Clinical trial results:
MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 TRIAL OF FULVESTRANT (FASLODEX) WITH OR WITHOUT PD-0332991 (PALBOCICLIB) ±GOSERELIN IN WOMEN WITH HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE METASTATIC BREAST CANCER WHOSE DISEASE PROGRESSED AFTER PRIOR ENDOCRINE THERAPY

Summary

EudraCT number	2013-002580-26
Trial protocol	BE NL IE IT GB DE PT FR
Global end of trial date	

Results information

Result version number	v1
This version publication date	17 March 2016
First version publication date	17 March 2016

Trial information

Trial identification

Sponsor protocol code	A5481023

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01942135
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 East 42nd Street,, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 800 718 1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 800 718 1021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	05 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 December 2014
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the superiority of palbociclib in combination with fulvestrant (with or without goserelin) over fulvestrant (with or without goserelin) along with prolonging investigator-assessed PFS in women with HR-positive/ HER2-negative metastatic breast cancer whose disease had progressed on prior endocrine therapy.

Protection of trial subjects:

The study was conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (GCP) (International Conference on Harmonisation [ICH] 1996), and the Declaration of Helsinki (World Medical Association 1996 and 2008). In addition, the study was conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 September 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 32
Country: Number of subjects enrolled	Belgium: 27
Country: Number of subjects enrolled	Canada: 39
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Italy: 36
Country: Number of subjects enrolled	Japan: 35
Country: Number of subjects enrolled	Korea, Republic of: 43
Country: Number of subjects enrolled	Netherlands: 9
Country: Number of subjects enrolled	Portugal: 6
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Russian Federation: 17
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	Turkey: 1
Country: Number of subjects enrolled	Ukraine: 44
Country: Number of subjects enrolled	United Kingdom: 13

Country: Number of subjects enrolled	United States: 201
Worldwide total number of subjects	521
EEA total number of subjects	105

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	392
From 65 to 84 years	126
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 144 sites in 17 countries that randomized 521 participants. Eligible participants were to have histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of recurrent (local or metastatic) disease.

Pre-assignment

Screening details:

The study consisted of a screening visit within 28 days before randomization, an active treatment phase, divided in cycles of 28 days each, and a post-treatment follow-up period during which survival and new anti-cancer therapy information was collected every 3 months for the first 9 months, then every 6 months from the last dose of study drug.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

The blinding details was either a manual or electronic process. Blinding codes were only broken in emergency for reasons of participants safety, or if the participant discontinued treatment due to disease progression, as determined by the study physician using Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 criteria.

Arms

Are arms mutually exclusive?	Yes
Arm title	Palbociclib + Fulvestrant

Arm description:

Participants were administered an initial dose of 125 mg per day orally continuously for 3 weeks followed by 1 week off that can be reduced to 100 mg or 75 mg in case of toxicity; repeated at each subsequent cycle and fulvestrant 500 mg intramuscularly on days 1 and 15 of cycle 1 and then every 28 days. Pre- and perimenopausal women received goserelin at least 4 weeks before study treatment start and continued receiving concurrent ovarian function suppression with goserelin administered subcutaneously every 28 days during the active treatment phase.

Arm type	Experimental
Investigational medicinal product name	Palbociclib
Investigational medicinal product code	PD-0332991
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Initial dose of 125 mg per day continuously for 3 weeks followed by 1 week off that can be reduced to 100 mg or 75 mg in case of toxicity; repeated at each subsequent cycle and fulvestrant 500 mg intramuscularly on days 1 and 15 of cycle 1 and then every 28 days.

Arm title	Placebo + Fulvestrant

Arm description:

Participants were administered placebo orally continuously dosed for 3 weeks followed by 1 week off; repeated at each subsequent cycle and Fulvestrant 500 mg intramuscularly on Days 1 and 15 of cycle 1 and then every 28 days. Pre- and perimenopausal women received goserelin at least 4 weeks before study treatment start and continued receiving concurrent ovarian function suppression with goserelin administered subcutaneously every 28 days during the active treatment phase.

Arm type	Active comparator

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Placebo orally dosed for 3 weeks continuously followed by 1 week off; repeated at each subsequent cycle and fulvestrant 500 mg intramuscularly on days 1 and 15 of cycle 1 and then every 28 days.

Number of subjects in period 1	Palbociclib + Fulvestrant	Placebo + Fulvestrant
Started	347	174
Completed	0	0
Not completed	347	174
Participant refused to continue treatment	1	1
Objective Progression + Progressive Disease	85	87
Consent withdrawn by subject	4	2
Global deterioration of health status	8	3
Adverse Event	9	3
Randomized not treated	2	2
Death	-	1
Ongoing at date of cut-off (05 Dec 2014)	238	75

Baseline characteristics

Reporting groups	
Reporting group title	Palbociclib + Fulvestrant
Reporting group description:	
Participants were administered an initial dose of 125 mg per day orally continuously for 3 weeks followed by 1 week off that can be reduced to 100 mg or 75 mg in case of toxicity; repeated at each subsequent cycle and fulvestrant 500 mg intramuscularly on days 1 and 15 of cycle 1 and then every 28 days. Pre- and perimenopausal women received goserelin at least 4 weeks before study treatment start and continued receiving concurrent ovarian function suppression with goserelin administered subcutaneously every 28 days during the active treatment phase.	
Reporting group title	Placebo + Fulvestrant
Reporting group description:	
Participants were administered placebo orally continuously dosed for 3 weeks followed by 1 week off; repeated at each subsequent cycle and Fulvestrant 500 mg intramuscularly on Days 1 and 15 of cycle 1 and then every 28 days. Pre- and perimenopausal women received goserelin at least 4 weeks before study treatment start and continued receiving concurrent ovarian function suppression with goserelin administered subcutaneously every 28 days during the active treatment phase.	

