This results in a hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant.

Pain (BPI-SF)

For worst pain, surveyed using the BPI-SF (item 3), no statistically significant difference was found between treatment groups. Hence, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant for this outcome; an added benefit is therefore not proven.

No usable data are available for the "pain intensity" and "pain interference" scales, which were also surveyed using the BPI-SF. Consequently, there is no hint of added benefit for these scales either; an added benefit is therefore not proven.

Health status (EQ-5D-5L VAS)

For health status, as documented using the EQ-5D-5L VAS, no statistically significant difference between treatment groups was found. Hence, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant for this outcome; an added benefit is therefore not proven.

Health-related quality of life

Global health status and the functioning scales, surveyed with EORTC QLQ-C30

For the EORTC QLQ-C30 physical, emotional, and cognitive functioning scales, no statistically significant differences between treatment groups were found. Consequently, for each of these outcomes, there is no hint of added benefit of alpelisib + fulvestrant in comparison with fulvestrant; an added benefit is therefore not proven for these outcomes.

For the outcome of global health status, there is likewise no statistically significant difference between treatment groups, but an effect modification exists by the characteristic of age (see Section 2.3.1.1). Overall, this results in no hint of added benefit for the outcome of global health status in patients < 65 years of age; an added benefit is therefore not proven for these patients. For patients ≥ 65 years of age, there is a hint of lesser benefit of alpelisib + fulvestrant in comparison with fulvestrant.

For social functioning, a statistically significant difference was found to the disadvantage of alpelisib + fulvestrant. Hence, there is a hint of lesser benefit of alpelisib + fulvestrant in comparison with fulvestrant.

AEs

Severe hyperglycaemia (SMQ, CTCAE grade 3 or 4)

For the outcome of severe hyperglycaemia, there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant in comparison with placebo + fulvestrant. For this outcome, the company reported the hazard ratio, including 95% confidence interval, as not calculable since no event occurred in the comparator arm. Hence, the effect size cannot be directly assessed for this outcome. Given the Kaplan-Meier curves and the similar time of occurrence of the events for this outcome for research question A1 (see Kaplan-Meier curves in the Appendix – Figure 17 and Figure 45), a similar effect size is likely to exist in this case. Therefore, despite the high risk of bias of results, the certainty of results for this outcome is also high. For this outcome, there is therefore an indication of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

Severe skin rash (SMQ, CTCAE grade 3 or 4)

For the outcome of severe skin rash, there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant in comparison with placebo + fulvestrant. For this outcome, there is therefore a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

Further specific AEs to the disadvantage of alpelisib + fulvestrant

Alopecia (PT, AEs)

For each of the outcomes of alopecia (PT, AEs) and pruritus (PTs, AEs), there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant in comparison with placebo + fulvestrant. For each of these outcomes, there is therefore a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

Gastrointestinal disorders (system organ class [SOC], AEs), diarrhoea (PT, severe AEs), stomatitis (PTs, SAEs)

For each of the outcomes of gastrointestinal disorders (SOC, AEs), diarrhoea (PT, severe AEs), and stomatitis, a statistically significant difference to the disadvantage of alpelisib + fulvestrant was found. For each of these outcomes, there is therefore a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

Mucosal inflammation (PT, AEs)

For the outcome of mucosal inflammation (PT, AEs), a statistically significant difference was found to the disadvantage of alpelisib + fulvestrant in comparison with placebo + fulvestrant. For this outcome, there is therefore a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

Weight decreased (PT, AEs)

For the outcome of weight decreased (PT, AEs), a statistically significant difference was found to the disadvantage of alpelisib + fulvestrant in comparison with placebo + fulvestrant. For this outcome, there is therefore a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

Musculoskeletal and connective tissue disorders (SOCs, SAEs)

For the outcome of musculoskeletal and connective tissue disorders (SOC, SAEs), a statistically significant difference was found to the disadvantage of alpelisib + fulvestrant in comparison with placebo + fulvestrant. For this outcome, there is therefore a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

General disorders and administration site conditions (SOC, severe AEs)

For the outcome of general disorders and administration site conditions (SOC, severe AEs), a statistically significant difference was found to the disadvantage of alpelisib + fulvestrant in

comparison with placebo + fulvestrant. For this outcome, there is therefore a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

Investigations (SOC, severe AEs)

For the outcome of investigations (SOC, severe AEs), a statistically significant difference was found to the disadvantage of alpelisib + fulvestrant in comparison with placebo + fulvestrant. For this outcome, there is therefore a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

Hypokalemia (PT, severe AEs)

For the outcome of hypokalemia (PT, severe AEs), a statistically significant difference was found to the disadvantage of alpelisib + fulvestrant in comparison with placebo + fulvestrant. For this outcome, there is therefore a hint of greater harm from alpelisib + fulvestrant in comparison with fulvestrant.

2.3.1.1 Subgroups and other effect modifiers

The effect modifiers and methods used in the present assessment are described in Section 2.2.1.1.

The results on the relevant effect modifiers regarding ECOG-PS are shown in Appendix A.

Table 12: Subgroups (health-related quality of life) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage)

Study Outcome	Alpelisib + fulvestrant		Placebo + fulvestrant		Alpelisib + fulvestrant vs. placebo + fulvestrant	
Characteristic Subgroup	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]	p-value[a]
SOLAR-1 (3rd data cut-off: 23/04/2020)						
Health-related quality of life						
EORTC QLQ-C30 – global health status and functioning scales[b]						
Global health status						
Age						
< 65 years	47	7.5 [4.2; NR] 18 (38.3)	42	9.2 [3.7; NR] 15 (35.7)	0.80 [0.39; 1.65]	0.558
≥ 65 years	32	5.6 [1.9; 5.6] 22 (68.8)	40	NR [3.8; NR] 12 (30.0)	2.30 [1.12; 4.72]	0.023
Total					Interaction[c]:	0.027

a. HR and CI: Cox proportional hazards model; p-value: log-rank test; each stratified by prior therapy with a CDK 4/6 inhibitor (yes vs. no) and by the presence of liver and/or lung metastases (yes vs. no).
b. Time to first deterioration by 15 points.
c. p-value for the interaction term "treatment*subgroup characteristic" in a Cox proportional hazards model.

CDK: cyclin-dependent kinase; CI: confidence interval; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HR: hazard ratio; n: number of patients with (at least 1) event; N: number of analysed patients; NR: not reached; RCT: randomized controlled trial

Health-related quality of life

Global health status (EORTC QLQ-C30)

For the outcome of global health status, there is an effect modification by the characteristic of age (< 65 years / ≥ 65 years). No statistically significant difference between treatment groups was found for patients < 65 years of age. For patients < 65 years of age, this results in no hint of added benefit; an added benefit is therefore not proven for these patients. For patients ≥ 65 years of age, there is a statistically significant difference to the disadvantage of alpelisib + fulvestrant. For these patients, this results in a hint of lesser benefit of alpelisib + fulvestrant in comparison with fulvestrant.

2.3.2 Extent and probability of added benefit

Assessment of added benefit at outcome level

On the basis of the results presented in Section 2.3.1, the extent of the respective added benefit at outcome level was estimated (see Table 13).

Determination of the outcome category for the outcomes of symptoms and AEs

Not for all outcomes examined in the present benefit assessment does the dossier permit inferences as to whether they were serious/severe or non-serious/non-severe. A rationale for the classification of these outcomes is provided below.

EORTC QLQ-C30 (symptom scales)

Module 4 of the dossier provides no data suitable for determining the severity of the outcomes of nausea and vomiting, dyspnoea, decreased appetite, or diarrhoea. Therefore, these outcomes are allocated to the outcome category of non-serious/non-severe symptoms / late complications.

Table 13: Extent of added benefit at outcome level: RCT, direct comparison: alpelisib + fulvestrant vs. fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage) (multi-page table)

Outcome category **Outcome** **Subgroup**	**Alpelisib + fulvestrant vs. fulvestrant** **Median time to event (months)** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Morbidity		
EORTC QLQ-C30 – symptom scales		
Fatigue	7.4 months vs. NR HR: 1.71 [0.98; 2.96]; p = 0.054	Lesser/added benefit not proven
Nausea and vomiting	7.4 vs. 12.9 months HR: 1.89 [1.12; 3.18] HR: 0.53 [0.31; 0.89][c] p = 0.016 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $0.80 \leq CI_u < 0.90$ Lesser benefit; extent: minor
Pain	9.2 vs. 6.5 months HR: 0.79 [0.49; 1.28]; p = 0.330	Lesser/added benefit not proven
Dyspnoea	22.6 vs. 9.2 months HR: 0.39 [0.22; 0.70]; p = 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.80$ Added benefit, extent: considerable
Insomnia	6.5 months vs. NR HR: 1.39 [0.83; 2.33]; p = 0.203	Lesser/added benefit not proven
Decreased appetite	4.0 vs. 13.9 months HR: 1.67 [1.02; 2.73] HR: 0.60 [0.37; 0.98][c] p = 0.045	Outcome category: non-serious/non-severe symptoms / late complications $0.90 \leq CI_u < 1.00$ Lesser benefit / added benefit not proven[d]
Constipation	28.6 vs. 9.3 months HR: 0.61 [0.34; 1.08]; p = 0.092	Lesser/added benefit not proven
Diarrhoea	5.6 months vs. NR HR: 2.86 [1.59; 5.12] HR: 0.35 [0.20; 0.63][c] p < 0.001 Probability: hint	Outcome category: non-serious/non-severe symptoms / late complications $CI_u < 0.80$ Lesser benefit; extent: considerable

Table 13: Extent of added benefit at outcome level: RCT, direct comparison: alpelisib + fulvestrant vs. fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage) (multi-page table)

Outcome category **Outcome** **Subgroup**	**Alpelisib + fulvestrant vs. fulvestrant** **Median time to event (months)** **Effect estimation [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
Worst pain (BPI-SF item 3)	12.9 vs. 9.2 months HR: 0.63 [0.37; 1.07]; p = 0.089	Lesser/added benefit not proven
Pain intensity (BPI-SF)	No usable data	Lesser/added benefit not proven
Pain interference (BPI-SF)	No usable data	Lesser/added benefit not proven
Health status (EQ-5D-5L VAS)	14.3 vs. 22.1 months HR: 1.06 [0.60; 1.89]; p = 0.839	Lesser/added benefit not proven
Health-related quality of life		
EORTC QLQ-C30 – global health status and functioning scales		
Global health status		
Age		
< 65 years	7.5 vs. 9.2 months HR: 0.80 [0.39; 1.65]; p = 0.558	Lesser/added benefit not proven
≥ 65 years	5.6 months vs. NR HR: 2.30 [1.12; 4.72] HR: 0.43 [0.21; 0.89][c] p = 0.023 Probability: hint	Outcome category: health-related quality of life $0.75 \leq CI_u < 0.90$ Lesser benefit; extent: considerable
Physical functioning	NR vs. NR HR: 1.01 [0.51; 1.98]; p = 0.990	Lesser/added benefit not proven
Role functioning	5.6 vs. 5.6 months HR: 1.07 [0.68; 1.69]; p = 0.827	Lesser/added benefit not proven
Emotional functioning	12.8 vs. 11.1 months HR: 1.01 [0.60; 1.71]; p = 0.965	Lesser/added benefit not proven
Cognitive functioning	7.4 vs. 11.1 months HR: 1.21 [0.73; 2.00]; p = 0.450	Lesser/added benefit not proven
Social functioning	4.7 vs. 14.8 months HR: 1.77 [1.07; 2.92] HR: 0.56 [0.34; 0.93][c] p = 0.027 Probability: hint	Outcome category: health-related quality of life $0.90 \leq CI_u < 1.00$ Lesser benefit; extent: minor

Table 13: Extent of added benefit at outcome level: RCT, direct comparison: alpelisib + fulvestrant vs. fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage) (multi-page table)

Outcome category **Outcome** **Subgroup**	**Alpelisib + fulvestrant vs. fulvestrant** **Median time to event (months)** **Effect estimation [95% CI]** **p-value** **Probability[a]**	**Derivation of extent[b]**
AEs		
Hyperglycaemia (SMQ, severe AEs[d])	NR vs. NR HR: NC; $p < 0.001$ Probability: Indication[f]	Outcome category: serious/severe AEs Greater harm; extent: major[g]
Skin rash (CMQ, severe AEs[e])	NR vs. NR HR: NC; $p < 0.001$ Probability: hint	Outcome category: serious/severe AEs Greater harm; extent: non-quantifiable
Alopecia (PT, AEs)	NR vs. NR HR: 17.39 [2.30; 131.33] HR: 0.06 [0.01; 0.43]; $p < 0.001$ Probability: hint	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ greater harm; extent: considerable
Pruritus (PT, AEs)	NR vs. NR HR: 6.09 [1.78; 20.85] HR: 0.16 [0.05; 0.56]; $p = 0.001$ Probability: hint	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ greater harm; extent: considerable
Gastrointestinal disorders (SOC, AEs)	0.3 vs. 5.4 months HR: 3.30 [2.20; 4.97] HR: 0.3 [0.2; 0.45]; $p < 0.001$ Probability: hint	Outcome category: non-serious/non-severe AEs greater harm; extent: considerable
Mucosal inflammation (PT, AEs)	NR vs. NR HR: 7.61 [1.73; 33.55] HR: 0.13 [0.03; 0.58]; $p = 0.002$ Probability: hint	Outcome category: non-serious/non-severe AEs $CI_u < 0.80$ greater harm; extent: considerable
Weight decreased (PT, AEs)	NR vs. NR HR: NC; $p < 0.001$ Probability: hint	Outcome category: non-serious/non-severe AEs Greater harm; extent: non-quantifiable
Stomatitis (PT, SAEs)	NR vs. NR HR: NC; $p = 0.048$ Probability: hint	Outcome category: serious/severe AEs Greater harm; extent: non-quantifiable

Table 13: Extent of added benefit at outcome level: RCT, direct comparison: alpelisib + fulvestrant vs. fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage) (multi-page table)

Outcome category **Outcome** **Subgroup**	**Alpelisib + fulvestrant vs. fulvestrant** **Median time to event (months)** **Effect estimation [95% CI]** **p-value** **Probability**[a]	**Derivation of extent**[b]
Musculoskeletal and connective tissue disorders (SOCs, SAEs)	NR vs. NR HR: NC; p = 0.033 Probability: hint	Outcome category: serious/severe AEs Greater harm; extent: non-quantifiable
Diarrhoea (PT, severe AEs[e])	NR vs. NR HR: NC; p = 0.029 Probability: hint	Outcome category: serious/severe AEs Greater harm; extent: non-quantifiable
General disorders and administration site conditions (SOC, severe AEs[e])	NR vs. NR HR: NC; p = 0.014 Probability: hint	Outcome category: serious/severe AEs Greater harm; extent: non-quantifiable
Investigations (SOC, severe AEs[e])	NR vs. NR HR: 2.50 [1.23; 5.08] HR: 0.4 [0.20; 0.81]; p = 0.009 Probability: hint	Outcome category: serious/severe AEs $0.75 \leq CI_u < 0.90$ greater harm; extent: considerable
Hypokalemia (PT, severe AEs[e])	NR vs. NR HR: NC; p = 0.032 Probability: hint	Outcome category: serious/severe AEs Greater harm; extent: non-quantifiable

a. Probability is stated if a statistically significant and relevant effect is present.
b. Estimations of effect size are made depending on the outcome category, with different limits according to the upper limit of the confidence interval (CI_u).
c. IQWiG calculation, reversed direction of effect to enable use of limits to derive the extent of added benefit.
d. The extent of the effect is no more than marginal for this non-serious/non-severe outcome.
e. Operationalized as CTCAE grade 3 or 4.
f. The certainty of results is deemed high since the observation of an effect of this size cannot be explained solely by different follow-up durations and incomplete follow-up for potentially informative reasons (also see research question A1).
g. Given the results and the Kaplan-Meier curves for research question A1 on this outcome, the same effect size as in research question A1 is assumed.

AE: adverse event; BPI-SF: Brief Pain Inventory – Short Form; CI: confidence interval; CI_u: upper limit of CI; CMQ: Customized MedDRA Query; CTCAE: Common Terminology Criteria for Adverse Events; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire – Core 30; EQ-5D-5L: European Quality of Life 5-Dimensions 5-Level; HR: hazard ratio; MedDRA: Medical Dictionary for Regulatory Activities; NC: not calculable; NR: not reached; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SMQ: standardized MedDRA query; SOC: system organ class; VAS: visual analogue scale

Overall conclusion on added benefit

Table 14 summarizes the results of the dossier assessment [1] and the addendum which are used to draw the overall conclusion on the extent of added benefit for research question B1.

Table 14: Favourable and unfavourable effects from the assessment of alpelisib plus fulvestrant in comparison with fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage)

Favourable effects	**Unfavourable effects**[a]
Non-serious/non-severe symptoms / late complications ▪ Dyspnoea: hint of added benefit – extent: considerable	Non-serious/non-severe symptoms / late complications ▪ Nausea and vomiting: hint of lesser benefit – extent: minor ▪ Diarrhoea: Hint of lesser harm – extent: considerable
–	Health-related quality of life ▪ Global health status ▫ Age (≥ 65 years): hint of lesser harm – extent: considerable ▪ Social functioning: hint of lesser benefit – extent: minor
–	Serious/severe AEs ▪ **SAEs: hint of greater harm – extent: considerable** Including ▫ stomatitis, musculoskeletal and connective tissue disorders: for each, hint of greater harm – extent: non-quantifiable ▪ **Severe AEs: indication of greater harm – extent: major** Including ▫ Hyperglycaemia: indication of greater harm – extent: major ▫ Investigations: hint of greater harm – extent: considerable ▫ Skin rash, diarrhoea, general disorders and administration site conditions: for each, hint of greater harm – extent: non-quantifiable
–	Non-serious/non-severe AEs ▪ **Discontinuation due to AEs: Hint of greater harm – extent: considerable** ▪ Alopecia, pruritus, gastrointestinal disorders, mucosal inflammation: for each, hint of greater harm – extent: considerable ▪ Weight decreased: hint of greater harm – extent: non-quantifiable
a. Results shown in bold have already been included in the overall conclusion on added benefit in the dossier assessment. AE: adverse event; SAE: serious adverse event	

When the data subsequently submitted in the commenting procedure are included, 1 favourable effect and a series of unfavourable effects are found for the outcomes of the morbidity and health-related quality of life categories. For the data on specific AEs, which were subsequently

submitted during the commenting procedure, exclusively unfavourable effects of alpelisib in combination with fulvestrant were found, some of them with the probability of indication.

In summary, there is an indication of lesser benefit of alpelisib plus fulvestrant in comparison with fulvestrant for postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer with PIK3CA mutation who experience progression of disease following endocrine monotherapy in the locally advanced or metastatic stage.

2.4 Summary

The data the company subsequently submitted during the commenting procedure change the conclusion drawn regarding the added benefit of alpelisib in combination with fulvestrant from dossier assessment A20-81 for research questions A1 and B1: instead of a hint of lesser benefit, an indication of lesser benefit is derived for both research questions on the basis of the data subsequently submitted by the company.

Table 15 below presents the results of the benefit assessment of alpelisib + fulvestrant on the basis of data from both dossier assessment A20-81 and the present addendum.

Table 15: Alpelisib in combination with fulvestrant – probability and extent of added benefit (multi-page table)

Research question	**Therapeutic indication**	**ACT**[a]	**Probability and extent of added benefit**[b]
Men and postmenopausal women with HR-positive, HER2-negative, locally advanced or metastatic breast cancer[c] with PIK3CA mutation			
A1	Postmenopausal women after disease progression following endocrine monotherapy in the (neo)adjuvant treatment situation	▪ Ribociclib in combination with a nonsteroidal aromatase inhibitor or ▪ Ribociclib in combination with fulvestrant or ▪ Anastrozole or ▪ Letrozole or ▪ Fulvestrant or ▪ Possibly tamoxifen if aromatase inhibitors are not suitable	**Indication of** lesser benefit[d]
A2	Men after disease progression following endocrine monotherapy in the (neo)adjuvant treatment situation	Therapy upon the physician's discretion	Added benefit not proven
B1	Postmenopausal women after disease progression following endocrine monotherapy in the locally advanced or metastatic stage	Another endocrine therapy with ▪ abemaciclib in combination with fulvestrant or ▪ ribociclib in combination with fulvestrant or ▪ tamoxifen or ▪ anastrozole or ▪ fulvestrant monotherapy; only for patients with recurrence or progression following antioestrogen treatment or ▪ letrozole, only for patients with recurrence or progression following antioestrogen treatment or ▪ exemestane, only for patients with progression following antioestrogen treatment or ▪ everolimus in combination with exemestane, only for patients without symptomatic visceral metastasis after progression following nonsteroidal aromatase inhibitor therapy	**Indication of** lesser benefit[d]
B2	Men after progression following endocrine monotherapy in the locally advanced or metastatic stage	Therapy upon the physician's discretion	Added benefit not proven

Table 15: Alpelisib in combination with fulvestrant – probability and extent of added benefit (multi-page table)

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit[b]
a. Presented is the ACT specified by the G-BA. b. Changes in comparison with dossier assessment A20-81 are shown in **bold**. c. For the given therapeutic indication, it is assumed that another endocrine therapy is indicated for the patient, while no indication exists for chemotherapy or (secondary) resection or radiotherapy with curative intent. d. The SOLAR-1 study includes data only on the comparison with fulvestrant (for research question B1, viewed by the G-BA as a sufficiently suitable comparator even after prior aromatase inhibitor therapy). Further, only patients with an ECOG-PS of 0 or 1 were included. It remains unclear whether the observed effects are transferable to patients with an ECOG-PS ≥ 2. Virtually all patients included in the study were in stage IV (breast cancer with distant metastases). ECOG-PS: Eastern Cooperative Oncology Group Performance Status; G-BA: Federal Joint Committee; HER2: human epidermal growth receptor 2; HR: hormone receptor; PIK3CA: phosphtidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha			

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Alpelisib (Mammakarzinom) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2020 [Accessed: 29.01.2021]. URL: https://www.iqwig.de/download/a20-81_alpelisib_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Novartis Pharma. Alpelisib (Piqray): Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2020 [Accessed: 16.12.2020]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/581/#dossier.

3. Novartis Pharma. Stellungnahme zum IQWiG-Bericht Nr. 1002: Alpelisib (Mammakarzinom); Nutzenbewertungen gemäß § 35a SGB V; Dossierbewertung; Auftrag A20-81. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/581/#beschluesse in the document "Zusammenfassende Dokumentation"].

4. Institute for Quality and Efficiency in Health Care. General methods 6.0 (German version) [online]. 2020 [Accessed: 13.11.2020]. URL: https://www.iqwig.de/download/Allgemeine-Methoden_Version-6-0.pdf.

Appendix A – Subgroup results on the characteristic of ECOG-PS (0/1)

Research question A1: postmenopausal women, first-line therapy in the advanced stage

Table 16: Subgroups (morbidity, AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Study Outcome Characteristic Subgroup	Alpelisib + fulvestrant N	Alpelisib + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Placebo + fulvestrant N	Placebo + fulvestrant Median time to event in months [95% CI] Patients with event n (%)	Alpelisib + fulvestrant vs. placebo + fulvestrant HR [95% CI][a]	 p-value[a]
SOLAR-1 (3rd data cut-off: 23/04/2020)						
Morbidity						
EORTC QLQ-C30 – symptom scales[c]						
Pain						
ECOG-PS						
0	59	11.1 [7.4; 27.6] 29 (49.2)	63	11.0 [3.7; NR 23 (36.5)]	1.06 [0.61; 1.85]	0.824
1	28	22.1 [5.6; NR] 7 (25.0)	26	5.6 [1.9; 11.2] 15 (57.5)	0.24 [0.08; 0.67]	0.005
Total					Interaction[b]:	0.019
Constipation						
ECOG-PS						
0	59	30.4 [22.1; NR] 17 (28.8)	63	NR [16.6; NR] 14 (22.2)	0.95 [0.47; 1.93]	0.884
1	28	NR [15.4; NR] 4 (14.3)	26	5.5 [1.9; NR] 12 (46.2)	0.17 [0.05; 0.66]	0.005
Total					Interaction[b]:	0.020
AEs						
Gastrointestinal disorders (SOC, AEs)						
ECOG-PS						
0	59	0.3 [0.2; 0.6] 52 (88.1)	63	21.2 [8.5; NR] 25 (39.7)	4.10 [2.51; 6.70]	< 0.001
1	28	0.5 [0.3; 1.4] 23 (82.1)	26	6.0 [0.5; 20.2] 15 (57.7)	1.86 [0.91; 3.82]	0.085
Total					Interaction[b]:	0.035

Table 16: Subgroups (morbidity, AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Study Outcome	Alpelisib + fulvestrant		Placebo + fulvestrant		Alpelisib + fulvestrant vs. placebo + fulvestrant	
Characteristic Subgroup	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]	p-value[a]

a. HR and CI: Cox proportional hazards model; p-value: log-rank test; each stratified by prior therapy with a CDK 4/6 inhibitor (yes vs. no) and by the presence of liver and/or lung metastases (yes vs. no).
b. p-value for the interaction term "treatment*subgroup characteristic" in a Cox proportional hazards model.
c. Time to first deterioration by 15 points.

CDK: cyclin-dependent kinase; ECOG: Eastern Cooperative Oncology Group; EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; HR: hazard ratio; CI: confidence interval; n: number of patients with (at least 1) event; N: number of analysed patients; NR: not reached; PS: performance status; RCT: randomized controlled trial

Research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage

Table 17: Subgroups (morbidity) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage)

Study Outcome	Alpelisib + fulvestrant		Placebo + fulvestrant		Alpelisib + fulvestrant vs. placebo + fulvestrant	
Characteristic Subgroup	N	Median time to event in months [95% CI] Patients with event n (%)	N	Median time to event in months [95% CI] Patients with event n (%)	HR [95% CI][a]	p-value[a]
SOLAR-1 (3rd data cut-off: 23/04/2020)						
Morbidity						
Worst pain (BPI-SF)[b]						
ECOG-PS						
0	51	9.7 [5.6; 28.6] 21 (41.2)	49	12.9 [5.6; NR] 16 (32.7)	1.21 [0.60; 2.43]	0.514
1	28	27.9 [9.4; NR] 8 (28.6)	32	3.9 [3.6; 9.2] 16 (50.0)	0.14 [0.04; 0.51]	< 0.001
Total					Interaction[c]:	0.030

a. HR and CI: Cox proportional hazards model; p-value: log-rank test; each stratified by prior therapy with a CDK 4/6 inhibitor (yes vs. no) and by the presence of liver and/or lung metastases (yes vs. no).
b. Time to first deterioration by 2 points.
c. p-value for the interaction term "treatment*subgroup characteristic" in a Cox proportional hazards model.

BPI-SF: Brief Pain Inventory – Short Form; CDK: cyclin-dependent kinase; ECOG: Eastern Cooperative Oncology Group Performance Status; HR: hazard ratio; CI: confidence interval; n: number of patients with (at least 1) event; N: number of analysed patients; NR: not reached; PS: performance status; RCT: randomized controlled trial

Appendix B – Kaplan-Meier curves

B.1 Research question A1: Postmenopausal women, first-line therapy in the advanced stage

B.1.1 Kaplan-Meier curves on the morbidity and health-related quality of life outcomes

Symptom scales of the EORTC QLQ-C30

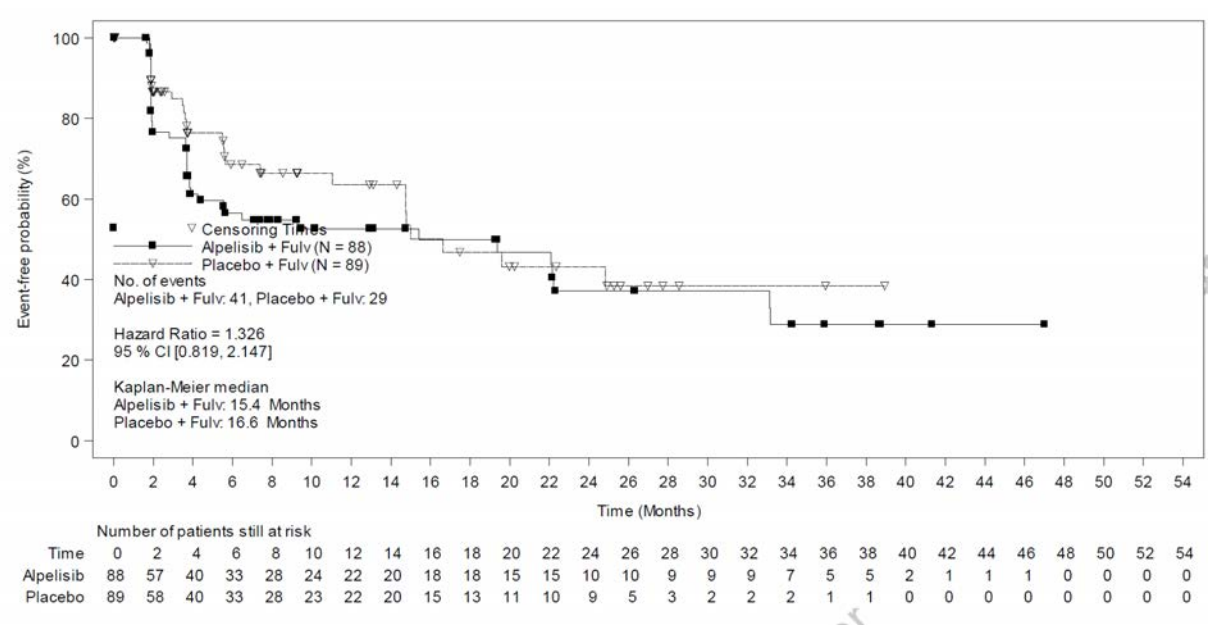

Figure 1: Kaplan-Meier curves for fatigue, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

For the subgroup characteristic of age, no Kaplan-Meier curves are available for the outcome of fatigue, time to first deterioration.

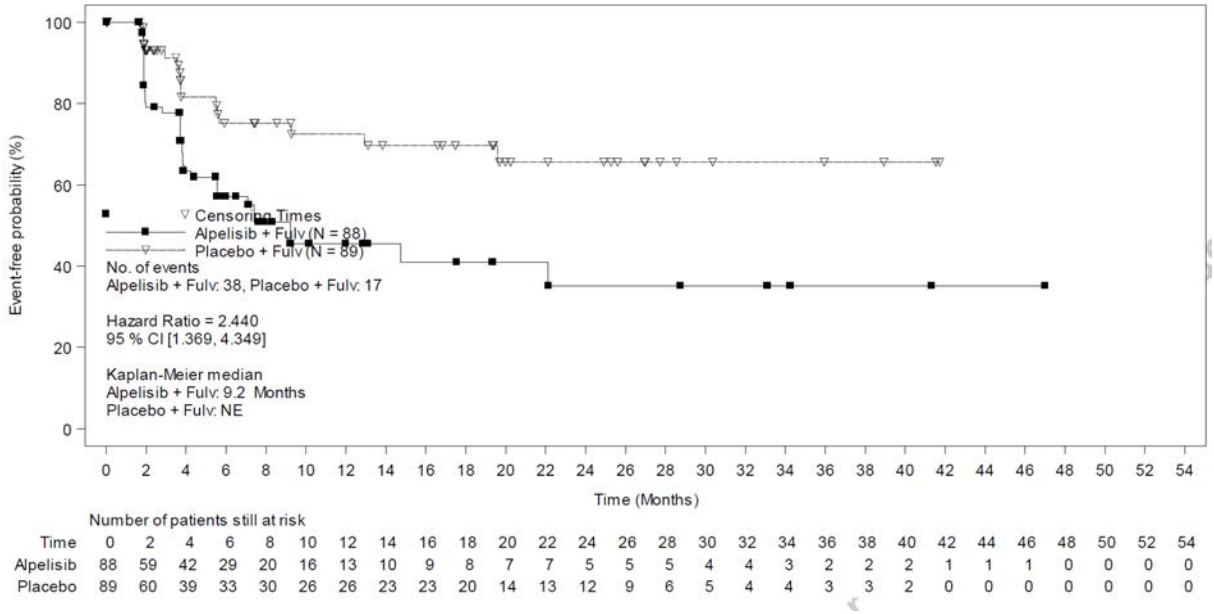

Figure 2: Kaplan-Meier curves for nausea and vomiting, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

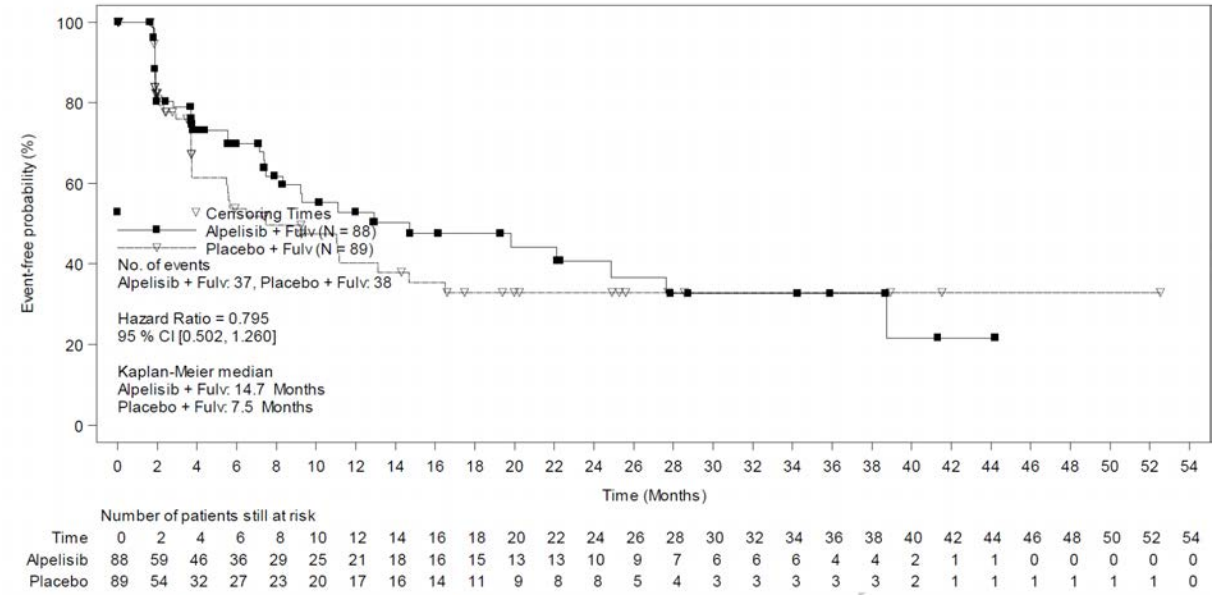

Figure 3: Kaplan-Meier curves for pain, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

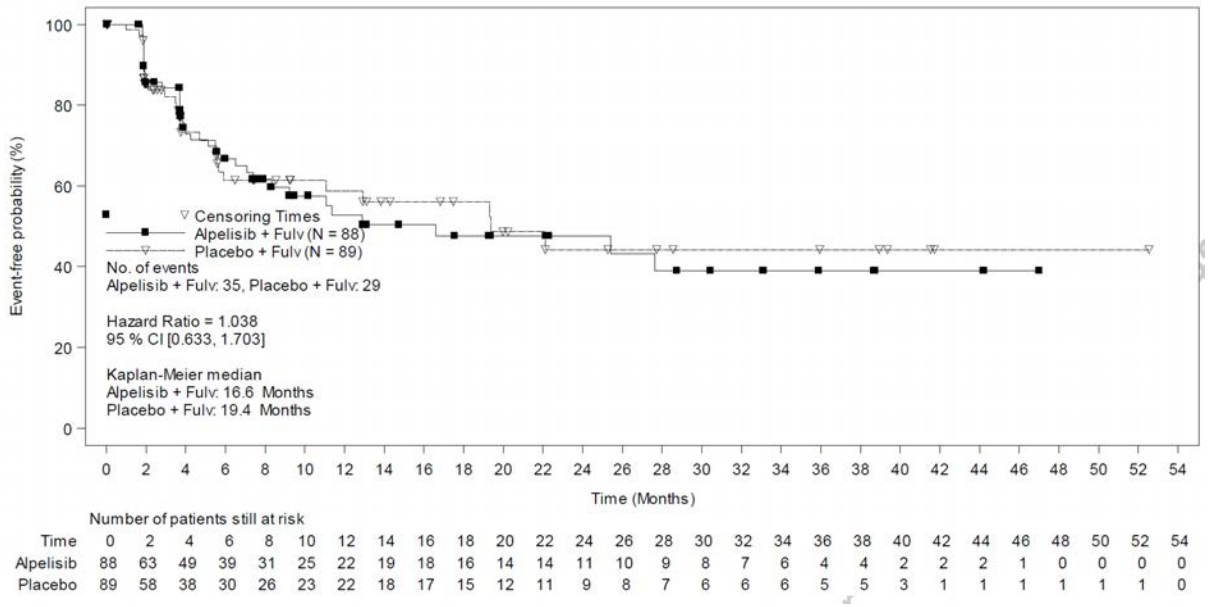

Figure 4: Kaplan-Meier curves for dyspnoea, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

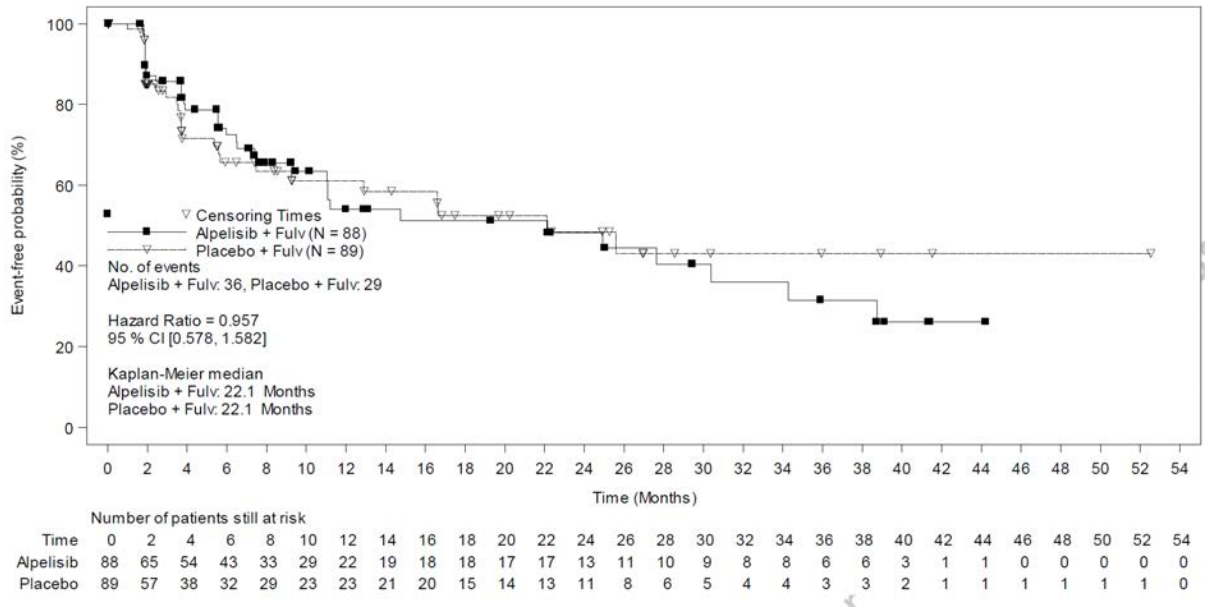

Figure 5: Kaplan-Meier curves for insomnia, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

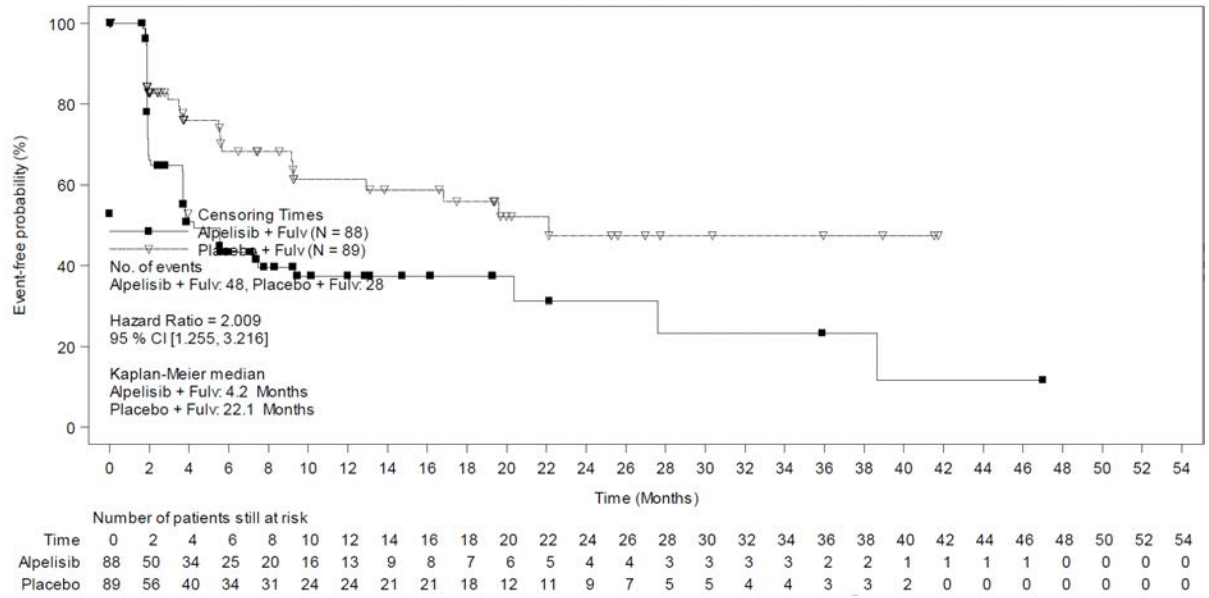

Figure 6: Kaplan-Meier curves for decreased appetite, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

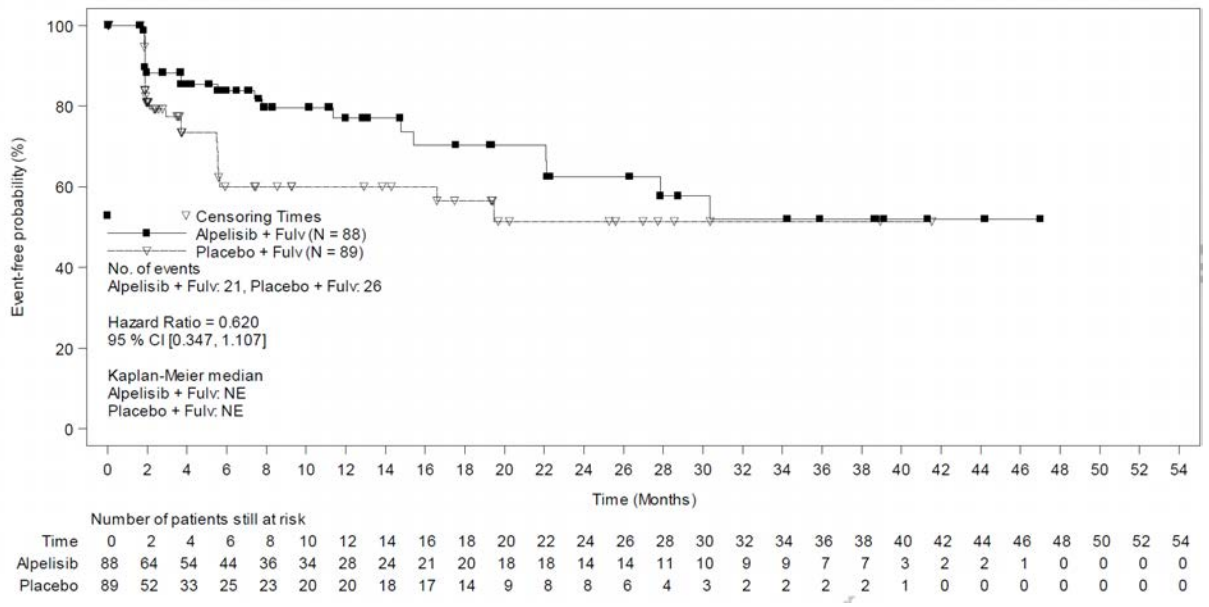

Figure 7: Kaplan-Meier curves for constipation, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