Reporting group values	Palbociclib + Fulvestrant	Placebo + Fulvestrant	Total
Number of subjects	347	174	521
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	261	131	392
From 65-84 years	83	43	126
85 years and over	3	0	3
Age Continuous | Units: Years			
arithmetic mean	56.9	56.8	
standard deviation	± 11.7	± 10.4	-
Gender, Male/Female Units: Participants			
Female	347	174	521
Male	0	0	0

End points

End points reporting groups

Reporting group title	Palbociclib + Fulvestrant

Reporting group description:

Participants were administered an initial dose of 125 mg per day orally continuously for 3 weeks followed by 1 week off that can be reduced to 100 mg or 75 mg in case of toxicity; repeated at each subsequent cycle and fulvestrant 500 mg intramuscularly on days 1 and 15 of cycle 1 and then every 28 days. Pre- and perimenopausal women received goserelin at least 4 weeks before study treatment start and continued receiving concurrent ovarian function suppression with goserelin administered subcutaneously every 28 days during the active treatment phase.

Reporting group title	Placebo + Fulvestrant

Reporting group description:

Participants were administered placebo orally continuously dosed for 3 weeks followed by 1 week off; repeated at each subsequent cycle and Fulvestrant 500 mg intramuscularly on Days 1 and 15 of cycle 1 and then every 28 days. Pre- and perimenopausal women received goserelin at least 4 weeks before study treatment start and continued receiving concurrent ovarian function suppression with goserelin administered subcutaneously every 28 days during the active treatment phase.

Primary: Progression-Free Survival (PFS) as assessed by the investigator

End point title	Progression-Free Survival (PFS) as assessed by the investigator

End point description:

PFS which was defined as the time from the date of randomization to the date of the first documentation of objective progression of disease (PD) or death due to any cause in the absence of documented PD. PFS data were censored on the date of the last tumor assessment on study for participants who did not have objective tumor progression and who did not die while on study. Participants lacking an evaluation of tumor response after randomization had their PFS time censored on the date of randomization with the duration of one day. Participants with documentation of PD or death after a long interval (ie, 2 or more incomplete or non-evaluable assessments) since the last tumor assessment were censored at the time of last objective assessment that did not show PD. The length of PFS was calculated as PFS time (months) = [progression/death date (censor date) - randomization date + 1]/30.4.

End point type	Primary

End point timeframe:

From randomization date to date of first documentation of progression or death (assessed up to 12 months)

End point values	Palbociclib + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347	174		
Units: Months				
median (confidence interval 95%)	9.2 (7.5 to 9999)	3.8 (3.5 to 5.5)		

Statistical analyses

Statistical analysis title	Statistical analysis 1 for PFS

Statistical analysis description:

The primary hypothesis to be tested was H0: $\lambda \geq 1$ versus. HA: $\lambda < 1$, where λ was the palbociclib plus

fulvestrant: placebo plus fulvestrant hazard ratio (HR). A HR less than 1 indicates a reduction in hazard rate in favor of Palbociclib + Fulvestrant. The study was planned to have 90% power and control the type-I error rate at 0.025.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001 [1]
Method	Stratified Log Rank Test (1-sided)
Parameter estimate	Hazard ratio (HR)
Point estimate	0.422
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.318
upper limit	0.56

Notes:

[1] - The overall Type-I error rate was persevered at 1-sided 0.025 level for the analysis of the primary endpoint PFS by the Haybittle-Peto efficacy boundary. The priori threshold for statistical significance at the interim analysis was 0.00135.

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS is defined as the time from date of randomization to date of death due to any cause. In the absence of confirmation of death, survival time was censored to last date the participant was known to be alive. For participants lacking survival data beyond the date of their last follow-up, the OS time was censored on the last date they were known to be alive. Participants lacking survival data beyond randomization were to have their OS times be censored at randomization. The length of OS was calculated as OS time (months) = [death date (censor date) – randomization date + 1]/30.4. No inferential statistical analysis were done because of the immaturity of the OS data.

End point type	Secondary

End point timeframe:

From randomization until death (up to approximately 36 months)

End point values	Palbociclib + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347	174		
Units: Number of deaths (participants)	19	9		

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response (OR)

End point title	Objective Response (OR)

End point description:

OR is defined as the overall complete response (CR) or partial response (PR) according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) Objective Response Rate (ORR) is defined as

the proportion of participants with CR or PR relative to (1) all randomized participants and (2) randomized participants with measurable disease at baseline. Designation of best response of stable disease (SD) requires the criteria to be met at least 8 weeks after randomization. Participants who do not have on-study radiographic tumor re-evaluation, who received anti-tumor treatment other than the study medication prior to reaching a CR or PR, or who died, progressed, or dropped out for any reason prior to reaching a CR or PR were counted as non-responders in the assessment of ORR. Percentage of participants with confirmed objective tumor response is mentioned below.