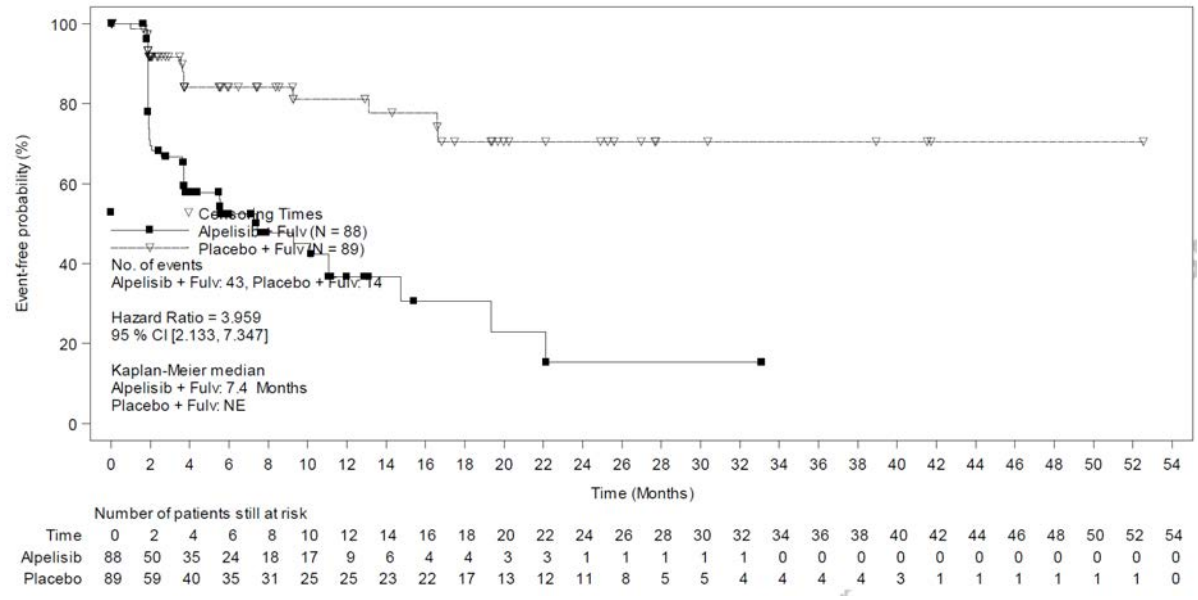

Figure 8: Kaplan-Meier curves for diarrhoea, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

BPI-SF

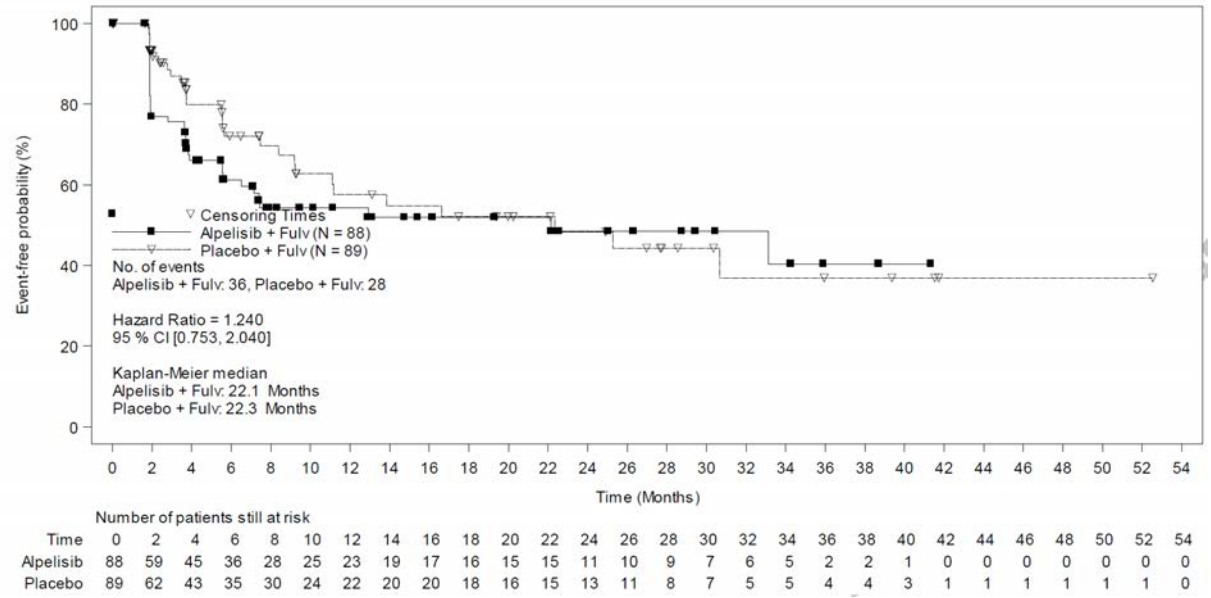

Figure 9: Kaplan-Meier curves for worst pain, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

EQ-5D-5L VAS

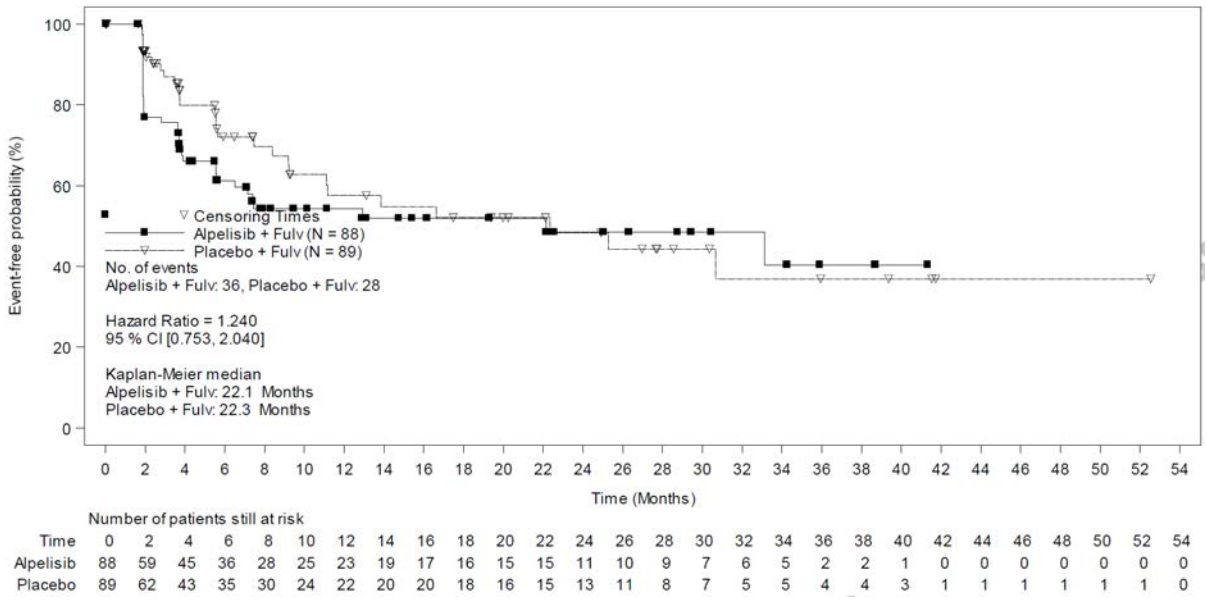

Figure 10: Kaplan-Meier curves for health status (EQ-5D-5L VAS), time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

EORTC QLQ-C30 – health status and functioning scales

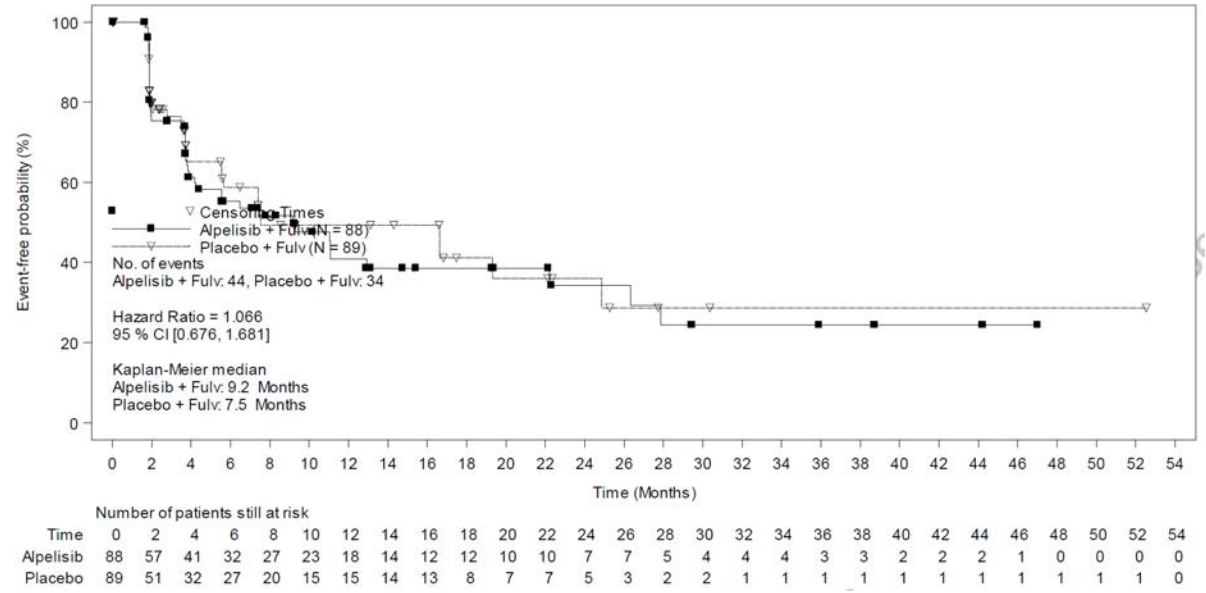

Figure 11: Kaplan-Meier curves for global health status, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

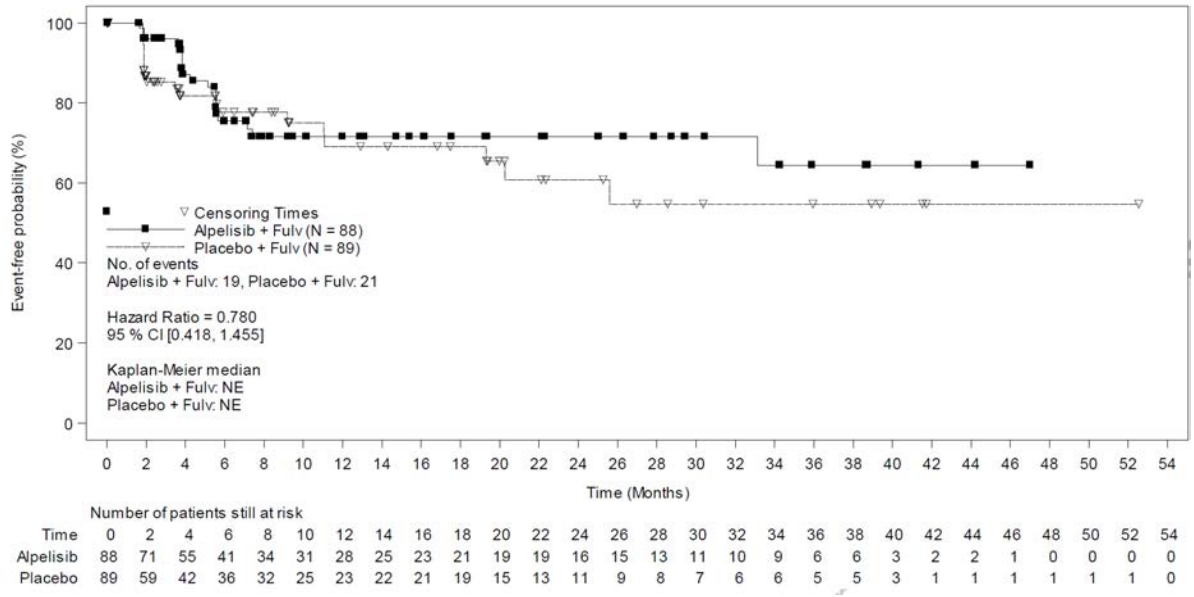

Figure 12: Kaplan-Meier curves for physical functioning, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

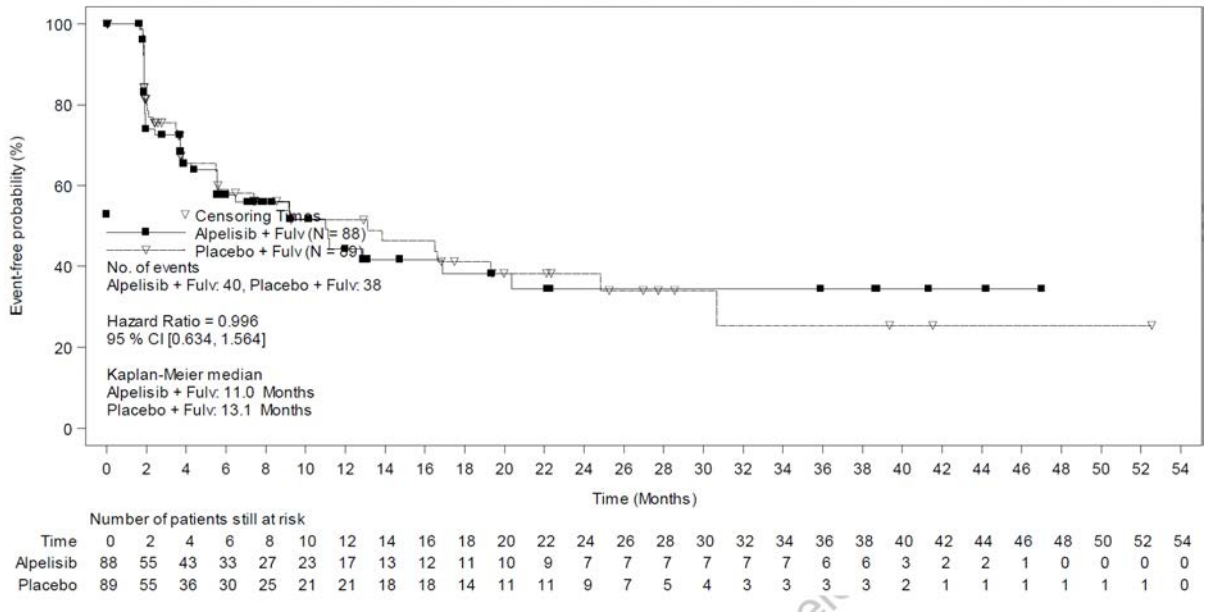

Figure 13: Kaplan-Meier curves for role functioning, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

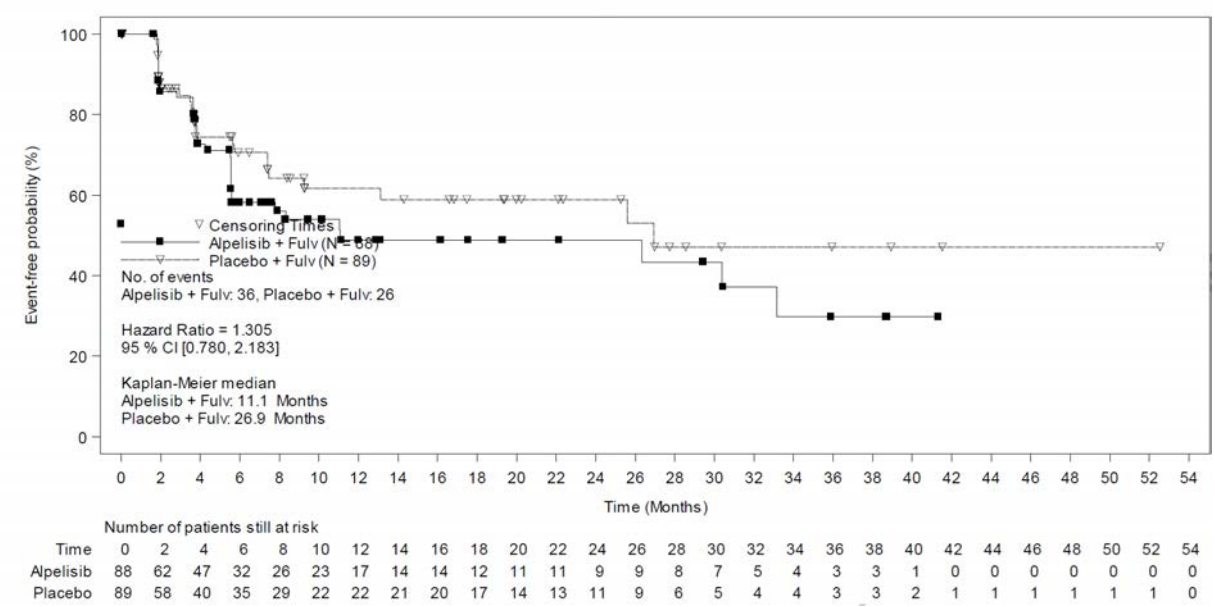

Figure 14: Kaplan-Meier curves for emotional functioning, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

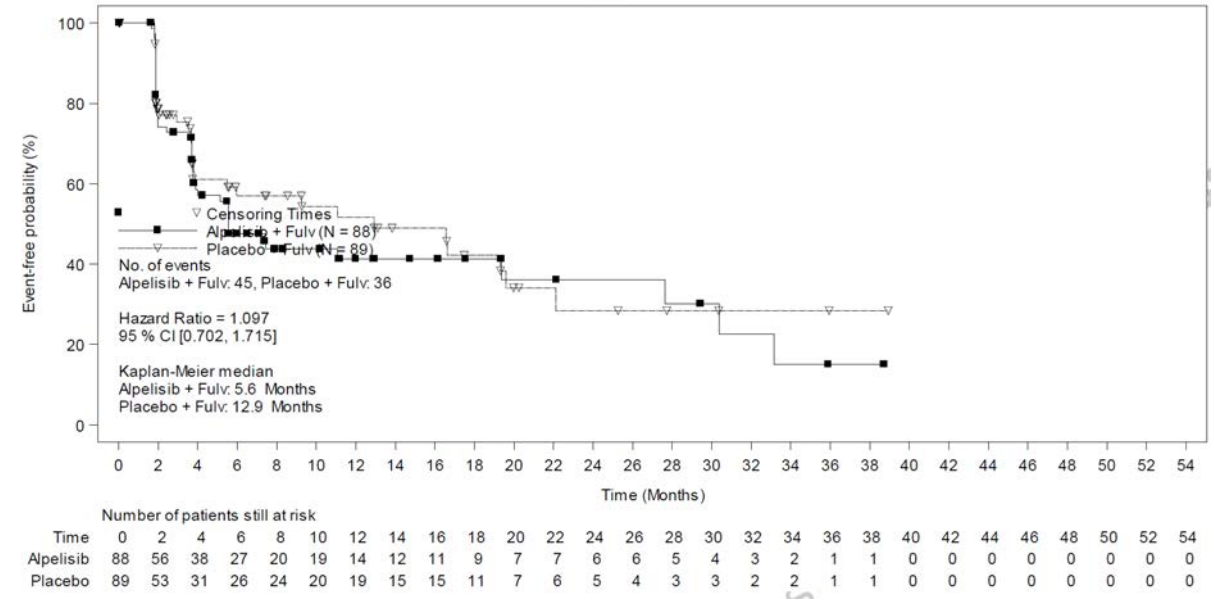

Figure 15: Kaplan-Meier curves for cognitive functioning, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

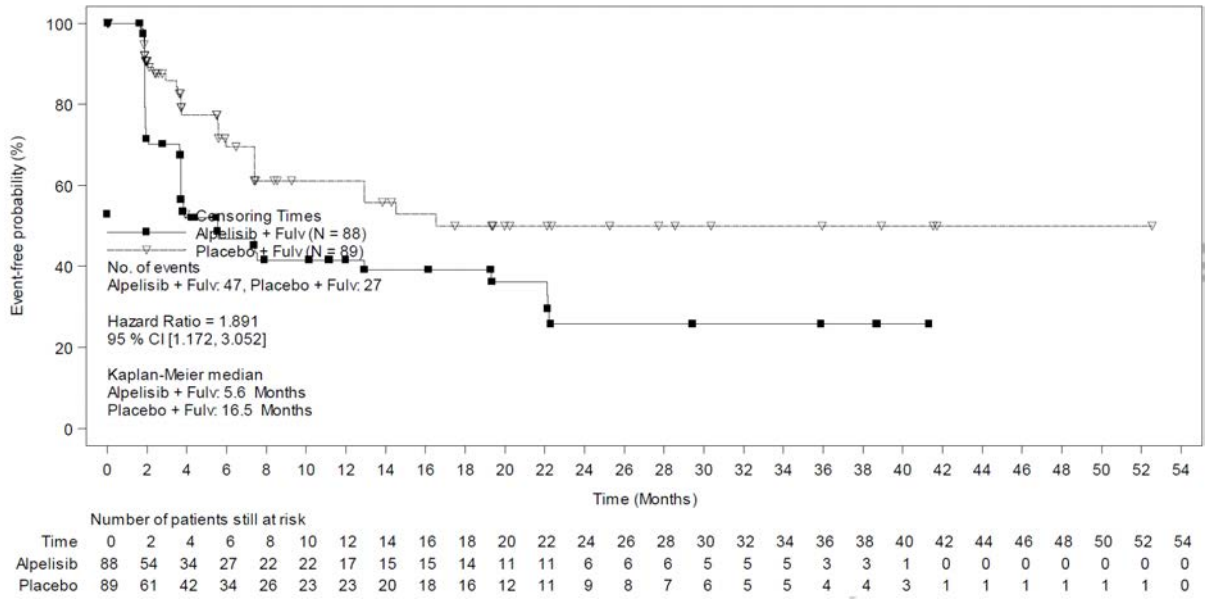

Figure 16: Kaplan-Meier curves for social functioning, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

B.1.2 Kaplan-Meier curves on AEs

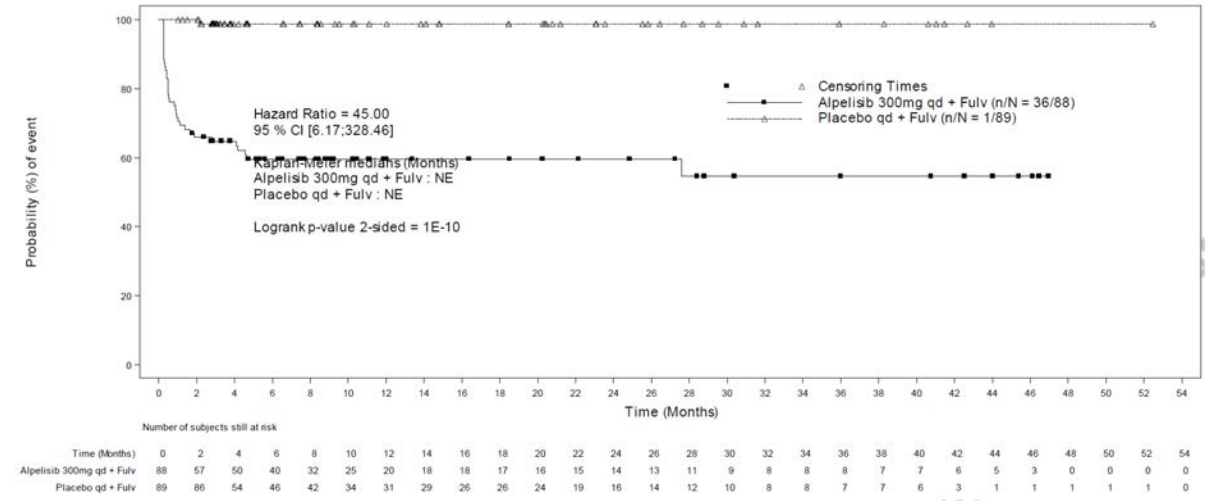

Figure 17: Kaplan-Meier curves for hyperglycaemia (SMQ, severe AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

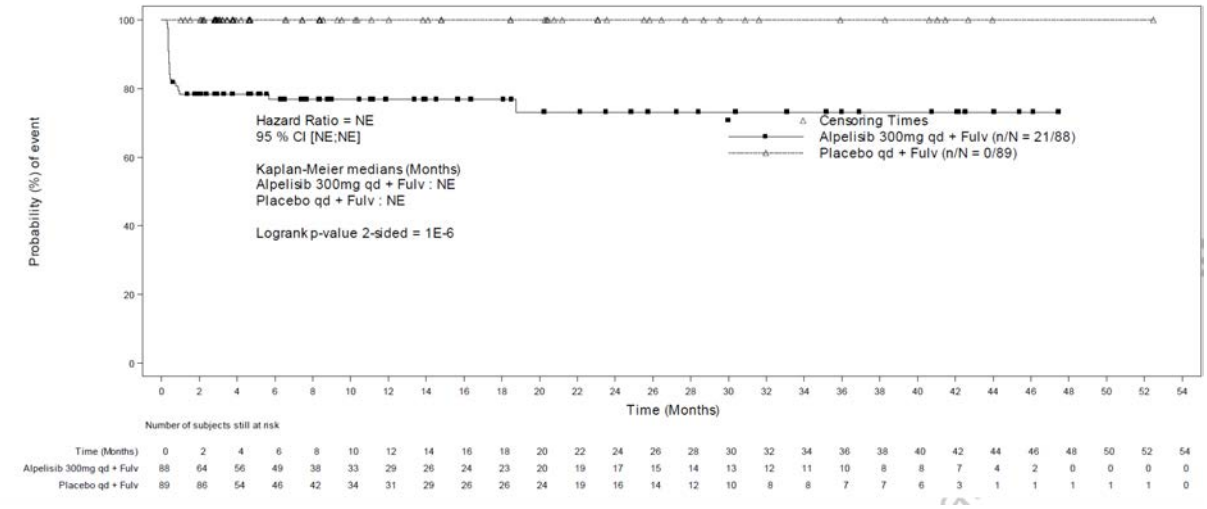

Figure 18: Kaplan-Meier curves for skin rash (CMQ, severe AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

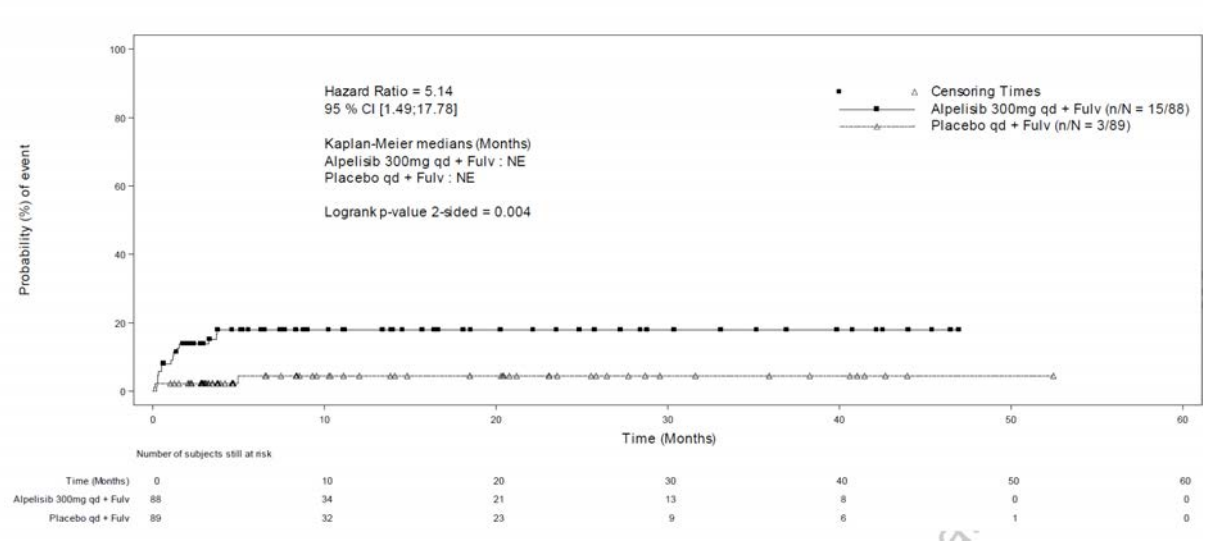

Figure 19: Kaplan-Meier curves for dysgeusia (PT, AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

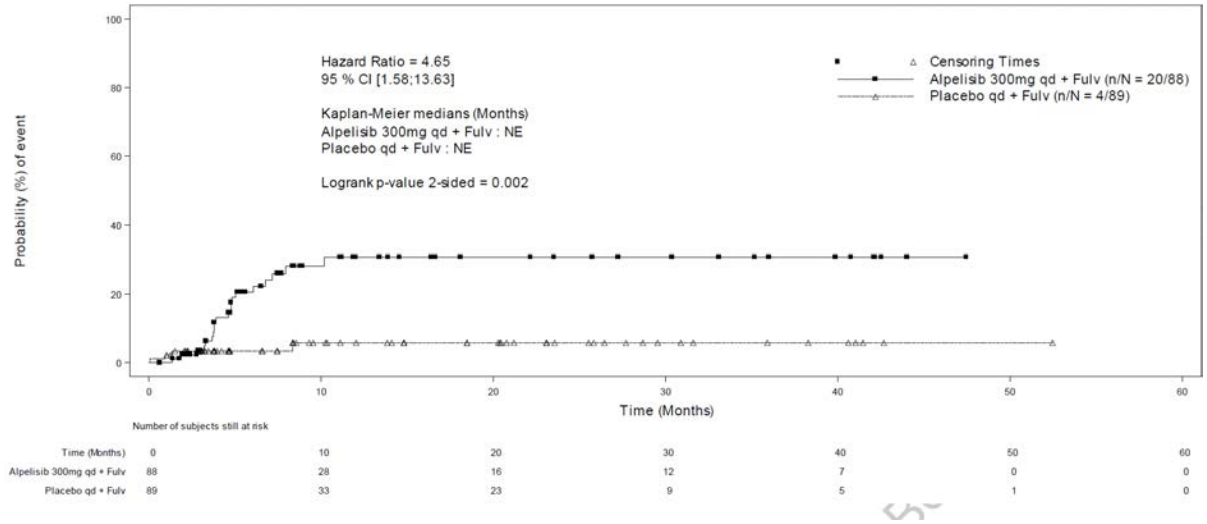

Figure 20: Kaplan-Meier curves for alopecia (PT, AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

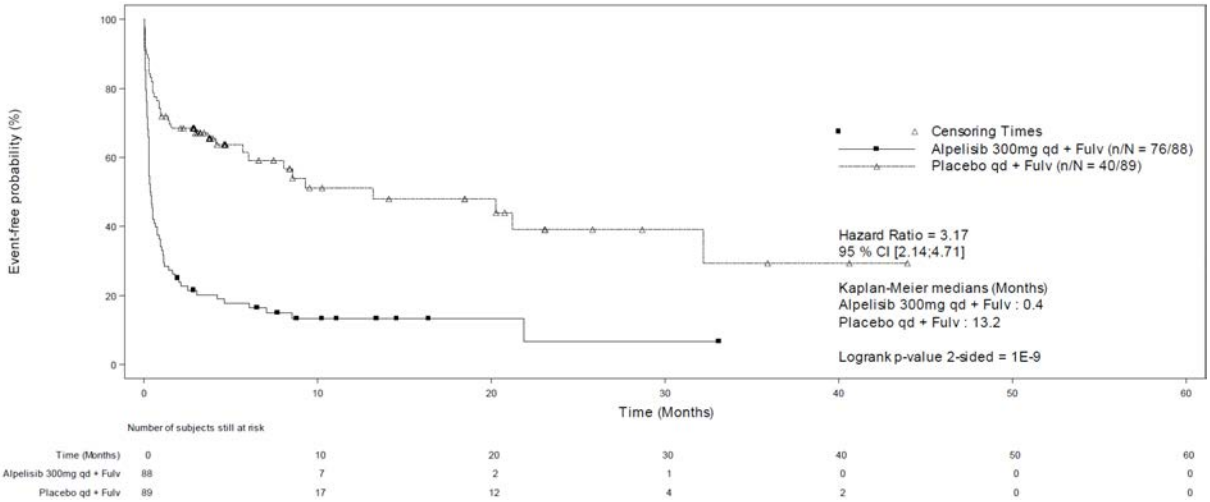

Figure 21: Kaplan-Meier curves for gastrointestinal disorders (SOC, AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

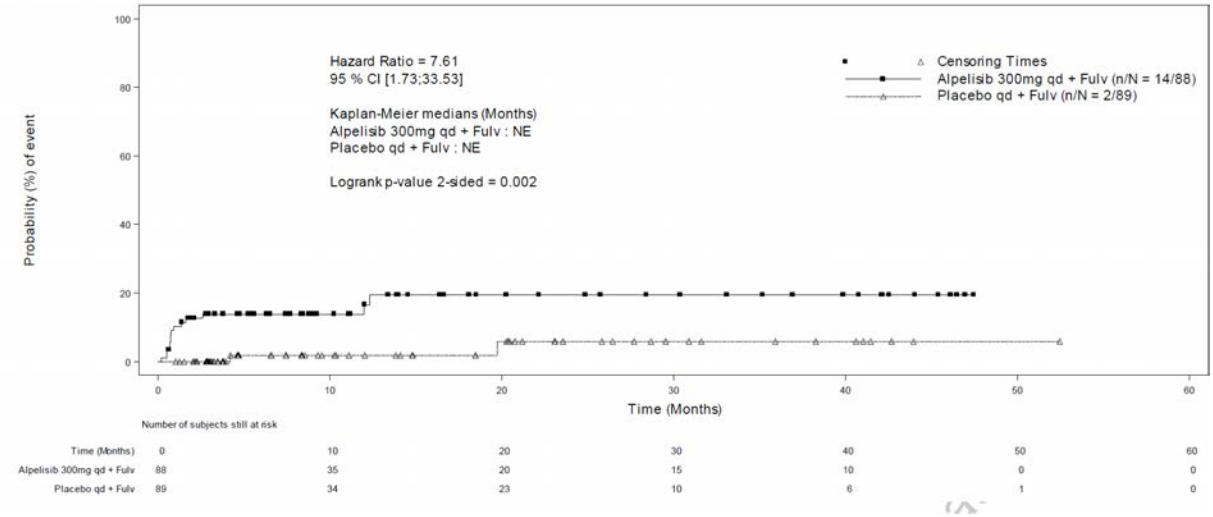

Figure 22: Kaplan-Meier curves for mucosal inflammation (PT, AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

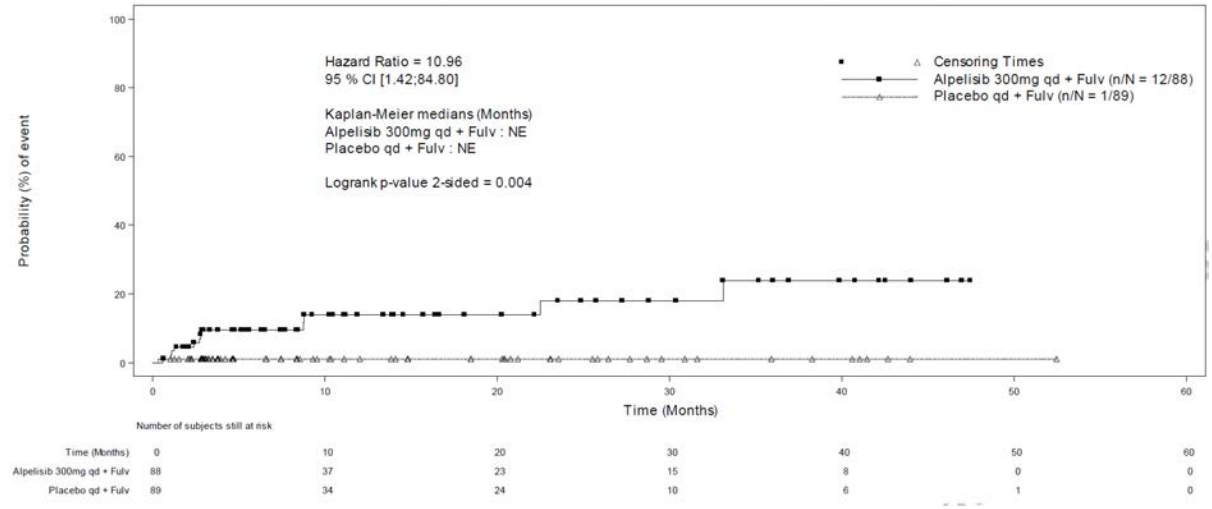

Figure 23: Kaplan-Meier curves for peripheral oedema (PT, AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

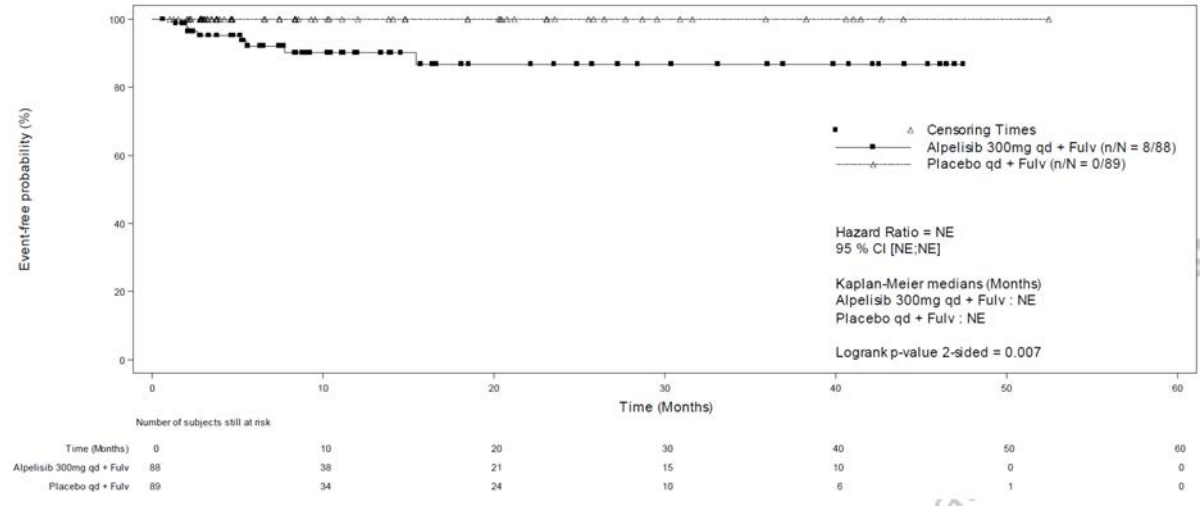

Figure 24: Kaplan-Meier curves for diarrhoea (PT, severe AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

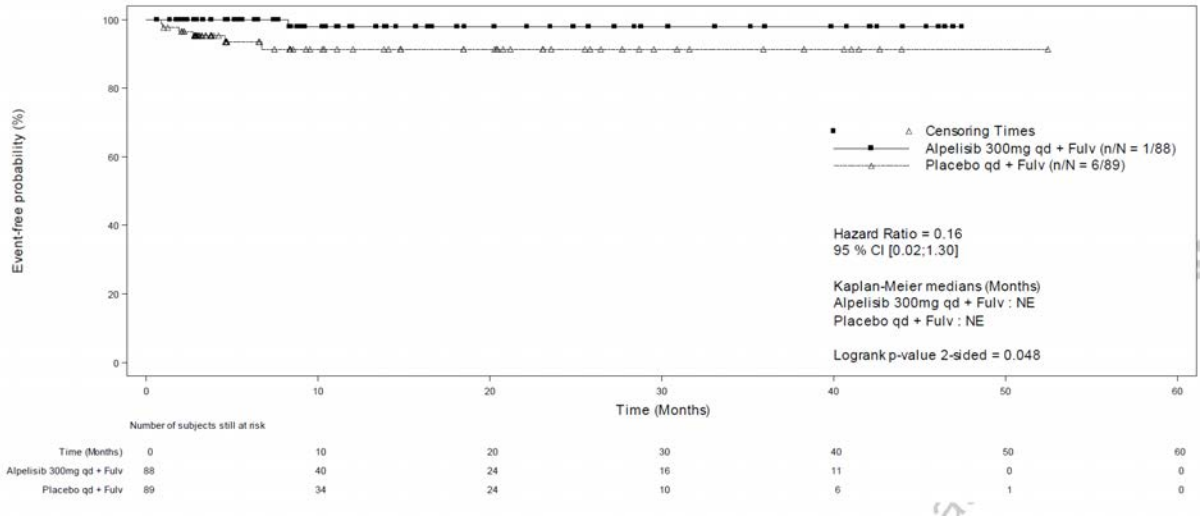

Figure 25: Kaplan-Meier curves for increased gamma glutamyltransferase (PT, severe AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

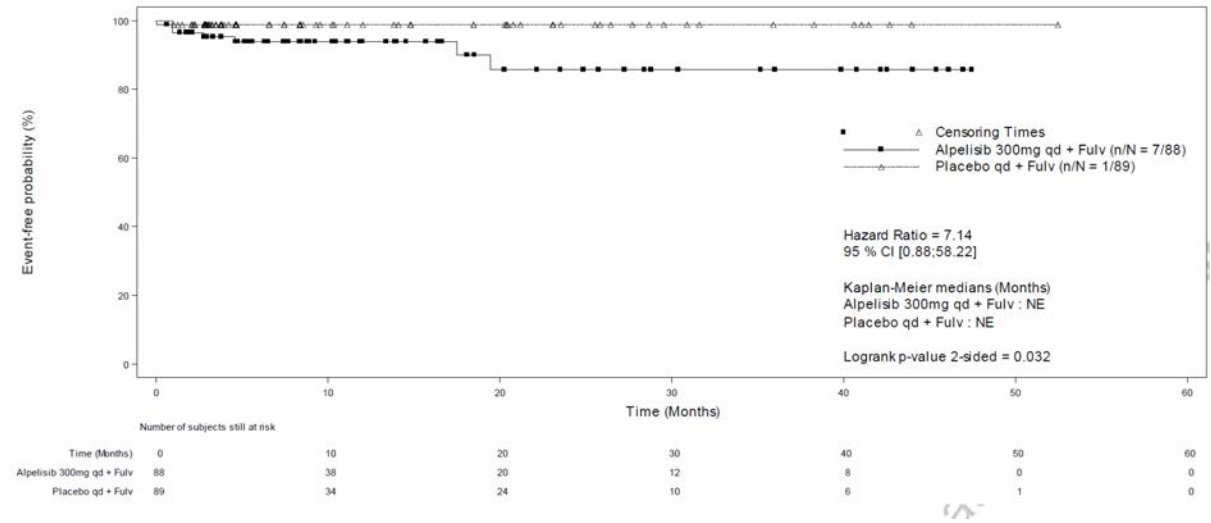

Figure 26: Kaplan-Meier curves for hypertension (PT, severe AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

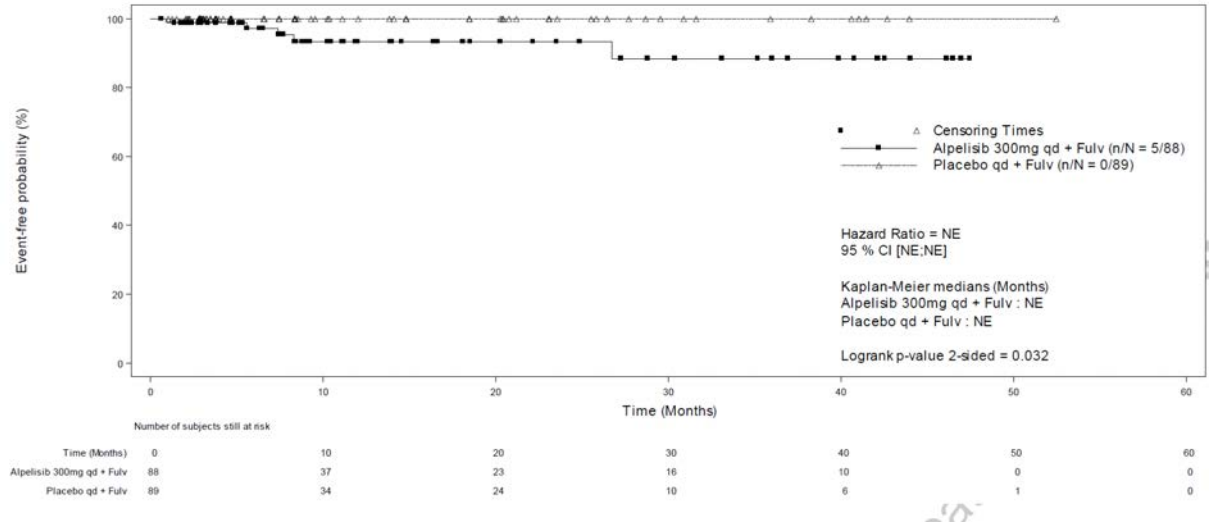

Figure 27: Kaplan-Meier curves for weight decreased (PT, severe AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