End point type	Secondary

End point timeframe:

From randomization until end of treatment (assessed up to 12 months)

End point values	Palbociclib + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347	174		
Units: percentage of participants				
median (confidence interval 95%)	10.4 (7.4 to 14.1)	6.3 (3.2 to 11)		

Statistical analyses

Statistical analysis title	Statistical analysis for OR

Statistical analysis description:

The exact test is testing the null hypothesis that the odds ratio of objective response rate is less than or equal to 1 vs. the alternative hypothesis that the odds ratio of objective response rate is greater than 1. An Odds Ratio >1 means better response in favor of palbociclib plus fulvestrant arm.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0791 [2]
Method	Exact test (1-sided)
Parameter estimate	Odds ratio (OR)
Point estimate	1.725
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.835
upper limit	3.896

Notes:

[2] - The p-value was not adjusted for multiple comparisons. The priori threshold for statistical significance is 1-sided, alpha=0.025.

Secondary: Duration of Response (DR)

End point title	Duration of Response (DR)

End point description:

DR is defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of disease progression or to death due to any cause, whichever occurs first. If tumor progression data included more than 1 date, the first date was used. DR was calculated as [the date response ended (ie, date of PD or death) – first CR or PR date + 1)]/30.4. DR was only be calculated for the subgroup of participants with an objective tumor response. Kaplan-Meier estimate of median of the

DR is provided below. No inferential statistical analysis were done for DR.

End point type	Secondary

End point timeframe:

From randomization until end of treatment (assessed up to 12 months)

End point values	Palbociclib + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347	174		
Units: Months				
median (confidence interval 95%)	9.3 (4 to 9999)	5.7 (3.7 to 5.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Response (CBR)

End point title	Clinical Benefit Response (CBR)

End point description:

CBR is defined as the overall complete response (CR), partial response (PR) , or stable disease (SD) ≥24 weeks according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1). Clinical Benefit Response Rate (CBRR) is defined as the proportion of participants with CR, PR, or SD ≥24 weeks relative to (1) all randomized participants and (2) randomized participants with measurable disease at baseline. Designation of best response of SD ≥24 weeks requires the criteria to be met at least 24 weeks after randomization. Participants who do not have on-study radiographic tumor re-evaluation, who received anti-tumor treatment other than the study medication prior to reaching a CR or PR, a best response of SD ≥24 weeks, or who died, progressed, or dropped out for any reason prior to reaching a CR or PR and a best response of SD ≥24 weeks was counted as non-responders in the assessment of CBR.

End point type	Secondary

End point timeframe:

From randomization until end of treatment (assessed up to 12 months)

End point values	Palbociclib + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347	174		
Units: percentage of participants				
number (confidence interval 95%)	34 (29 to 39.3)	19 (13.4 to 25.6)		

Statistical analyses

Statistical analysis title	Statistical analysis of CBR

Statistical analysis description:

The exact test is testing the null hypothesis that the odds ratio of objective response rate is less than or equal to 1 vs. the alternative hypothesis that the odds ratio of objective response rate is greater than 1. An Odds Ratio >1 means better response in favor of palbociclib plus fulvestrant arm.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	521
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [3]
Method	Exact test (1-sided)
Parameter estimate	Odds ratio (OR)
Point estimate	2.189
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.391
upper limit	3.523

Notes:

[3] - The p-value was not adjusted for multiple comparisons. The priori threshold for statistical significance is 1-sided, alpha=0.025.

Secondary: Survival probabilities at Month 12

End point title	Survival probabilities at Month 12

End point description:

One-, Two- or Three-year Survival Probability is defined as the probability of survival 1 year, 2 or 3 years after the date of randomization based on the Kaplan-Meier estimate. The survival-probability for Months 24 and 36 were not estimable due to less follow-up time and insufficient number of participants with events. Hence, survival probability at Month 12 is presented below.

End point type	Secondary

End point timeframe:

From randomization until death (assessed up to 36 months)

End point values	Palbociclib + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347	174		
Units: Units on a scale				
number (confidence interval 95%)	89.3 (78.1 to 95)	89.3 (77.8 to 95)		

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Plasma Trough Concentration (Ctrough) for Palbociclib

End point title	Observed Plasma Trough Concentration (Ctrough) for Palbociclib[4]

End point description:

Ctrough for palbociclib (if applicable). The method of dispersion applied here is "percent coefficient of variation" (%CV). The participants who were treated with Palbociclib + fulvestrant (with or without goserelin) or placebo + fulvestrant (with or without goserelin) and have at least one measured plasma drug concentration. The geometric mean and coefficient of variation was not estimable for Cycle 1/Day 15 and Cycle 2/Day 15 for the reporting arm placebo plus fulvestrant.

End point type	Secondary

End point timeframe:

Cycles 1 and 2

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The geometric mean and coefficient of variation was not estimable for Cycle 1/Day 15 and Cycle 2/Day 15 for the reporting arm placebo plus fulvestrant due to insufficient number of participants with events.

End point values	Palbociclib + Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	347			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1/Day 15 (N= 165)	70.7 (± 44)			
Cycle 2/Day 15 (N= 160)	75.29 (± 44)			

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough for Fulvestrant

End point title	Ctrough for Fulvestrant

End point description:

Ctrough for Fulvestrant (if applicable). The method of dispersion applied here is "percent coefficient of variation" (%CV). The 40 participants who participated in the early safety review, who are treated with palbociclib + fulvestrant ± goserelin or placebo + fulvestrant ± goserelin and have at least one measured plasma drug concentration.

End point type	Secondary

End point timeframe:

Cycles 2/Day 1 and Cycle 3/Day 1

End point values	Palbociclib + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347	174		
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 2/Day 1 (N= 35, 19)	11.75 (± 41)	9.31 (± 52)		
Cycle 3/Day 1 (N= 29, 14)	9.9 (± 42)	7.6 (± 72)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ctrough for Goserelin

End point title	Ctrough for Goserelin

End point description:

Cmin for goserelin (if applicable). The method of dispersion applied here is "percent coefficient of variation" (%CV). The 40 participants who participated in the early safety review, who are treated with palbociclib + fulvestrant ± goserelin or placebo + fulvestrant ± goserelin and have at least one measured plasma drug concentration.

End point type	Secondary

End point timeframe:

Cycles 2/ Day 1 and Cycle 3/ Day 1

End point values	Palbociclib + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	347	174		
Units: pg/mL				
geometric mean (geometric coefficient of variation)				
Cycle 2/Day 1 (N= 9, 5)	295.1 (± 153)	302.5 (± 74)		
Cycle 3/Day 1 (N= 7, 3)	344.8 (± 64)	288.5 (± 40)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Functional Scale Scores

End point title	Change from Baseline in European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) Functional Scale Scores

End point description:

The EORTC-QLQ-C30 is a 30-item questionnaire composed of five multi-item functional subscales (physical, role, emotional, cognitive , and social functioning), three multi-item symptom scales (fatigue, nausea/vomiting, and pain), a global quality of life (QOL) subscale, and six single item symptom scales assessing other cancer-related symptoms (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and the financial impact of cancer). The questionnaire employs 28 4-point Likert scales with responses from “not at all” to “very much” and two 7-point Likert scales for global health and overall QOL. Responses to all items are then converted to a 0 to 100 scale. For functional and global QOL scales, higher scores represent a better level of functioning/QOL. For symptom-oriented scales, a higher

score represents more severe symptoms. A 10-point or higher change in scores from baseline is considered clinically significant.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycles 2 to 4, Day 1 of every alternate cycle after that until the end of treatment

End point values	Palbociclib + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	166		
Units: Units on a scale				
least squares mean (confidence interval 95%)				
Global health status / QoL	-0.9 (-2.5 to 0.7)	-4 (-6.3 to -1.7)		
Physical functioning	-0.7 (-2.1 to 0.7)	-1.7 (-3.7 to 0.2)		
Role functioning	-1.8 (-3.7 to 0.1)	-3.7 (-6.5 to -0.9)		
Emotional functioning	2.7 (1.1 to 4.3)	-1.9 (-4.2 to 0.5)		
Cognitive functioning	-1.7 (-3.1 to -0.2)	-2.9 (-5 to -0.7)		
Social functioning	-0.5 (-2.5 to 1.5)	-0.6 (-3.4 to 2.3)		

Statistical analyses

Statistical analysis title	Statistical significance for Global health status

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0313 [5]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	3.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	6

Notes:

[5] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for physical functioning

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4 [6]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	3.5

Notes:

[6] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for role functioning

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2615 [7]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	1.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	5.3

Notes:

[7] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for emotional functioning

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0016 [8]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	4.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.7
upper limit	7.4

Notes:

[8] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for cognitive functioning

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.365 [9]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	3.8

Notes:

[9] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for social functioning

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9615 [10]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.4
upper limit	3.5

Notes:

[10] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Secondary: Change from Baseline in EORTC QLQ-C30 Symptom Scale Scores

End point title	Change from Baseline in EORTC QLQ-C30 Symptom Scale Scores

End point description:

The EORTC-QLQ-C30 is a 30-item questionnaire composed of five multi-item functional subscales (physical, role, emotional, cognitive , and social functioning), three multi-item symptom scales (fatigue, nausea/vomiting, and pain), a global quality of life (QOL) subscale, and six single item symptom scales assessing other cancer-related symptoms (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and the financial impact of cancer). The questionnaire employs 28 4-point Likert scales with responses from "not at all" to "very much" and two 7-point Likert scales for global health and overall QOL. Responses to all items are then converted to a 0 to 100 scale. For functional and global QOL scales, higher scores represent a better level of functioning/QOL. For symptom-oriented scales, a higher score represents more severe symptoms. A 10-point or higher change in scores from baseline is considered clinically significant.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycles 2 to 4, Day 1 of every alternate cycle after that until the end of treatment