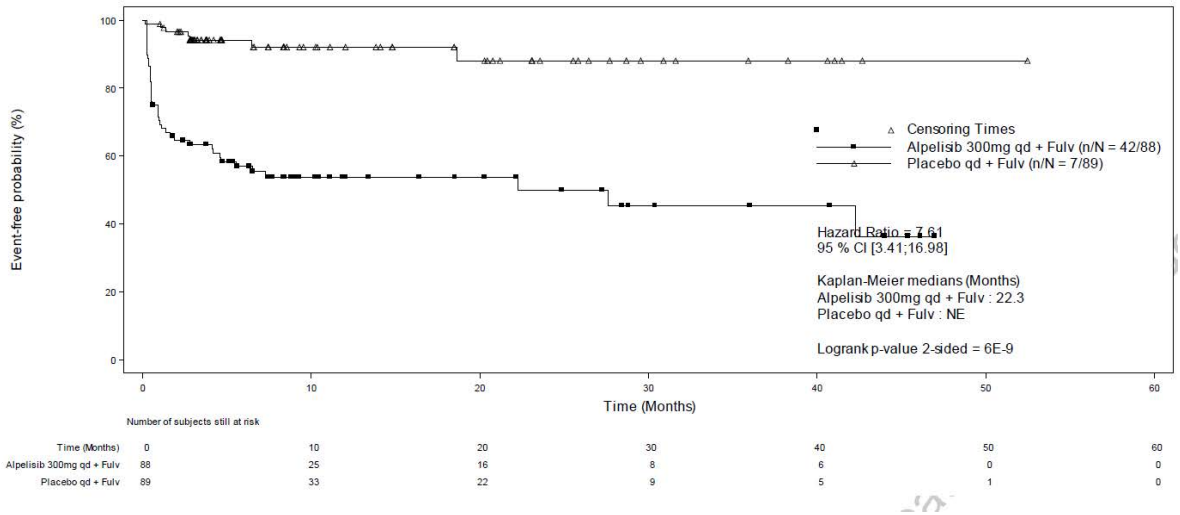

Figure 28: Kaplan-Meier curves for metabolic and nutritional disorders (SOC, severe AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

B.2 Research question B1: Postmenopausal women, second-line and subsequent-line therapy in the advanced stage

B.2.1 Kaplan-Meier curves on morbidity and health-related quality of life outcomes

Symptom scales of the EORTC QLQ-C30

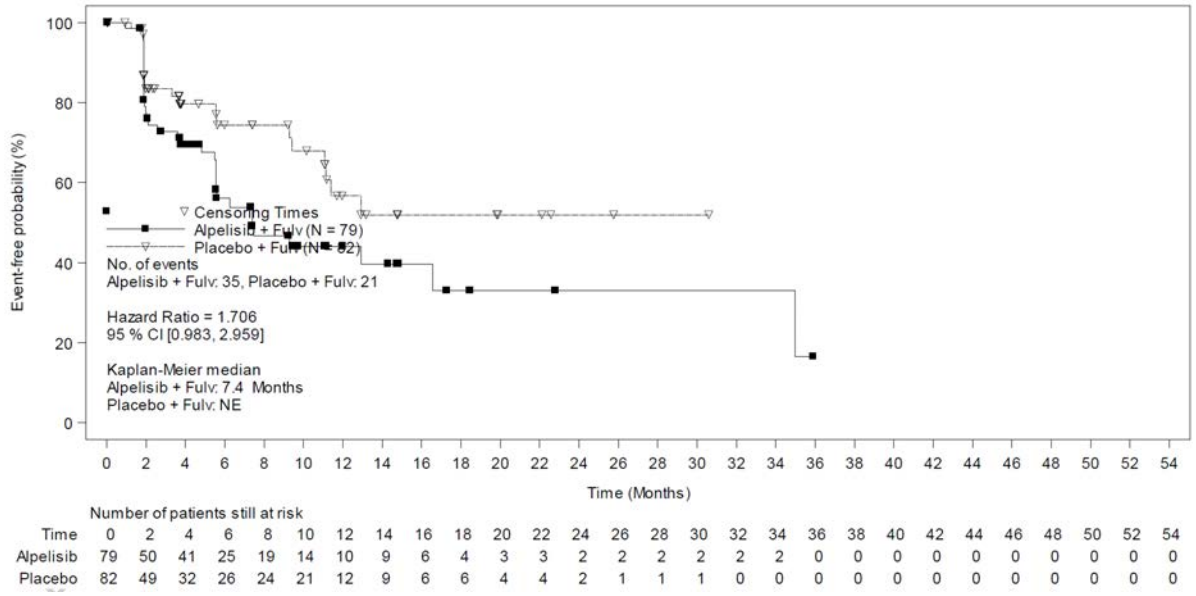

Figure 29: Kaplan-Meier curves for fatigue, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

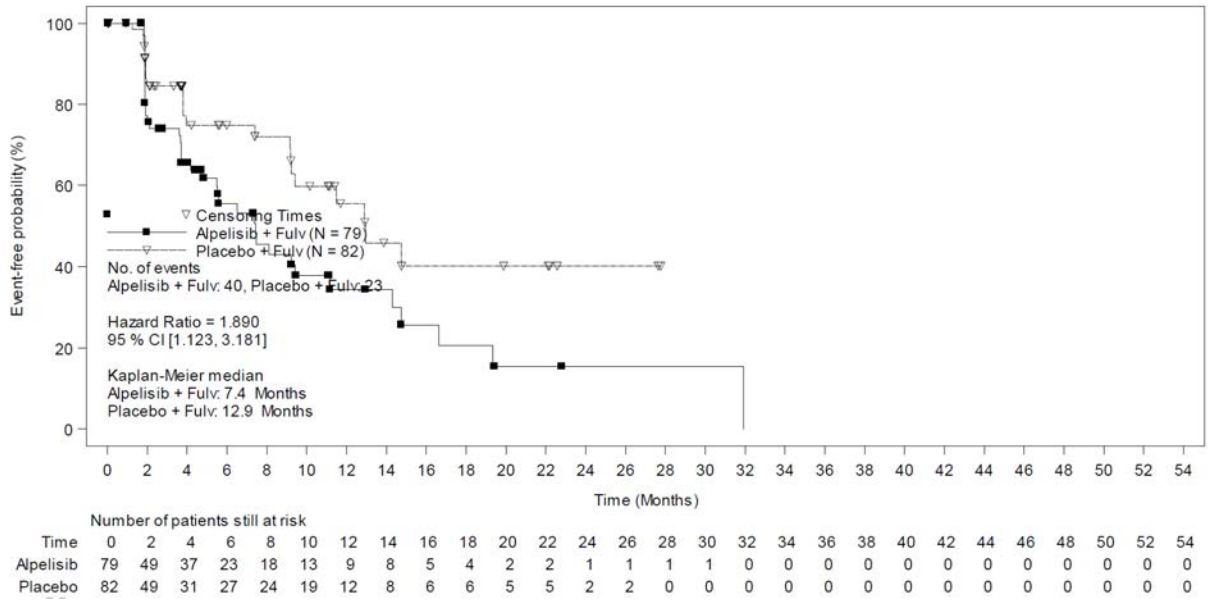

Figure 30: Kaplan-Meier curves for nausea and vomiting, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

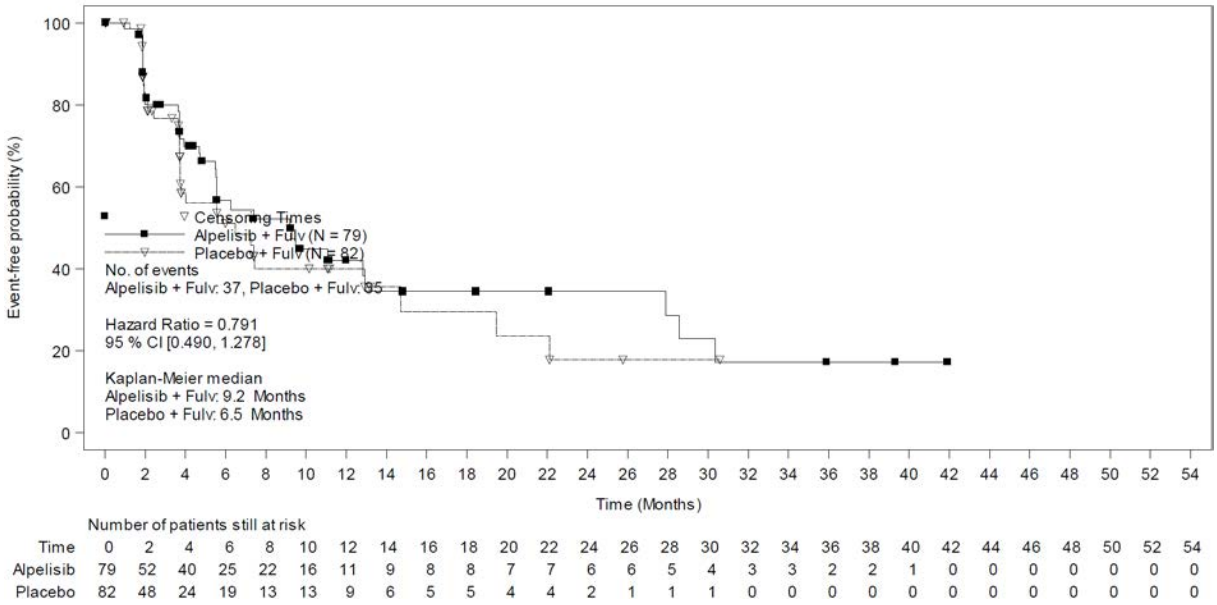

Figure 31: Kaplan-Meier curves for pain, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

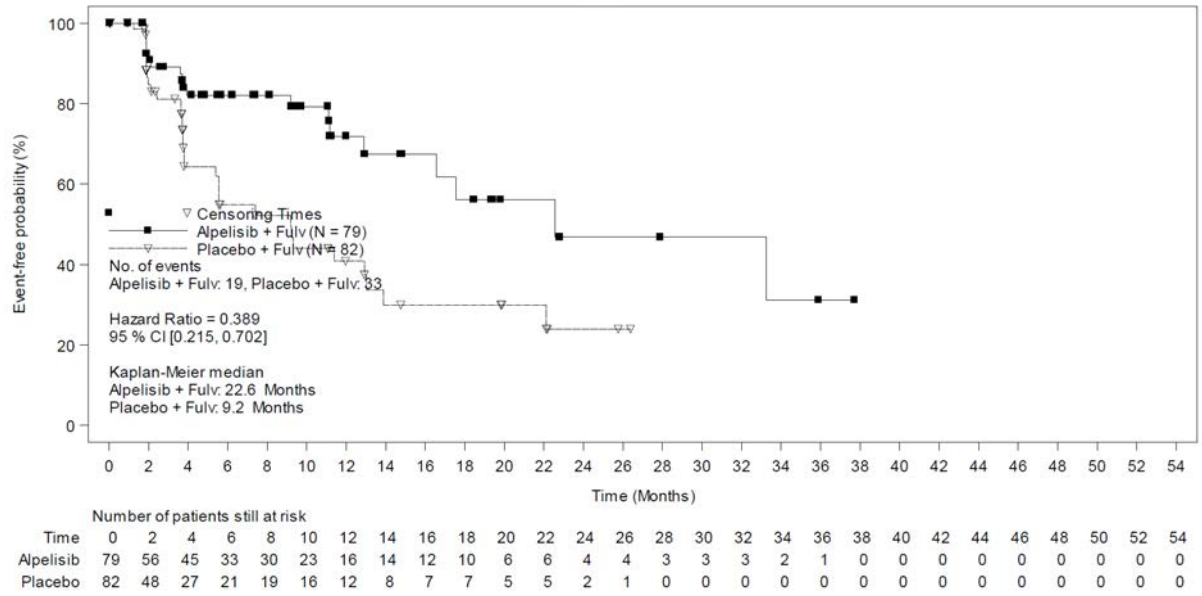

Figure 32: Kaplan-Meier curves for dyspnoea, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

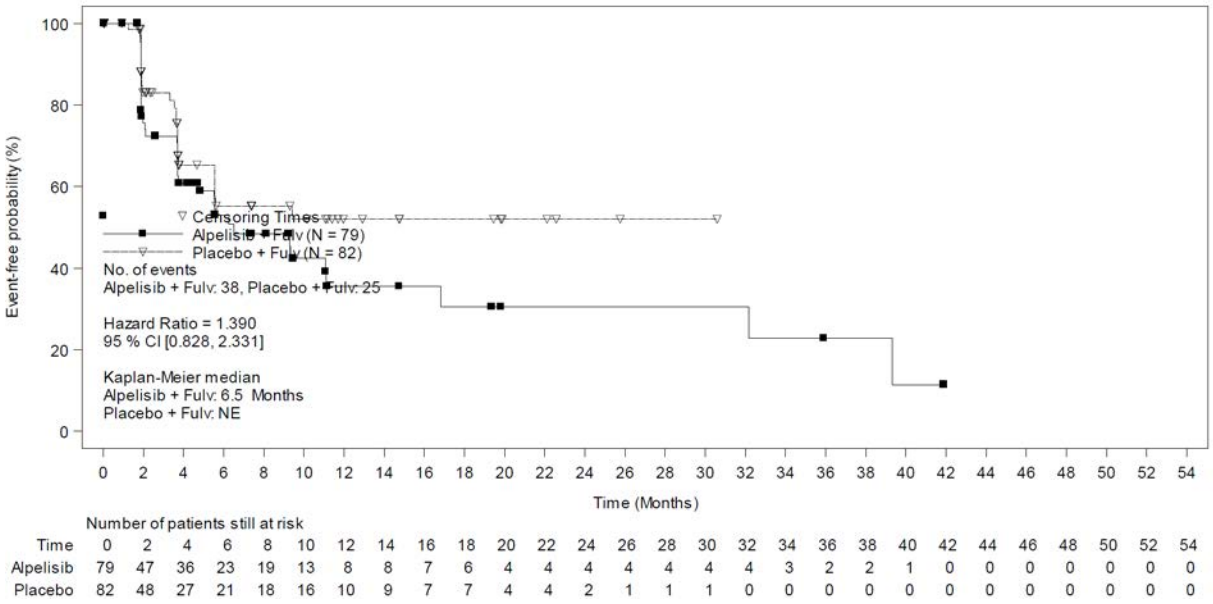

Figure 33: Kaplan-Meier curves for insomnia, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

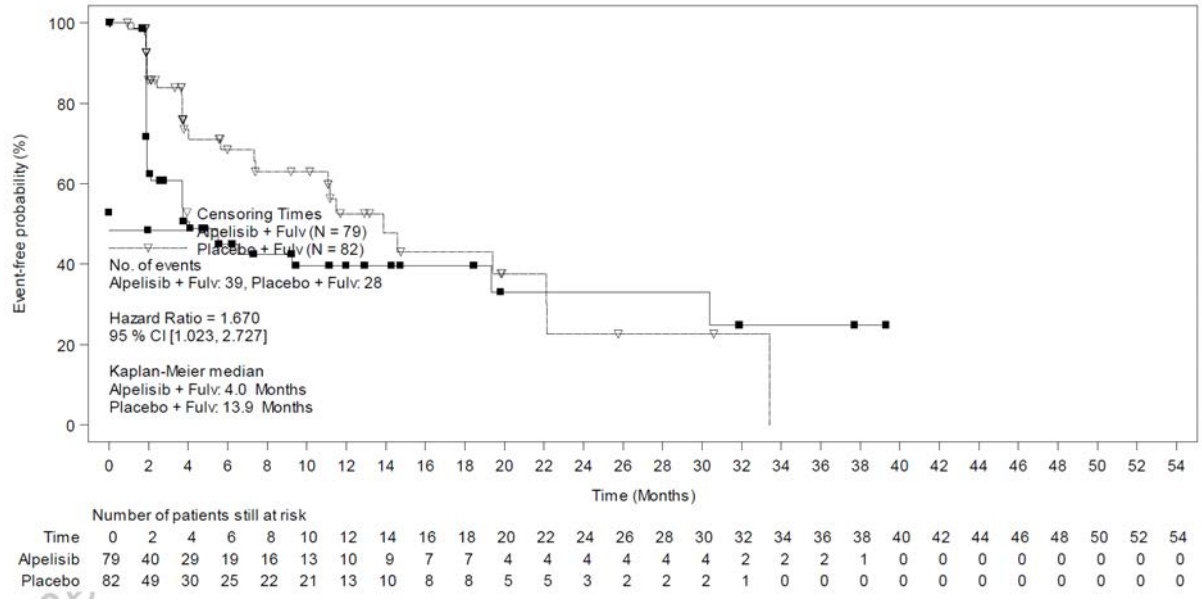

Figure 34: Kaplan-Meier curves for decreased appetite, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

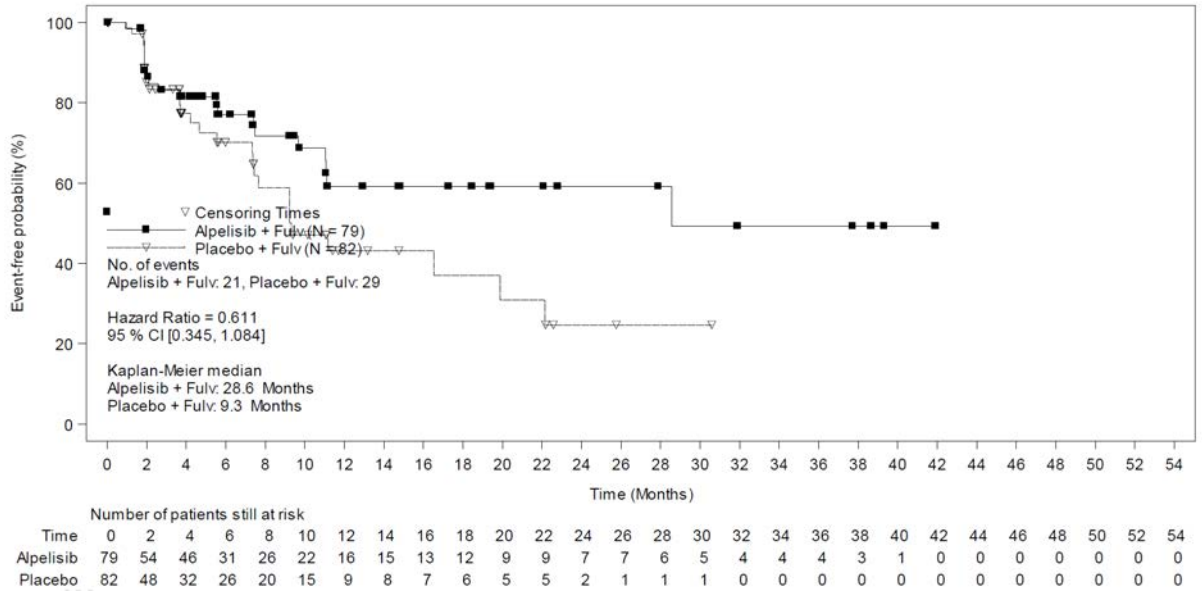

Figure 35: Kaplan-Meier curves for constipation, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

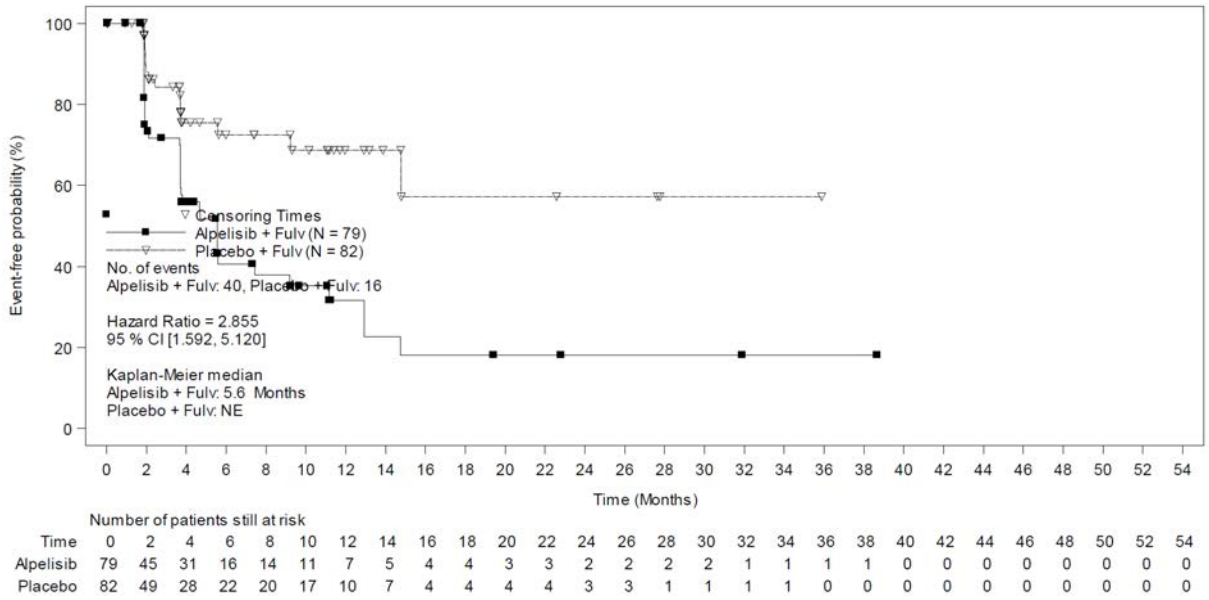

Figure 36: Kaplan-Meier curves for diarrhoea, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

BPI-SF

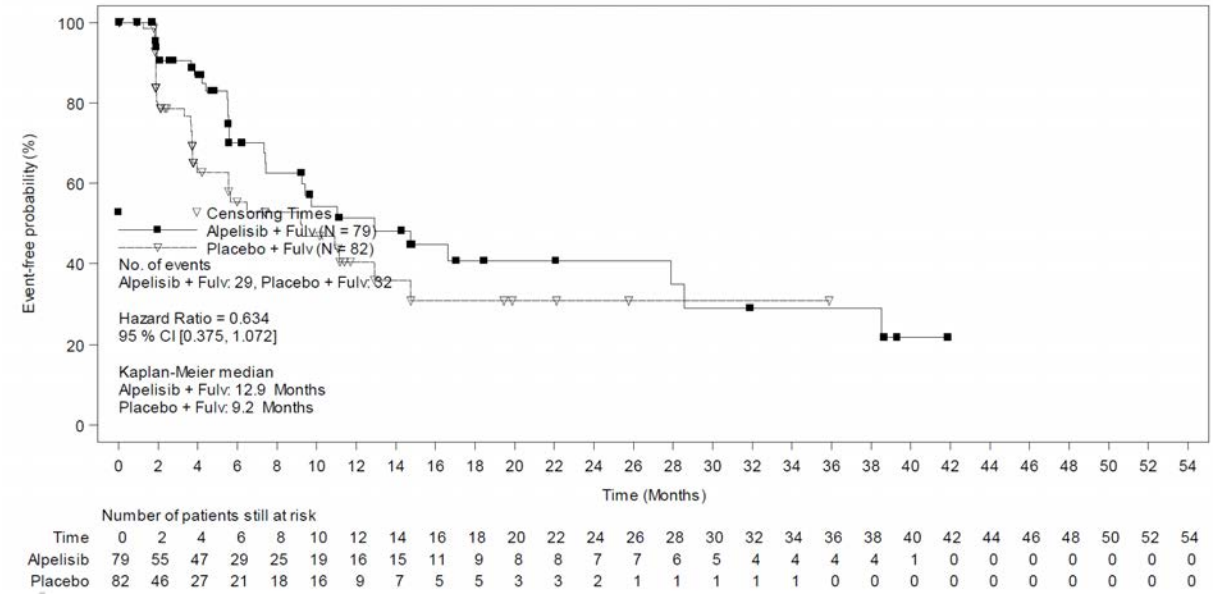

Figure 37: Kaplan-Meier curves for worst pain, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

EQ-5D-5L VAS

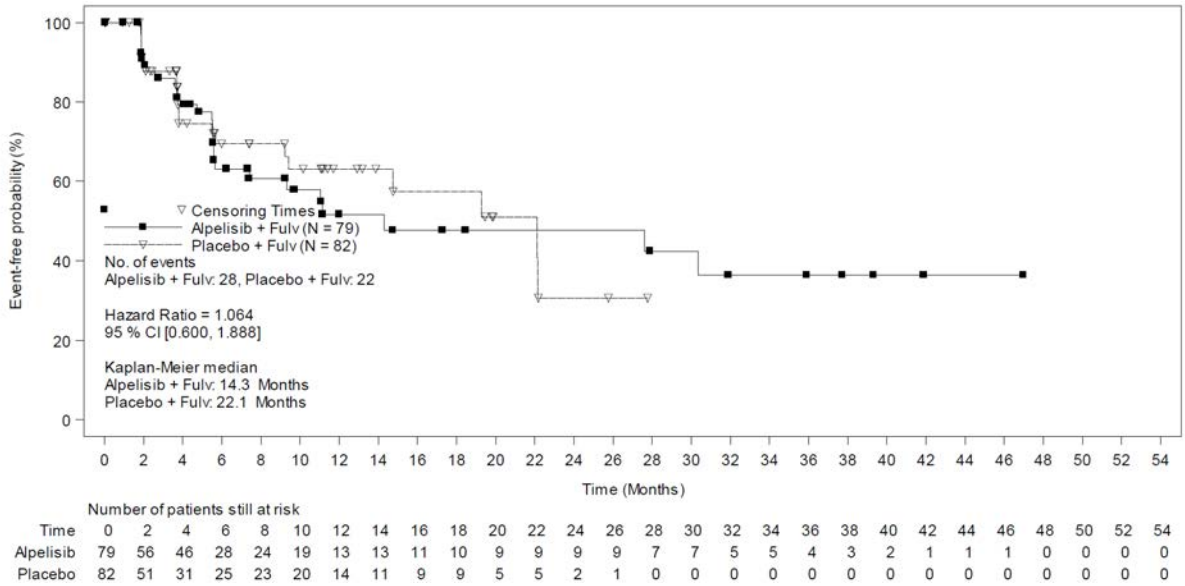

Figure 38: Kaplan-Meier curves for health status (EQ-5D-5L VAS), time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

EORTC QLQ-C30 – health status and functioning scales

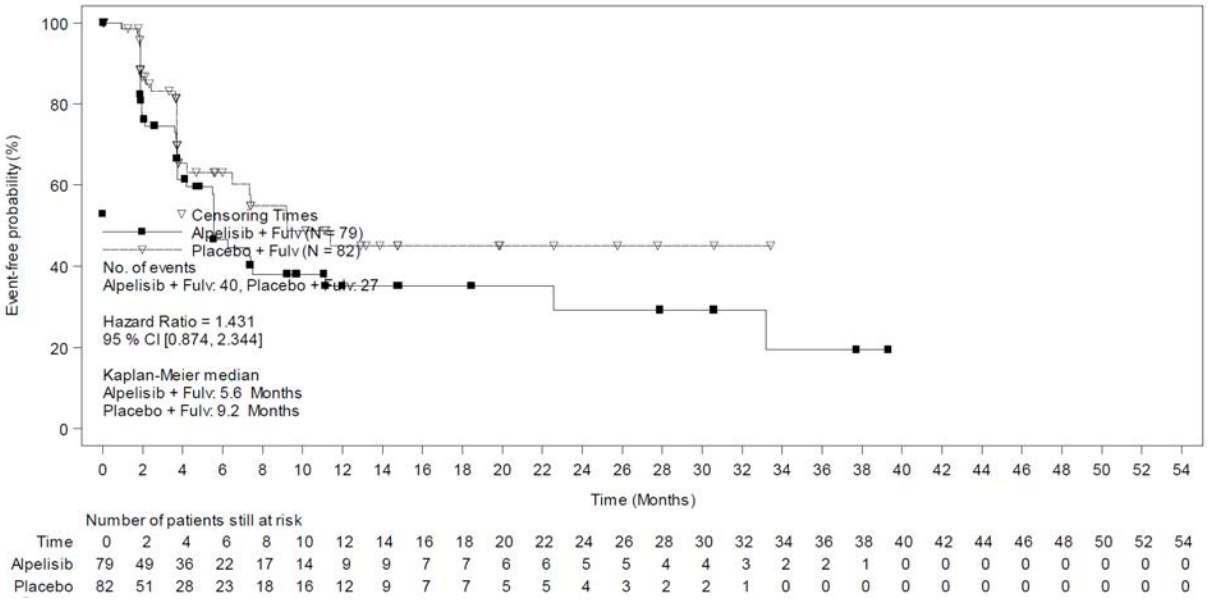

Figure 39: Kaplan-Meier curves for global health status, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

For the subgroup characteristic of age, no Kaplan-Meier curves on the outcome of global health status are available.

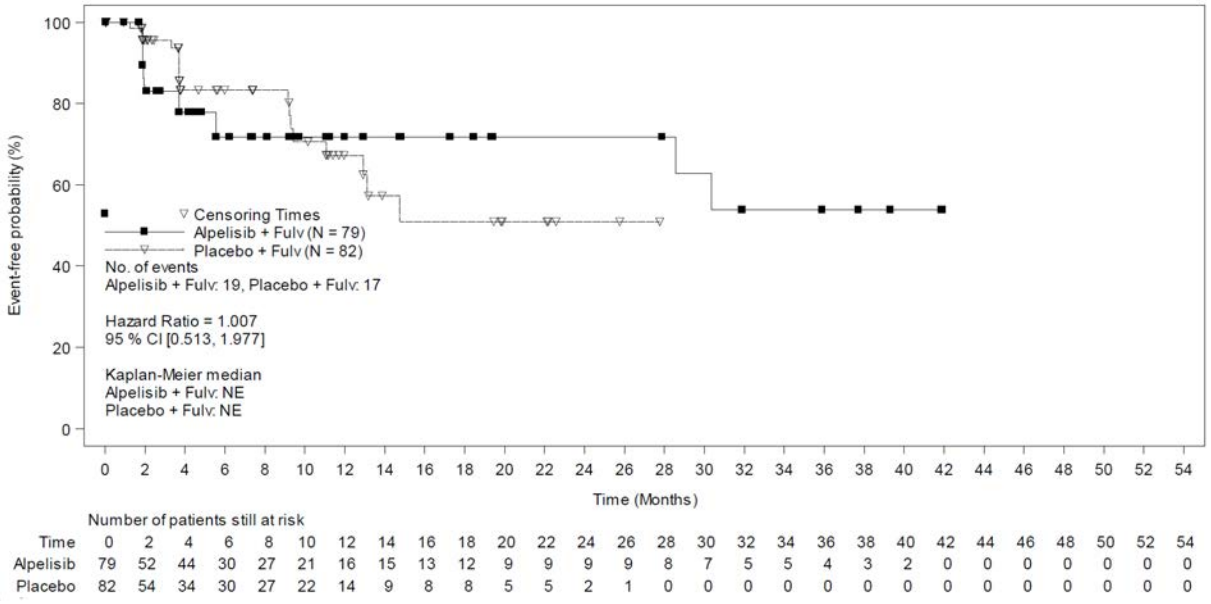

Figure 40: Kaplan-Meier curves for physical functioning, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

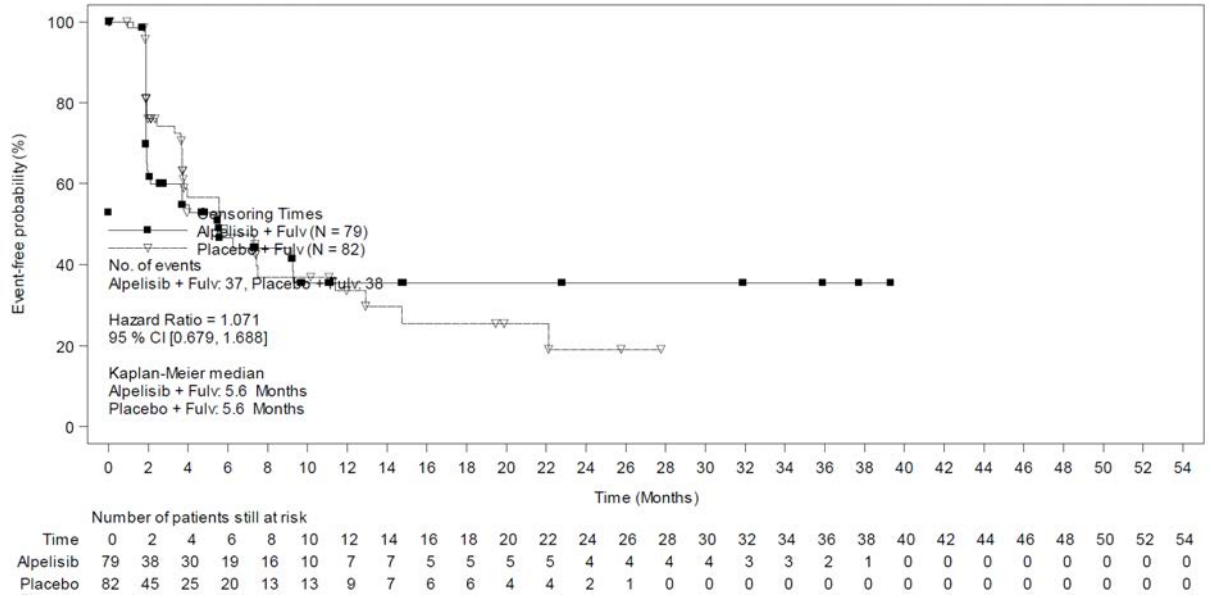

Figure 41: Kaplan-Meier curves for role functioning, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

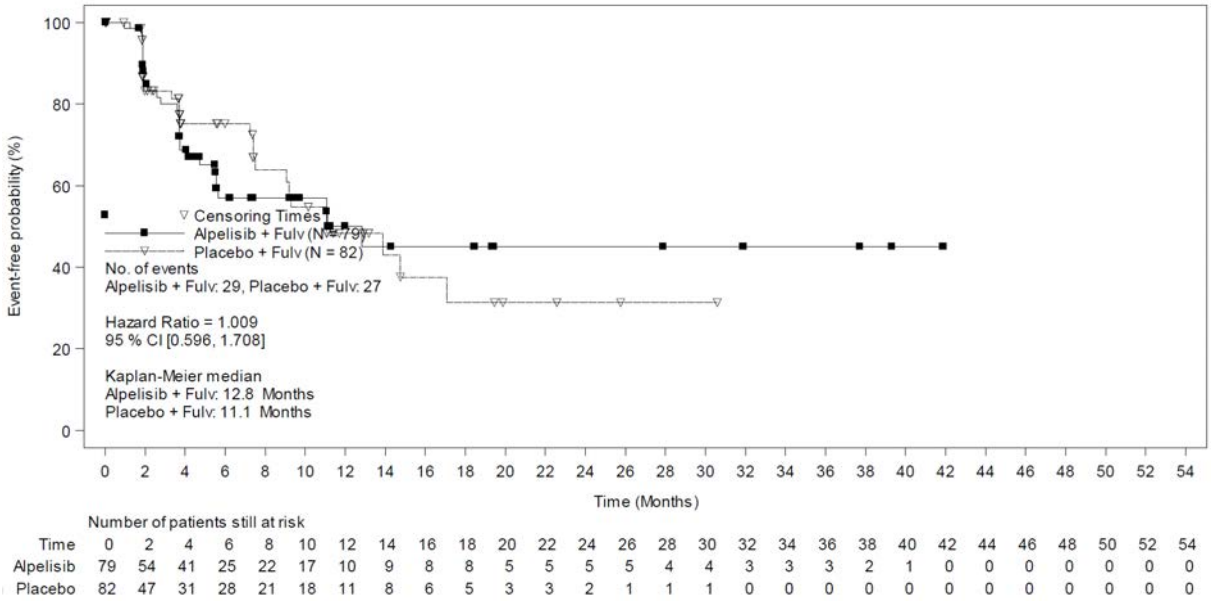

Figure 42: Kaplan-Meier curves for emotional functioning, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

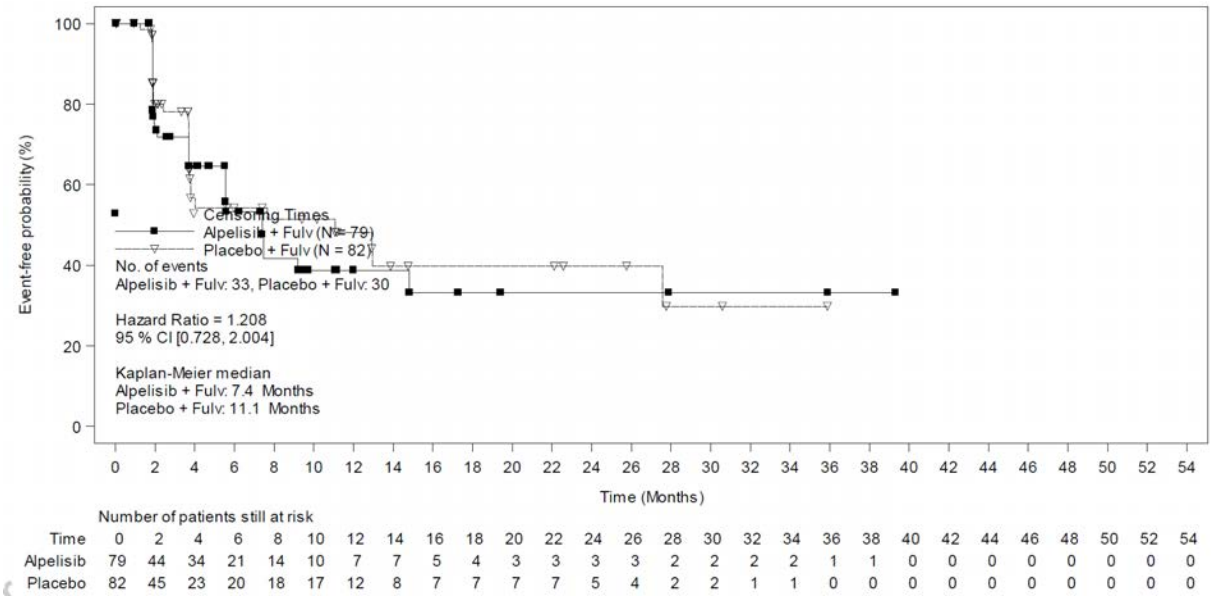

Figure 43: Kaplan-Meier curves for cognitive functioning, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

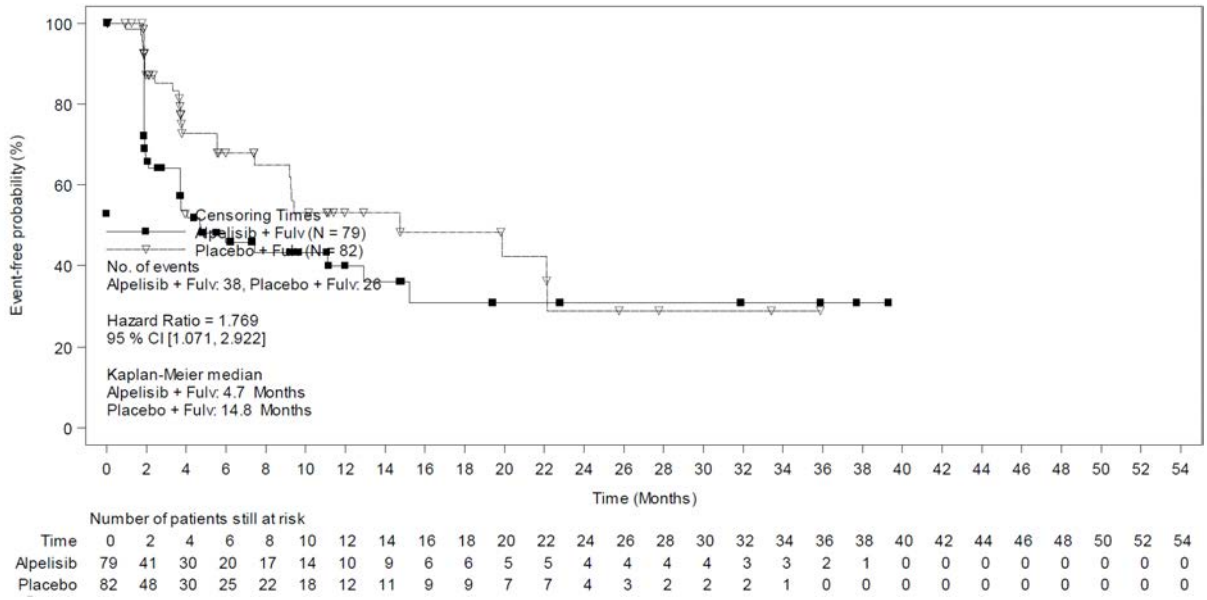

Figure 44: Kaplan-Meier curves for social functioning, time to first deterioration – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

B.2.2 Kaplan-Meier curves on AEs

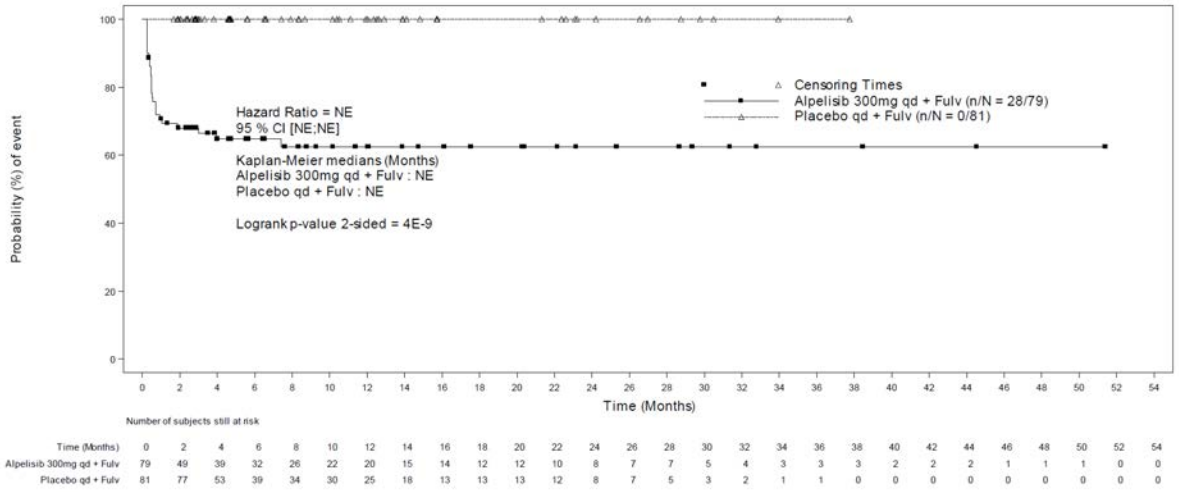

Figure 45: Kaplan-Meier curves for hyperglycaemia (SMQ, severe AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