End point values	Palbociclib + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	166		
Units: Units on a scale				
least squares mean (confidence interval 95%)				
Fatigue	1.8 (0.1 to 3.5)	3.3 (0.9 to 5.8)		
Nausea and vomiting	1.7 (0.4 to 3)	4.2 (2.3 to 6.1)		
Pain	-3.3 (-5.1 to -1.5)	2 (-0.6 to 4.6)		
Dyspnoea	2.8 (1 to 4.7)	3.3 (0.6 to 6)		
Insomnia	-2.4 (-4.4 to -0.4)	-0.4 (-3.3 to 2.5)		
Appetite loss	1.1 (-0.8 to 3.1)	1.7 (-1.1 to 4.6)		
Constipation	3.5 (1.7 to 5.3)	2.8 (0.1 to 5.4)		
Diarrhoea	1.9 (0.6 to 3.1)	2.4 (0.5 to 4.3)		
Financial difficulties	-3.7 (-5.6 to -1.9)	-4 (-6.7 to -1.3)		

Statistical analyses

Statistical analysis title	Statistical significance for fatigue

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.32 [11]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	-1.5

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.5
upper limit	1.5

Notes:

[11] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for nausea/vomiting

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0369 [12]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	-2.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.8
upper limit	-0.2

Notes:

[12] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for pain

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0011 [13]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	-5.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-8.5
upper limit	-2.1

Notes:

[13] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for dyspnoea

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7699 [14]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	-0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.7
upper limit	2.8

Notes:

[14] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for insomnia

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2721 [15]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	-2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	1.6

Notes:

[15] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for appetite loss

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7334 [16]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	-0.6

Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.1
upper limit	2.9

Notes:

[16] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for constipation

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6491 [17]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.5
upper limit	3.9

Notes:

[17] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for diarrhoea

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6293 [18]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	-0.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.8
upper limit	1.7

Notes:

[18] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for financial difficulty

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8812 [19]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	3.6

Notes:

[19] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Secondary: Change from Baseline in European Organization for Research and Treatment of Cancer Breast Cancer Module (EORTC QLQ BR23) Functional Scale Scores

End point title	Change from Baseline in European Organization for Research and Treatment of Cancer Breast Cancer Module (EORTC QLQ BR23) Functional Scale Scores

End point description:

The EORTC-QLQ-BR23 is a 23-item breast cancer-specific companion module to the EORTC-QLQ-C30 and consists of four functional scales (body image, sexual functioning, sexual enjoyment, future perspective) and four symptom scales (systemic side effects, breast symptoms, arm symptoms, upset by hair loss). QLQ-BR23 questionnaire employs 4-point scales with responses from 'not at all' to 'very much'. All scores are converted to a 0 to 100 scale. For functional scales, higher scores represent a better level of functioning.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycles 2 to 4, Day 1 of every alternate cycle after that until the end of treatment

End point values	Palbociclib + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	166		
Units: Units on a scale				
least squares mean (confidence interval 95%)				
Body image	1.9 (0.2 to 3.6)	-0.3 (-2.8 to 2.1)		
Sexual functioning	-1.1 (-2.5 to 0.2)	-0.4 (-2.3 to 1.5)		
Sexual enjoyment	-5.2 (-8.3 to -2.1)	-6.6 (-11.6 to -1.7)		
Future perspective	8.1 (5.8 to 10.4)	4.5 (1.2 to 7.9)		

Statistical analyses

Statistical analysis title	Statistical significance for body image

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1386 [20]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	2.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	5.2

Notes:

[20] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for sexual functioning

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5235 [21]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.1
upper limit	1.6

Notes:

[21] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for sexual enjoyment

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time,

treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6271 [22]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.4
upper limit	7.3

Notes:

[22] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for future perspective

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0845 [23]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	3.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	7.6

Notes:

[23] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Secondary: Change from Baseline in EORTC QLQ BR23 Symptom Scale Scores

End point title	Change from Baseline in EORTC QLQ BR23 Symptom Scale Scores

End point description:

The EORTC-QLQ-BR23 is a 23-item breast cancer-specific companion module to the EORTC-QLQ-C30 and consists of four functional scales (body image, sexual functioning, sexual enjoyment, future perspective) and four symptom scales (systemic side effects, breast symptoms, arm symptoms, upset by hair loss). QLQ-BR23 questionnaire employs 4-point scales with responses from ’not at all’ to ’very much’. All scores are converted to a 0 to 100 scale. For symptom-oriented scales, a higher score represent more severe symptoms.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycles 2 to 4, Day 1 of every alternate cycle after that until the end of treatment

End point values	Palbociclib + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	166		
Units: Units on a scale				
least squares mean (confidence interval 95%)				
Systemic therapy side effects	3.8 (2.6 to 4.9)	3.4 (1.8 to 5)		
Breast symptoms	-2.2 (-3.2 to -1.3)	-1.3 (-2.7 to 0)		
Arm symptoms	-2.2 (-3.6 to -0.9)	-2 (-4 to -0.1)		
Upset by hair loss	2.9 (-1.7 to 7.4)	-6 (-12.3 to 0.3)		

Statistical analyses

Statistical analysis title	Statistical significance for systemic therapy

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7273 [24]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	2.3

Notes:

[24] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for breast symptoms

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant

Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2671 [25]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	0.7

Notes:

[25] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for arm symptoms

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.875 [26]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	-0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.6
upper limit	2.2

Notes:

[26] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Statistical analysis title	Statistical significance for upset by hair loss

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0255 [27]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	8.9

Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	16.6

Notes:

[27] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Secondary: Change from Baseline in EuroQoL 5D (EQ-5D)- Health Index scores

End point title	Change from Baseline in EuroQoL 5D (EQ-5D)- Health Index scores

End point description:

The EuroQol-5D (version 3L) is a brief self-administered, validated instrument consisting of 2 parts. The first part consists of 5 descriptors of current health state (mobility, self care, usual activities, pain/discomfort, and anxiety/ depression); a participant is asked to rate each state on a three level scale (1=no problem, 2=some problem, and 3=extreme problem) with higher levels indicating greater severity/ impairment Published weights are available that allow for the creation of a single summary score called the EQ-5D index, which basically ranges from 0 to 1 with low scores representing a higher level of dysfunction and 1 as perfect health. The second part consists of the EQ-5D general health status as measured by a visual analog scale (EQ-5D VAS). EQ-5D VAS measures the participant's self-rated health status on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycles 2 to 4, Day 1 of every alternate cycle after that until the end of treatment

End point values	Palbociclib + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	166		
Units: Units on a scale				
least squares mean (confidence interval 95%)	0.006 (-0.01 to 0.03)	-0.031 (-0.06 to 0)		

Statistical analyses

Statistical analysis title	Statistical Analysis for EQ-5D-Health Index scores

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0308 [28]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	0.037

Confidence interval	
level	95 %
sides	2-sided
lower limit	0
upper limit	0.07

Notes:

[28] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Secondary: Change from Baseline in EQ-5D Visual Analog Scale (VAS) scores scale

End point title	Change from Baseline in EQ-5D Visual Analog Scale (VAS) scores scale

End point description:

The EuroQol-5D (version 3L) is a brief self-administered, validated instrument consisting of 2 parts. The second part consists of the EQ-5D general health status as measured by a visual analog scale (EQ-5D VAS). EQ-5D VAS measures the participant's self-rated health status on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state).

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycles 2 to 4, Day 1 of every alternate cycle after that until the end of treatment

End point values	Palbociclib + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	166		
Units: Units on a scale				
least squares mean (confidence interval 95%)	-1.8 (-3.3 to -0.3)	-2.6 (-4.8 to -0.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis for EQ-5D VAS scores scale

Statistical analysis description:

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5523 [29]
Method	Mixed Model Analysis (2-sided)
Parameter estimate	Mean difference (final values)
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.9
upper limit	3.5

Notes:

[29] - The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Secondary: Time to Deterioration (TTD)

End point title	Time to Deterioration (TTD)

End point description:

A time to event analysis was pre-specified for pain. An analysis of TTD in pain defined as time between baseline and first occurrence of increase of ≥10 points in pain. Deterioration will be defined increase in score of 10 points or greater from baseline. The Kaplan-Meier estimates of quartiles (time to deterioration) with 95% CI is mentioned below.

End point type	Secondary

End point timeframe:

Baseline, Day 1 of Cycles 2 to 4, Day 1 of every alternate cycle after that until the end of treatment

End point values	Palbociclib + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	166		
Units: Units on a scale				
median (confidence interval 95%)				
25% quartile	1.9 (1.2 to 2.2)	1 (1 to 1.9)		
50% quartile	8 (5.6 to 9999)	2.8 (2.3 to 5.4)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for TTD

Statistical analysis description:

Treatment with palbociclib plus fulvestrant significantly delayed TTD in pain symptom compared with placebo plus fulvestrant for unstratified analysis.

Comparison groups	Palbociclib + Fulvestrant v Placebo + Fulvestrant
Number of subjects included in analysis	501
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [30]
Method	Unstratified log-rank test (1-sided)
Parameter estimate	Hazard ratio (HR)
Point estimate	0.642
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.487
upper limit	0.846

Notes:

[30] - The priori threshold for statistical significance is 1-sided alpha=0.025. The p-value was not adjusted for multiple comparisons.

Secondary: Percentage of participants with Treatment-Emergent Adverse Events (TEAEs; All Causalities)

End point title	Percentage of participants with Treatment-Emergent Adverse Events (TEAEs; All Causalities)

End point description:

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. An SAE is any untoward medical occurrence at any dose that results in death; is life-threatening; requires hospitalization; results in persistent or significant disability or in congenital anomaly/birth defect. Severity will be graded by the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0.

End point type	Secondary

End point timeframe:

From the signing of the informed consent until 28 days after the last dose of study medication

End point values	Palbociclib + Fulvestrant	Placebo + Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	345	172		
Units: Percentage of Participants				
number (not applicable)				
With AEs	97.7	89		
With SAEs	9.6	14		
With Grade 3 or 4 AEs	70.1	18		
With Grade 5 AEs	0.9	1.2		
Discontinued palbociclib/ placebo due to AEs	3.8	4.1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of randomization up to 28 calendar days (±7 days) after last dose of study medication.