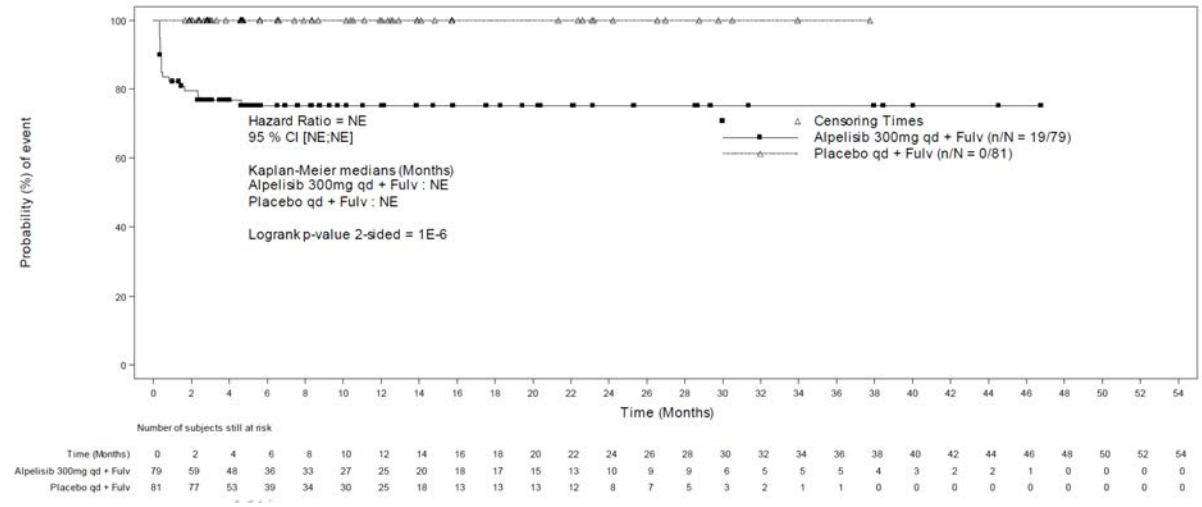

Figure 46: Kaplan-Meier curves for skin rash (CMQ, severe AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

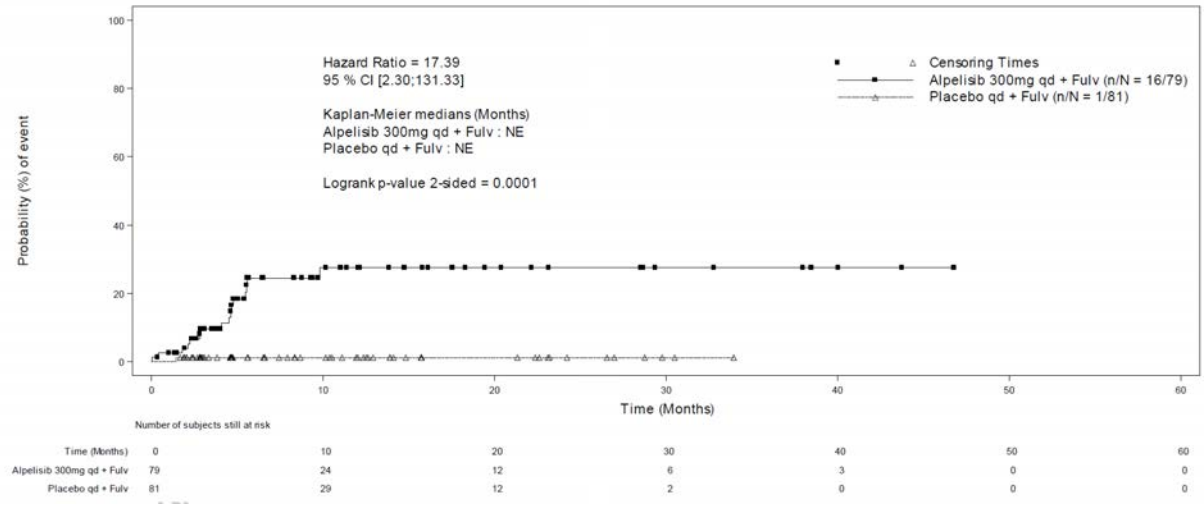

Figure 47: Kaplan-Meier curves for alopecia (PT, AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

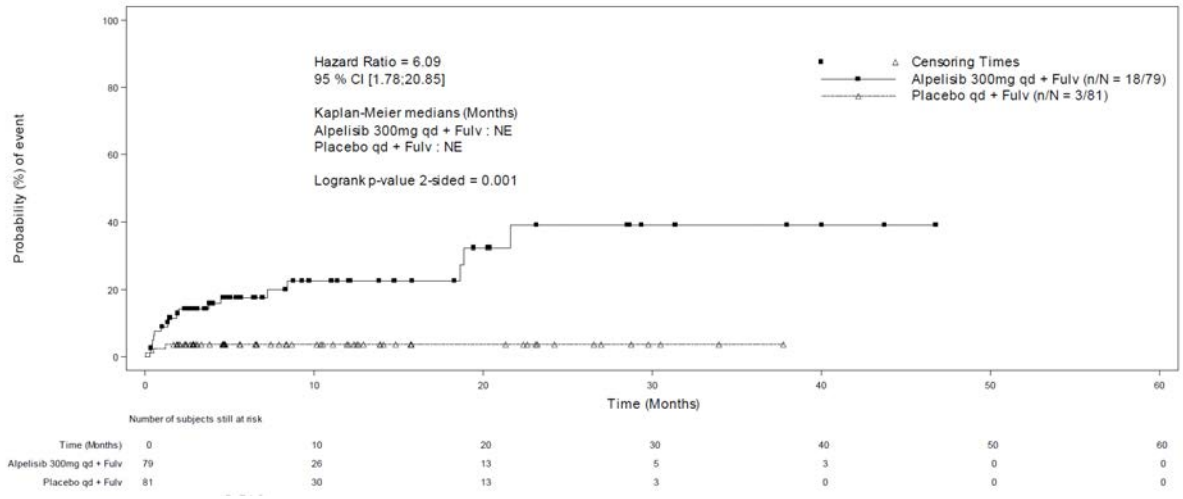

Figure 48: Kaplan-Meier curves for pruritus (PT, AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

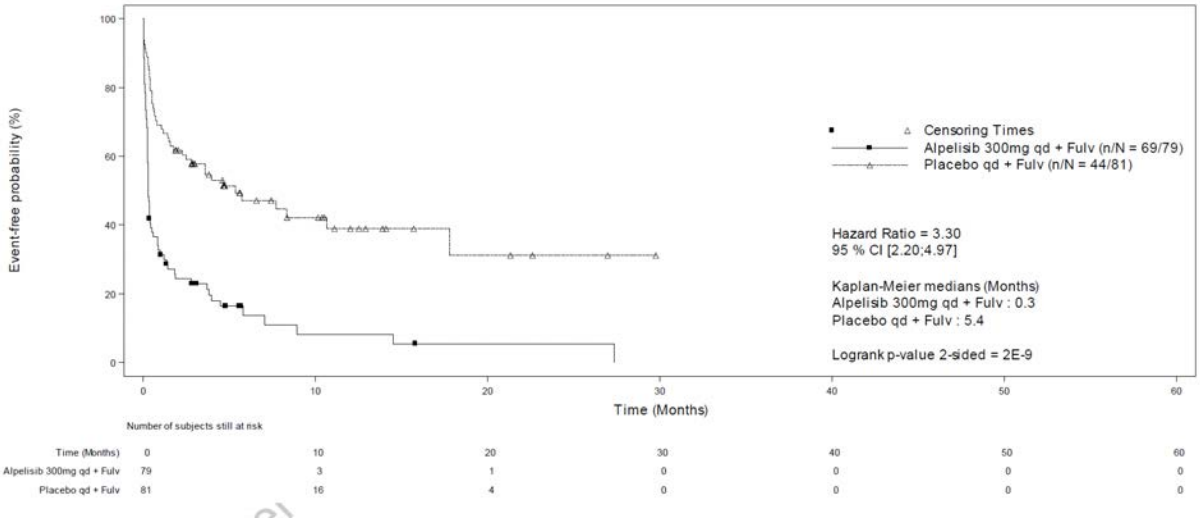

Figure 49: Kaplan-Meier curves for gastrointestinal disorders (SOC, AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

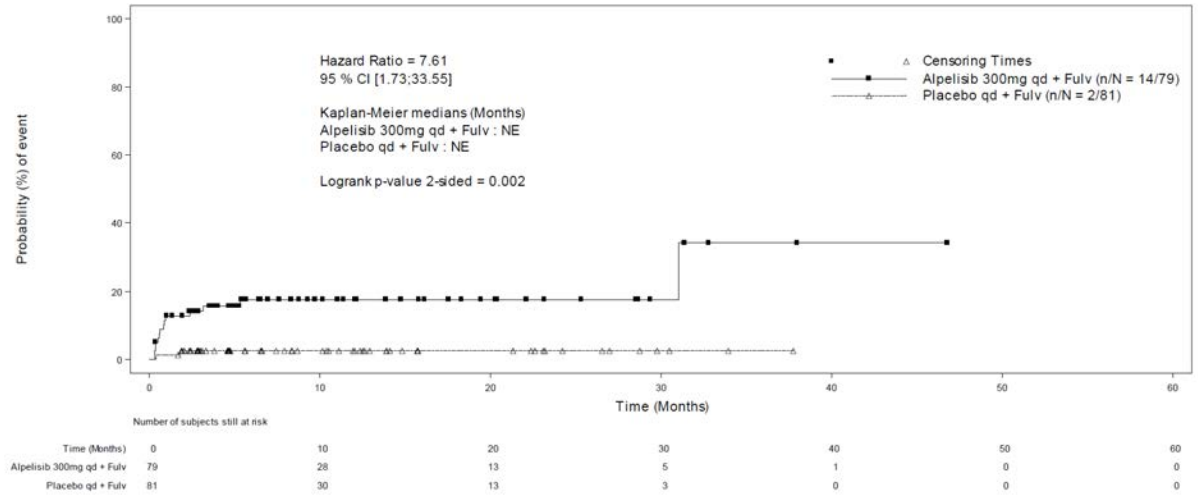

Figure 50: Kaplan-Meier curves for mucosal inflammation (PT, AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

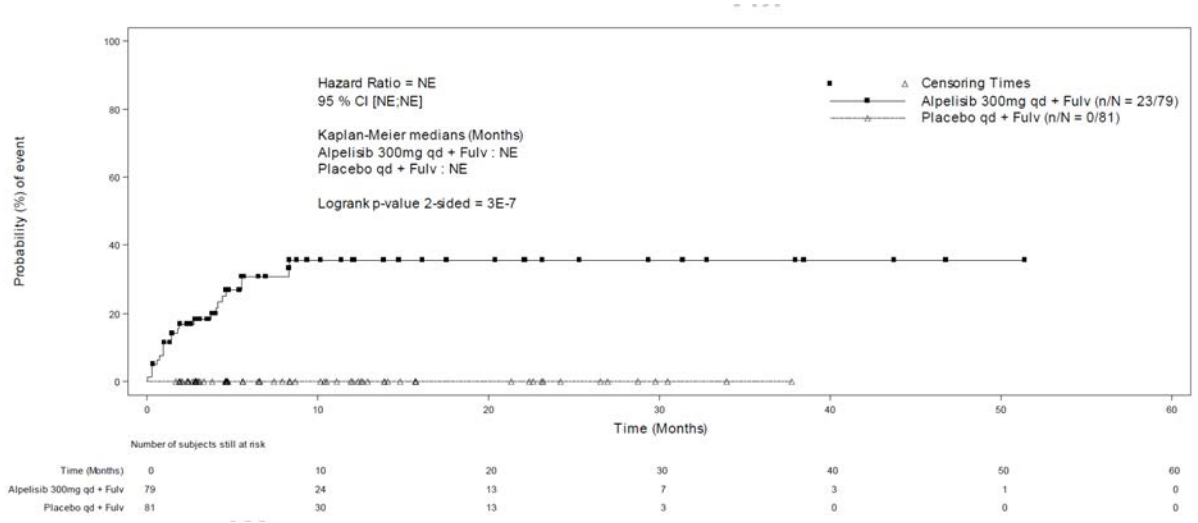

Figure 51: Kaplan-Meier curves for weight decreased (PT, severe AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

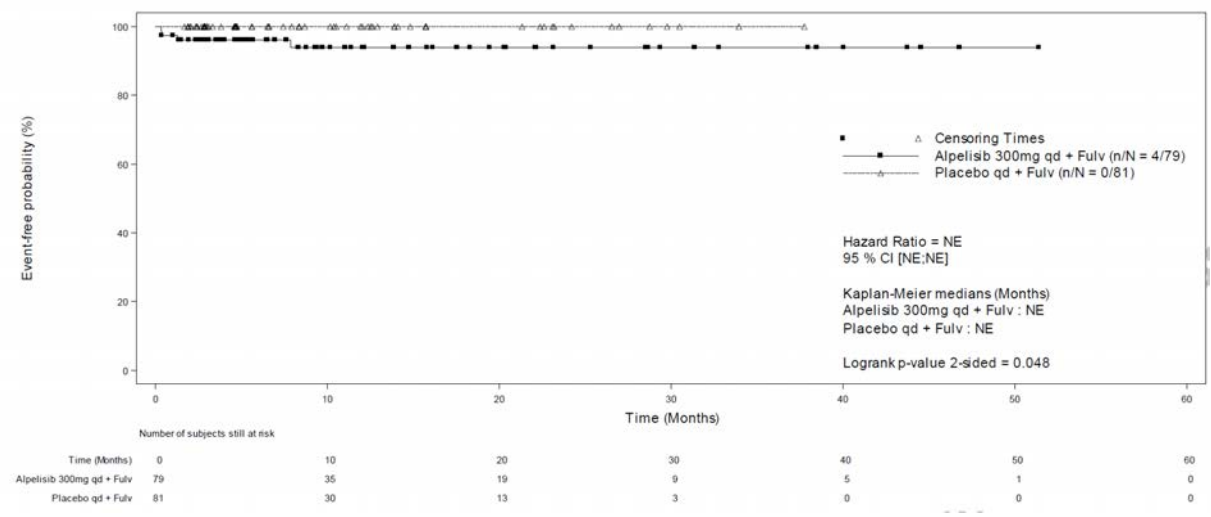

Figure 52: Kaplan-Meier curves for stomatitis (PT, SAEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

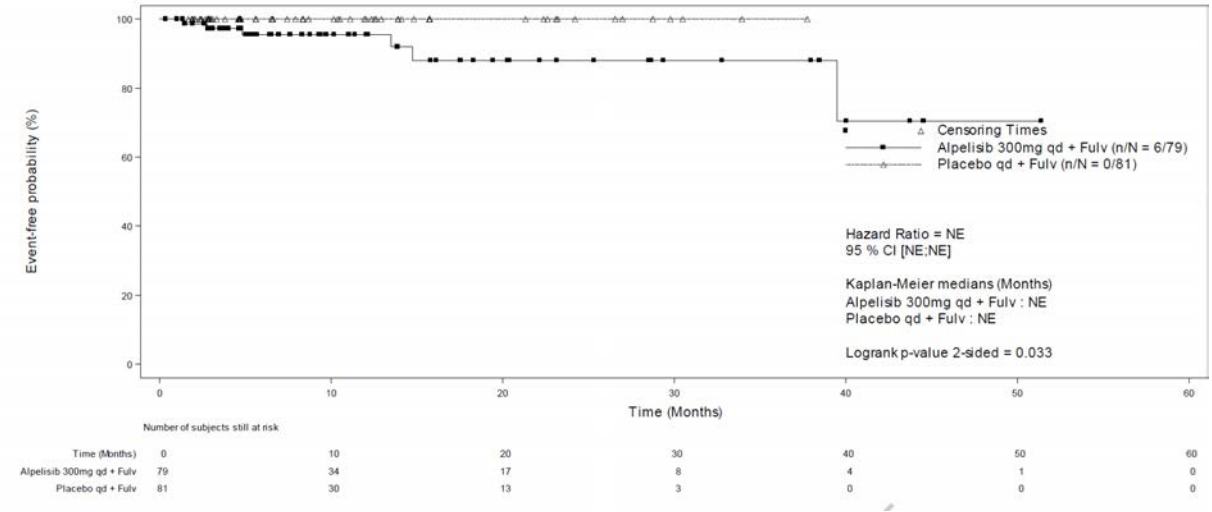

Figure 53: Kaplan-Meier curves for musculoskeletal and connective tissue disorders (SOCs, SAEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

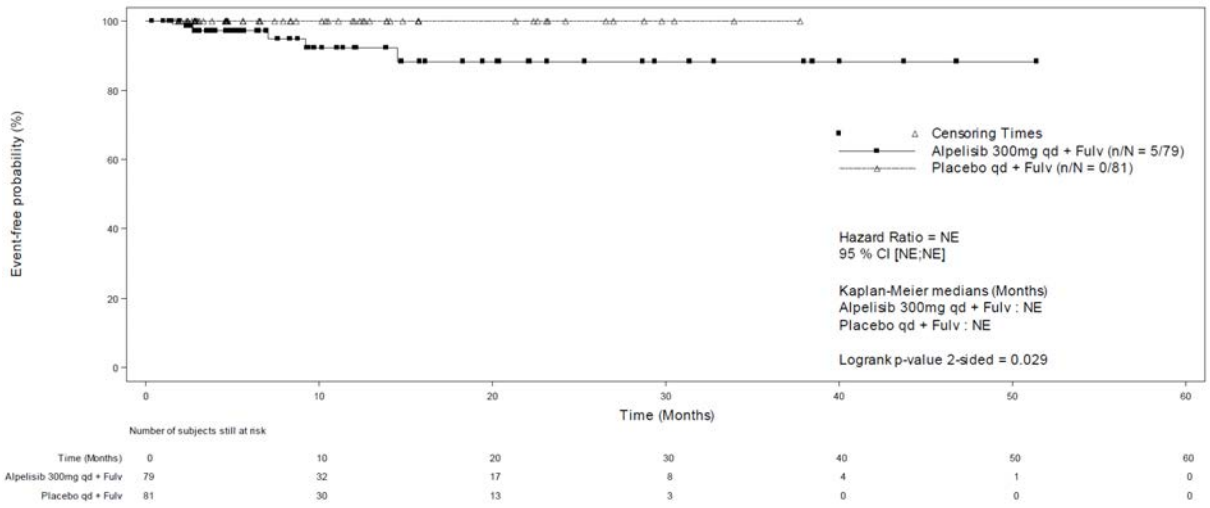

Figure 54: Kaplan-Meier curves for diarrhoea (PT, severe AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

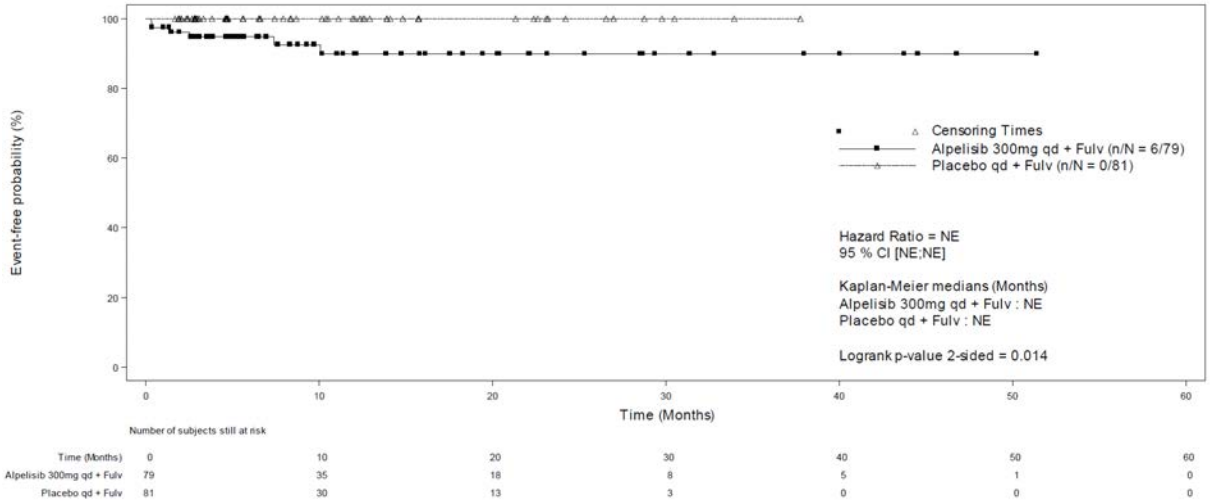

Figure 55: Kaplan-Meier curves for general disorders and administration site conditions (SOC, severe AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

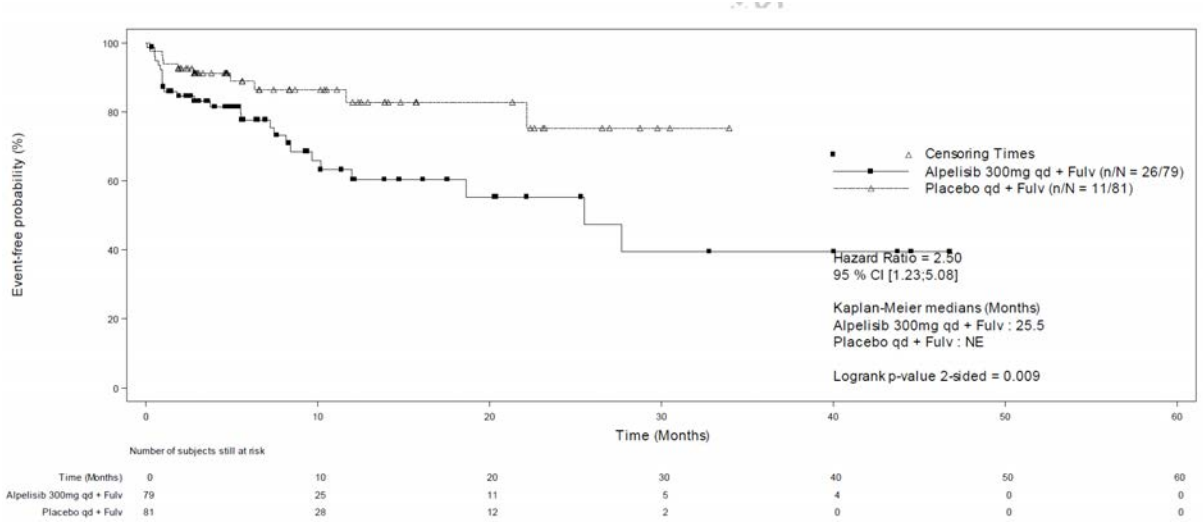

Figure 56: Kaplan-Meier curves for investigations (SOC, severe AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

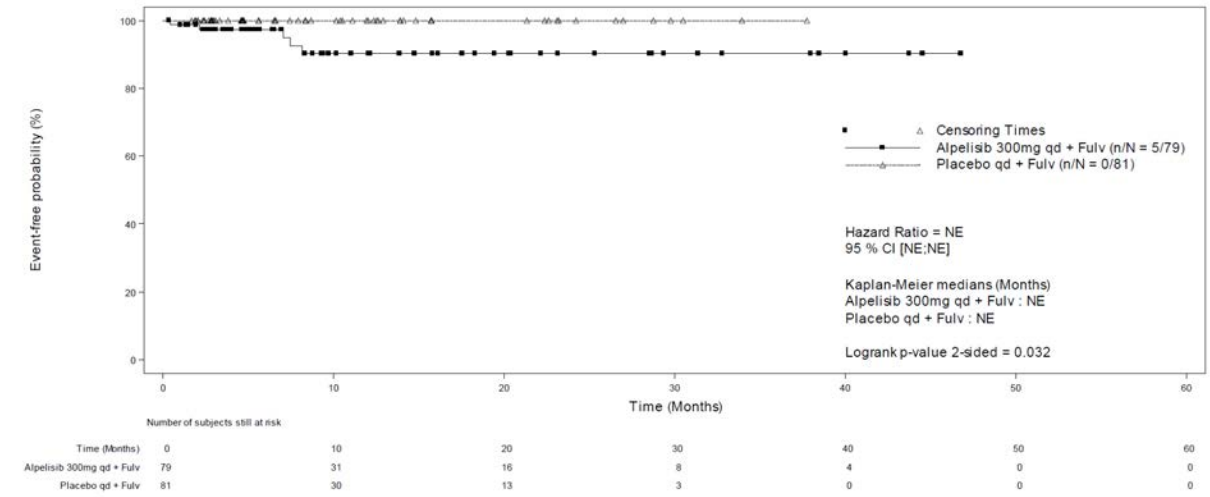

Figure 57: Kaplan-Meier curves for hypokalemia (PT, severe AEs) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant

Appendix C – Results on AEs

The tables below present total rates of AE, SAE, and severe AE (CTCAE grade 3 or 4) events for SOCs and PTs as per Medical Dictionary for Regulatory Activities (MedDRA), each according to the following criteria:

- Total rate of AEs (any severity): Events which occurred in at least 10% of patients in 1 study arm
- Total rates of severe AEs (CTCAE grade 3 or 4) and SAEs: Events which occurred in at least 5% of patients in 1 study arm
- Additionally, for all events of any severity: Events which occurred in at least 10 patients and in at least 1% of patients in 1 study arm

For the outcome of discontinuation due to AEs, all events (SOCs/PTs) which lead to discontinuation are presented.