Adverse event reporting additional description:

The safety analysis set included participants who received at least 1 dose of study medication, with treatment assignments designated according to actual study treatment received.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo + Fulvestrant

Reporting group description:

Participants were administered placebo orally continuously dosed for 3 weeks followed by 1 week off; repeated at each subsequent cycle and Fulvestrant 500 mg intramuscularly on Days 1 and 15 of cycle 1 and then every 28 days. Pre- and perimenopausal women received goserelin at least 4 weeks before study treatment start and continued receiving concurrent ovarian function suppression with goserelin administered subcutaneously every 28 days during the active treatment phase.

Reporting group title	Palbociclib + Fulvestrant

Reporting group description:

Participants were administered an initial dose of 125 mg per day orally continuously for 3 weeks followed by 1 week off that can be reduced to 100 mg or 75 mg in case of toxicity; repeated at each subsequent cycle and fulvestrant 500 mg intramuscularly on days 1 and 15 of cycle 1 and then every 28 days. Pre- and perimenopausal women received goserelin at least 4 weeks before study treatment start and continued receiving concurrent ovarian function suppression with goserelin administered subcutaneously every 28 days during the active treatment phase.

Serious adverse events	Placebo + Fulvestrant	Palbociclib + Fulvestrant	
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 172 (13.95%)	33 / 345 (9.57%)	
number of deaths (all causes)	2	3	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Device occlusion			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disease progression			
subjects affected / exposed	0 / 172 (0.00%)	2 / 345 (0.58%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 2	
General physical health deterioration			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Non-cardiac chest pain			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 172 (0.58%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 172 (0.58%)	3 / 345 (0.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 172 (0.58%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 172 (0.58%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	3 / 172 (1.74%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 172 (0.00%)	3 / 345 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pericarditis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysarthria			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paresis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sedation			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Somnolence			

subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Disseminated intravascular coagulation			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 172 (0.58%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	2 / 172 (1.16%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenogastric reflux			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Nausea			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 172 (0.58%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			

subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 172 (1.16%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Gastrointestinal infection			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Otitis media acute			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 172 (1.16%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 172 (0.58%)	0 / 345 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 172 (0.00%)	1 / 345 (0.29%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo + Fulvestrant	Palbociclib + Fulvestrant	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	147 / 172 (85.47%)	333 / 345 (96.52%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	8 / 172 (4.65%)	19 / 345 (5.51%)	
occurrences (all)	12	25	
Neutrophil count decreased			
subjects affected / exposed	3 / 172 (1.74%)	73 / 345 (21.16%)	
occurrences (all)	4	263	
White blood cell count decreased			
subjects affected / exposed	5 / 172 (2.91%)	92 / 345 (26.67%)	
occurrences (all)	6	280	
Platelet count decreased			
subjects affected / exposed	0 / 172 (0.00%)	27 / 345 (7.83%)	
occurrences (all)	0	64	
Vascular disorders			
Hot flush			
subjects affected / exposed	28 / 172 (16.28%)	51 / 345 (14.78%)	
occurrences (all)	29	58	
Nervous system disorders			
Dizziness			
subjects affected / exposed	16 / 172 (9.30%)	37 / 345 (10.72%)	
occurrences (all)	19	45	
Dysgeusia			
subjects affected / exposed	3 / 172 (1.74%)	22 / 345 (6.38%)	
occurrences (all)	3	29	
Headache			
subjects affected / exposed	30 / 172 (17.44%)	73 / 345 (21.16%)	
occurrences (all)	41	109	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	17 / 172 (9.88%)	88 / 345 (25.51%)	
occurrences (all)	29	149	

Leukopenia			
subjects affected / exposed	2 / 172 (1.16%)	70 / 345 (20.29%)	
occurrences (all)	4	153	
Neutropenia			
subjects affected / exposed	3 / 172 (1.74%)	212 / 345 (61.45%)	
occurrences (all)	4	668	
Thrombocytopenia			
subjects affected / exposed	0 / 172 (0.00%)	40 / 345 (11.59%)	
occurrences (all)	0	83	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	8 / 172 (4.65%)	23 / 345 (6.67%)	
occurrences (all)	9	25	
Chest pain			
subjects affected / exposed	9 / 172 (5.23%)	6 / 345 (1.74%)	
occurrences (all)	12	7	
Fatigue			
subjects affected / exposed	46 / 172 (26.74%)	131 / 345 (37.97%)	
occurrences (all)	60	208	
Injection site pain			
subjects affected / exposed	16 / 172 (9.30%)	19 / 345 (5.51%)	
occurrences (all)	21	30	
Oedema peripheral			
subjects affected / exposed	8 / 172 (4.65%)	25 / 345 (7.25%)	
occurrences (all)	8	28	
Pain			
subjects affected / exposed	12 / 172 (6.98%)	15 / 345 (4.35%)	
occurrences (all)	13	20	
Pyrexia			
subjects affected / exposed	6 / 172 (3.49%)	27 / 345 (7.83%)	
occurrences (all)	7	34	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	9 / 172 (5.23%)	21 / 345 (6.09%)	
occurrences (all)	10	26	
Abdominal pain upper			