C.1 Research question A1: postmenopausal women, first-line therapy in the advanced stage

Table 18: Common AEs[a] – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Study	Patients with event n (%)	
SOC[b] PT[b]	Alpelisib + fulvestrant N = 88	Placebo + fulvestrant N = 89
SOLAR-1		
Total rate of AEs	88 (100)	82 (92.1)
Disorders of the blood and lymphatic system	15 (17.0)	14 (15.7)
Anaemia	11 (12.5)	6 (6.7)
Nervous system disorders	37 (42.0)	27 (30.3)
Dysgeusia	15 (17.0)	3 (3.4)
Headache	17 (19.3)	11 (12.4)
Psychiatric disorders	19 (21.6)	7 (7.9)
Renal and urinary disorders	11 (12.5)	5 (5.6)
Respiratory, thoracic, and mediastinal disorders	26 (29.5)	31 (34.8)
Cough	11 (12.5)	10 (11.2)
Dyspnoea	7 (8.0)	13 (14.6)
Skin and subcutaneous tissue disorders	62 (70.5)	18 (20.2)
Alopecia	20 (22.7)	4 (4.59)
Dry skin	15 (17.0)	3 (3.4)
Pruritus	11 (12.5)	4 (4.5)
Rash	33 (37.5)	5 (5.6)
Macular rash	16 (18.2)	0 (0)
Vascular disorders	21 (23.9)	15 (16.9)
Hypertension	12 (13.6)	3 (3.4)
Heart disease	9 (10.2)	11 (12.4)
Eye disorders	16 (18.2)	7 (7.9)
Gastrointestinal disorders	76 (86.4)	40 (44.9)
Abdominal pain	12 (13.6)	6 (6.7)
Constipation	6 (6.8)	10 (11.2)
Diarrhoea	51 (58.0)	10 (11.2)
Dry mouth	11 (12.5)	3 (3.4)
Dyspepsia	13 (14.8)	2 (2.2)
Nausea	42 (47.7)	16 (18.0)
Stomatitis	25 (28.4)	5 (5.6)
Vomiting	23 (26.1)	11 (12.4)

Table 18: Common AEs[a] – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Alpelisib + fulvestrant** **N = 88**	**Placebo + fulvestrant** **N = 89**
General disorders and administration site conditions	54 (61.4)	37 (41.6)
Asthenia	16 (18.2)	9 (10.1)
Fatigue	20 (22.7)	14 (15.7)
Mucosal inflammation	14 (15.9)	2 (2.2)
Peripheral oedema	12 (13.6)	1 (1.1)
Fever	11 (12.5)	6 (6.7)
Infections and infestations	42 (47.7)	35 (39.3)
Nasopharyngitis	11 (12.5)	13 (14.6)
Injury, poisoning, and procedural complications	12 (13.6)	6 (6.7)
Investigations	48 (54.5)	24 (27.0)
Aspartate aminotransferase increased	10 (11.4)	3 (3.4)
Blood creatinine increased	13 (14.8)	0 (0)
Weight decreased	23 (26.1)	2 (2.2)
Metabolic and nutritional disorders	74 (84.1)	24 (27.0)
Decreased appetite	27 (30.7)	8 (9.0)
Hyperglycaemia	60 (68.2)	6 (6.7)
Hypokalemia	12 (13.6)	2 (2.2)
Musculoskeletal and connective tissue disorders	46 (52.3)	45 (50.6)
Arthralgia	9 (10.2)	16 (18.0)
Back pain	15 (17.0)	18 (20.2)
Myalgia	9 (10.2)	3 (3.4)
Pain in extremity	6 (6.8)	12 (13.5)

a. Events that occurred in at least 1 study arm in ≥ 10% of patients.
b. MedDRA version 20.1 as per Module 4; SOC and PT terminology unmodified from MedDRA.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; NC: not calculable; PT: preferred term; RCT: randomized controlled trial; SOC: system organ class

Table 19: Common AEs[a] – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Alpelisib + fulvestrant N = 88**	**Placebo + fulvestrant N = 89**
SOLAR-1		
Total rate of SAEs	32 (36.4)	18 (20.2)
Respiratory, thoracic, and mediastinal disorders	3 (3.4)	7 (7.9)
Skin and subcutaneous tissue disorders	6 (6.8)	0 (0)
Gastrointestinal disorders	5 (5.7)	5 (5.6)
General disorders and administration site conditions		
Infections and infestations		
Metabolic and nutritional disorders	12 (13.6)	2 (2.2)
Hyperglycaemia	9 (10.2)	0 (0)
Injury, poisoning, and procedural complications	5 (5.7)	1 (1.1)
Musculoskeletal and connective tissue disorders		

a. Events that occurred in at least 1 study arm in ≥ 5% of patients.
b. MedDRA version 20.1 as per Module 4; SOC and PT terminology unmodified from MedDRA.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; NC: not calculable; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class

Table 20: Common severe AEs[a] (CTCAE grade 3 or 4) – RCT, alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Alpelisib + fulvestrant** **N = 88**	**Placebo + fulvestrant** **N = 89**
SOLAR-1		
Total rate of severe AEs (CTCAE grade 3 or 4)	71 (80.7)	33 (37.1)
Disorders of the blood and lymphatic system	8 (9.1)	6 (6.7)
Anaemia	5 (5.7)	1 (1.1)
Respiratory, thoracic, and mediastinal disorders	3 (3.4)	6 (6.7)
Gastrointestinal disorders	13 (14.8)	4 (4.5)
Diarrhoea	8 (9.1)	0 (0)
General disorders and administration site conditions	8 (9.1)	1 (1.1)
Increased gamma glutamyltransferase	1 (1.1)	6 (6.7)
Hyperglycaemia	34 (38.6)	1 (1.1)
Vascular disorders	9 (10.2)	1 (1.1)
Hypertension	7 (8.0)	1 (1.1)
Hypokalemia	6 (6.8)	1 (1.1)
Increased lipase	4 (4.5)	5 (5.6)
Skin and subcutaneous tissue disorders	25 (28.4)	0 (0)
Rash	12 (13.6)	0 (0)
Macular rash	8 (9.1)	0 (0)
Investigations	13 (14.8)	16 (18)
Weight decreased	5 (5.7)	0 (0)
Metabolic and nutritional disorders	42 (47.7)	7 (7.9)
Musculoskeletal and connective tissue disorders	6 (6.8)	2 (2.2)

a. Events that occurred in at least 1 study arm in ≥ 5% of patients.
b. MedDRA version 20.1 as per Module 4; PT terminology unmodified from MedDRA.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; NC: not calculable; PT: preferred term; RCT: randomized controlled trial; SOC: system organ class

Table 21: Discontinuation due to AEs – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Alpelisib + fulvestrant N = 88**	**Placebo + fulvestrant N = 89**
SOLAR-1		
Total rate of discontinuation due to AEs	25 (28.4)	6 (6.7)
Disorders of the blood and lymphatic system	0 (0)	2 (2.2)
Lymphopoenia	0 (0)	1 (1.1)
Neutropoenia	0 (0)	1 (1.1)
Heart disease	1 (1.1)	0 (0)
Cardiac arrest	1 (1.1)	0 (0)
Eye disorders	1 (1.1)	0 (0)
Xerophthalmia	1 (1.1)	0 (0)
Skin and subcutaneous tissue disorders	9 (10.2)	0 (0)
Rash	5 (5.7)	0 (0)
Erythema multiforme	1 (1.1)	0 (0)
Folliculitis	1 (1.1)	0 (0)
Maculopapular rash	1 (1.1)	0 (0)
Skin reaction	1 (1.1)	0 (0)
Stevens-Johnson syndrome	1 (1.1)	0 (0)
Gastrointestinal disorders	7 (8.0)	0 (0)
Diarrhoea	3 (3.4)	0 (0)
Nausea	2 (2.3)	0 (0)
Dry mouth	1 (1.1)	0 (0)
Stomatitis	1 (1.1)	0 (0)
Vomiting	1 (1.1)	0 (0)
General disorders and administration site conditions	3 (3.4)	0 (0)
Fatigue	2 (2.3)	0 (0)
Asthenia	1 (1.1)	0 (0)
Infections and infestations	3 (3.4)	0 (0)
Abscess	2 (2.3)	0 (0)
Investigations	1 (1.1)	3 (3.4)
Weight decreased	1 (1.1)	0 (0)
Increased lipase	0 (0)	3 (3.4)

Table 21: Discontinuation due to AEs – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question A1: postmenopausal women, first-line therapy in the advanced stage) (multi-page table)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**Alpelisib + fulvestrant** **N = 88**	**Placebo + fulvestrant** **N = 89**
Metabolic and nutritional disorders	10 (11.4)	1 (1.1)
Hyperglycaemia	6 (6.8)	0 (0)
Decreased appetite	3 (3.4)	0 (0)
Diabetes mellitus	1 (1.1)	0 (0)
Hypokalemia	1 (1.1)	0 (0)
Hyperlipasaemia	0 (0)	1 (1.1)
Interstitial lung disease	0 (0)	1 (1.1)
Injury, poisoning, and procedural complications	2 (2.3)	0 (0)
Hip fracture	1 (1.1)	0 (0)
Radiation proctitis	1 (1.1)	0 (0)
Renal and urinary disorders	1 (1.1)	0 (0)
Acute renal failure	1 (1.1)	0 (0)
Respiratory, thoracic, and mediastinal disorders	1 (1.1)	1 (1.1)
Pneumonitis	1 (1.1)	0 (0)
Pneumonia	1 (1.1)	0 (0)
Dyspnoea	0 (0)	1 (1.1)
Pleural effusion	0 (0)	1 (1.1)
Vascular disorders	0 (0)	1 (1.1)
Thrombosis	0 (0)	1 (1.1)

a. MedDRA version 20.1 as per Module 4; SOC and PT terminology unmodified from MedDRA.

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: randomized controlled trial; SOC: system organ class

C.2 Research question B1: Postmenopausal women, second-line and subsequent-line therapy in the advanced stage

Table 22: Common AEs[a] – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage) (multi-page table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Alpelisib + fulvestrant** **N = 79**	**Placebo + fulvestrant** **N = 81**
SOLAR-1		
Total rate of AEs	78 (98.7)	72 (88.9)
Disorders of the blood and lymphatic system	12 (15.2)	5 (6.2)
Anaemia	9 (11.4)	3 (3.7)
Nervous system disorders	36 (45.6)	20 (24.7)
Dysgeusia	8 (10.1)	1 (1.2)
Headache	14 (17.7)	11 (13.6)
Psychiatric disorders	15 (19.0)	10 (12.3)
Insomnia	10 (12.7)	0 (0)
Renal and urinary disorders	9 (11.4)	4 (4.9)
Respiratory, thoracic, and mediastinal disorders	26 (32.9)	21 (25.9)
Cough	9 (11.4)	8 (9.9)
Dyspnoea	9 (11.4)	9 (11.1)
Reproductive system and breast disorders	9 (11.4)	6 (7.4)
Skin and subcutaneous tissue disorders	61 (77.2)	16 (19.8)
Alopecia	16 (20.3)	1 (1.2)
Dry skin	10 (12.7)	2 (2.5)
Pruritus	18 (22.8)	3 (3.7)
Rash	34 (43.0)	6 (7.4)
Maculopapular rash	9 (11.4)	1 (1.2)
Vascular disorders	16 (20.3)	15 (18.5)
Heart disease	5 (6.3)	9 (11.1)
Eye disorders	14 (17.7)	7 (8.6)
Gastrointestinal disorders	69 (87.3)	44 (54.3)
Abdominal pain	8 (10.1)	6 (7.4)
Diarrhoea	45 (57.0)	9 (11.1)
Dry mouth	8 (10.1)	2 (2.5)
Dyspepsia	10 (12.7)	5 (6.2)
Nausea	40 (50.6)	19 (23.5)
Stomatitis	21 (26.6)	5 (6.2)
Vomiting	23 (29.1)	6 (7.4)

Table 22: Common AEs[a] – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage) (multi-page table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Alpelisib + fulvestrant** **N = 79**	**Placebo + fulvestrant** **N = 81**
General disorders and administration site conditions	55 (69.6)	44 (54.3)
Asthenia	15 (19.0)	14 (17.3)
Fatigue	21 (26.6)	14 (17.3)
Mucosal inflammation	14 (17.7)	2 (2.5)
Peripheral oedema	11 (13.9)	8 (9.9)
Fever	15 (19.0)	8 (9.9)
Infections and infestations	37 (46.8)	22 (27.2)
Urinary tract infection	12 (15.2)	3 (3.7)
Investigations	44 (55.7)	19 (23.5)
Alanine aminotransferase increased	9 (11.4)	7 (8.6)
Aspartate aminotransferase increased	9 (11.4)	5 (6.2)
Blood creatinine increased	8 (10.1)	1 (1.2)
Gamma glutamyltransferase increased	12 (15.2)	7 (8.6)
Increased lipase	9 (11.4)	4 (4.9)
Weight decreased	23 (29.1)	0 (0)
Metabolic and nutritional disorders	63 (79.7)	21 (25.9)
Decreased appetite	31 (39.2)	5 (6.2)
Hyperglycaemia	53 (67.1)	9 (11.1)
Hypokalemia	8 (10.1)	2 (2.5)
Musculoskeletal and connective tissue disorders	44 (55.7)	31 (38.3)
Arthralgia	15 (19.0)	13 (16.0)
Back pain	10 (12.7)	4 (4.9)
Pain in extremity	9 (11.4)	4 (4.9)

a. Events that occurred in at least 1 study arm in ≥ 10% of patients.
b. MedDRA version 20.1 as per Module 4; SOC and PT terminology unmodified from MedDRA.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; NI: not interpretable; PT: preferred term; RCT: randomized controlled trial; SOC: system organ class

Table 23: Common SAEs[a] – direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Alpelisib + fulvestrant N = 79**	**Placebo + fulvestrant N = 81**
SOLAR-1		
Total rate of SAEs	34 (43.0)	15 (18.5)
Respiratory, thoracic, and mediastinal disorders	4 (5.1)	2 (2.5)
Skin and subcutaneous tissue disorders	5 (6.3)	0 (0)
Gastrointestinal disorders	8 (10.1)	1 (1.2)
Stomatitis	4 (5.1)	0 (0)
General disorders and administration site conditions	5 (6.3)	0 (0)
Infections and infestations	6 (7.6)	7 (8.6)
Metabolic and nutritional disorders	11 (13.9)	1 (1.2)
Hyperglycaemia	8 (10.1)	0 (0)
Musculoskeletal and connective tissue disorders	6 (7.6)	0 (0)

a. Events that occurred in at least 1 study arm in ≥ 5% of patients.
b. MedDRA version 20.1 as per Module 4; SOC and PT terminology unmodified from MedDRA.

MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; NI: not interpretable; PT: preferred term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: system organ class

Table 24: Common severe AEs[a] (CTCAE grade 3 or 4) – RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Alpelisib + fulvestrant N = 79**	**Placebo + fulvestrant N = 81**
SOLAR-1		
Total rate of severe AEs (CTCAE grade 3 or 4)	67 (84.8)	25 (30.9)
Nervous system disorders	4 (5.1)	2 (2.5)
Respiratory, thoracic, and mediastinal disorders	5 (6.3)	3 (3.7)
Skin and subcutaneous tissue disorders	20 (25.3)	0 (0)
Rash	10 (12.7)	0 (0)
Maculopapular rash	7 (8.9)	0 (0)
Gastrointestinal disorders	13 (16.5)	2 (2.5)
Diarrhoea	5 (6.3)	0 (0)
General disorders and administration site conditions	6 (7.6)	0 (0)
Infections and infestations	8 (10.1)	6 (7.4)
Investigations	26 (32.9)	11 (13.6)
Alanine aminotransferase increased	4 (5.1)	1 (1.2)
Gamma glutamyltransferase increased	7 (8.9)	5 (6.2)
Increased lipase	7 (8.9)	4 (4.9)
Weight decreased	4 (5.1)	0 (0)
Metabolic and nutritional disorders	34 (43.0)	6 (7.4)
Hyperglycaemia	28 (35.4)	0 (0)
Hypokalemia	5 (6.3)	0 (0)
Musculoskeletal and connective tissue disorders	7 (8.9)	2 (2.5)

a. Events that occurred in at least 1 study arm in ≥ 5% of patients.
b. MedDRA version 20.1 as per Module 4; SOC and PT terminology unmodified from MedDRA.

AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least 1 event; N: number of analysed patients; NI: not interpretable; PT: preferred term; RCT: randomized controlled trial; SOC: system organ class

Table 25: Discontinuation due to AEs – RCT, direct comparison: RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage) (multi-page table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Alpelisib + fulvestrant** **N = 79**	**Placebo + fulvestrant** **N = 81**
SOLAR-1		
Total rate of discontinuation due to AEs	21 (26.6)	4 (4.9)
Skin and subcutaneous tissue disorders	5 (6.3)	0 (0)
Rash	3 (3.8)	0 (0)
Erythema	1 (1.3)	0 (0)
Maculopapular rash	1 (1.3)	0 (0)
Gastrointestinal disorders	6 (7.6)	1 (1.2)
Diarrhoea	3 (3.8)	0 (0)
Stomatitis	2 (2.5)	1 (1.2)
Dysphagia	1 (1.3)	0 (0)
Nausea	1 (1.3)	0 (0)
Vomiting	1 (1.3)	0 (0)
Oral pain	0 (0)	1 (1.2)
General disorders and administration site conditions	4 (5.1)	0 (0)
Mucosal inflammation	2 (2.5)	0 (0)
Adverse drug reaction	1 (1.3)	0 (0)
Fatigue	1 (1.3)	0 (0)
Dry mucosa	1 (1.3)	0 (0)
Fever	1 (1.3)	0 (0)
Immune system disorders	1 (1.3)	0 (0)
Hypersensitivity	1 (1.3)	0 (0)
Infections and infestations	0 (0)	1 (1.3)
Pneumonia	0 (0)	1 (1.2)
Investigations	5 (6.3)	1 (1.2)
Increased lipase	3 (3.8)	1 (1.2)
Blood creatinine increased	1 (1.3)	0 (0)
Increased glycated haemoglobin	1 (1.3)	0 (0)
Increased amylase	0 (0)	1 (1.2)
Metabolic and nutritional disorders	5 (6.3)	0 (0)
Hyperglycaemia	5 (6.3)	0 (0)
Musculoskeletal and connective tissue disorders	1 (1.3)	0 (0)
Osteonecrosis of the jaw	1 (1.3)	0 (0)

Table 25: Discontinuation due to AEs – RCT, direct comparison: RCT, direct comparison: alpelisib + fulvestrant vs. placebo + fulvestrant (research question B1: postmenopausal women, second-line and subsequent-line therapy in the advanced stage) (multi-page table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Alpelisib + fulvestrant** **N = 79**	**Placebo + fulvestrant** **N = 81**
Nervous system disorders	1 (1.3)	1 (1.2)
Dizziness	1 (1.3)	0 (0)
Spinal cord compression	0 (0)	1 (1.2)

a. MedDRA version 20.1 as per Module 4; SOC and PT terminology unmodified from MedDRA.

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: randomized controlled trial; SOC: system organ class