subjects affected / exposed	11 / 172 (6.40%)	12 / 345 (3.48%)	
occurrences (all)	12	18	
Constipation			
subjects affected / exposed	24 / 172 (13.95%)	58 / 345 (16.81%)	
occurrences (all)	25	71	
Diarrhoea			
subjects affected / exposed	30 / 172 (17.44%)	66 / 345 (19.13%)	
occurrences (all)	35	99	
Dry mouth			
subjects affected / exposed	14 / 172 (8.14%)	22 / 345 (6.38%)	
occurrences (all)	15	23	
Dyspepsia			
subjects affected / exposed	7 / 172 (4.07%)	25 / 345 (7.25%)	
occurrences (all)	8	30	
Nausea			
subjects affected / exposed	44 / 172 (25.58%)	100 / 345 (28.99%)	
occurrences (all)	51	137	
Stomatitis			
subjects affected / exposed	4 / 172 (2.33%)	40 / 345 (11.59%)	
occurrences (all)	5	75	
Vomiting			
subjects affected / exposed	20 / 172 (11.63%)	50 / 345 (14.49%)	
occurrences (all)	23	72	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	18 / 172 (10.47%)	45 / 345 (13.04%)	
occurrences (all)	18	48	
Dyspnoea			
subjects affected / exposed	10 / 172 (5.81%)	37 / 345 (10.72%)	
occurrences (all)	11	45	
Epistaxis			
subjects affected / exposed	2 / 172 (1.16%)	19 / 345 (5.51%)	
occurrences (all)	2	21	
Oropharyngeal pain			

subjects affected / exposed	9 / 172 (5.23%)	32 / 345 (9.28%)	
occurrences (all)	9	36	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	10 / 172 (5.81%)	51 / 345 (14.78%)	
occurrences (all)	10	52	
Rash			
subjects affected / exposed	7 / 172 (4.07%)	31 / 345 (8.99%)	
occurrences (all)	8	36	
Pruritus			
subjects affected / exposed	10 / 172 (5.81%)	19 / 345 (5.51%)	
occurrences (all)	10	21	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	9 / 172 (5.23%)	14 / 345 (4.06%)	
occurrences (all)	9	15	
Depression			
subjects affected / exposed	10 / 172 (5.81%)	16 / 345 (4.64%)	
occurrences (all)	10	19	
Insomnia			
subjects affected / exposed	12 / 172 (6.98%)	27 / 345 (7.83%)	
occurrences (all)	12	32	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	28 / 172 (16.28%)	45 / 345 (13.04%)	
occurrences (all)	34	61	
Back pain			
subjects affected / exposed	25 / 172 (14.53%)	38 / 345 (11.01%)	
occurrences (all)	33	47	
Muscle spasms			
subjects affected / exposed	11 / 172 (6.40%)	21 / 345 (6.09%)	
occurrences (all)	13	32	
Musculoskeletal chest pain			
subjects affected / exposed	9 / 172 (5.23%)	9 / 345 (2.61%)	
occurrences (all)	10	9	
Musculoskeletal pain			

subjects affected / exposed	11 / 172 (6.40%)	20 / 345 (5.80%)	
occurrences (all)	11	23	
Myalgia			
subjects affected / exposed	12 / 172 (6.98%)	23 / 345 (6.67%)	
occurrences (all)	13	31	
Pain in extremity			
subjects affected / exposed	19 / 172 (11.05%)	33 / 345 (9.57%)	
occurrences (all)	21	37	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 172 (5.23%)	25 / 345 (7.25%)	
occurrences (all)	9	29	
Upper respiratory tract infection			
subjects affected / exposed	7 / 172 (4.07%)	20 / 345 (5.80%)	
occurrences (all)	8	21	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	13 / 172 (7.56%)	44 / 345 (12.75%)	
occurrences (all)	15	52	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 April 2014	In protocol amendment 1, schedule of assessments was updated with ocular safety assessments procedures to newly enrolled lens grading evaluable participants to assess the potential risk of palbociclib-associated lens changes. In human pharmacokinetic data, included preliminary results from two clinical pharmacology studies of palbociclib. Clarified inclusion criteria #6 and exclusion criteria #4, 5 and 6 to address frequent questions from investigational sites. Added prohibition to take proton-pump inhibitors while receiving study drug. Clarified that routine safety assessments must continue if patient continues study treatment despite progression of disease.
30 September 2014	In protocol amendment 2, In schedule of activities, laboratory safety assessments: added prospective monitoring of hemoglobin A1c to characterize whether or not palbociclib affects glucose metabolism. Added clarification to the schedule of administration of fulvestrant and goserelin. Editorial changes made to differentiate between strong and moderate CYP3A nducers/inhibitors. Added clarification of adverse events follow-up procedure (telephone contact) at 28 calendar days after treatment discontinuation. Additional editorial changes made to clarify follow-up procedures for patients who discontinue treatment for reasons other than disease progression and for patients who discontinue treatment due to disease progression.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported