Clinical trial results:
A Randomized, Multicenter, Double Blind Phase 3 Study of PD 0332991 (Oral CDK 4/6 Inhibitor) Plus Letrozole Versus Placebo Plus Letrozole for the Treatment of Postmenopausal Women With ER (+), HER2 (-) Breast Cancer Who Have Not Received Any Prior Systemic Anti Cancer Treatment for Advanced Disease

Summary

EudraCT number	2012-004601-27
Trial protocol	DE BE IE FR GB ES HU IT PL
Global end of trial date	

Results information

Result version number	v1
This version publication date	16 December 2016
First version publication date	16 December 2016

Trial information

Trial identification

Sponsor protocol code	A5481008

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01740427
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 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 8007181021, 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	26 February 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 February 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the combination of palbociclib with letrozole is superior to placebo plus letrozole in prolonging progression-free survival (PFS) in postmenopausal women with ER-positive/HER2-negative ABC who have not received any prior systemic anti cancer therapies for their advanced/metastatic disease.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council on Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines . In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of study participants.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 February 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	46 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 20
Country: Number of subjects enrolled	Belgium: 28
Country: Number of subjects enrolled	Canada: 70
Country: Number of subjects enrolled	France: 33
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Ireland: 22
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Japan: 46
Country: Number of subjects enrolled	Korea, Democratic People's Republic of: 24
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Russian Federation: 60
Country: Number of subjects enrolled	Spain: 57
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	Ukraine: 39
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	United States: 197

Worldwide total number of subjects	666
EEA total number of subjects	208

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)	404
From 65 to 84 years	262
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between 28 February 2013 and 29 July 2014, 666 women were randomized at 186 sites in 17 countries.

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 6 months (±7 days) from the last dose of study treatment.

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	Investigator, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Palbociclib plus Letrozole

Arm description:

Participants received letrozole 2.5 milligram (mg) orally QD (once daily) combined with palbociclib 125 mg QD for 21 days of every-28-day cycle, followed by 7 days off treatment.

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:

Palbociclib was supplied as capsules containing 75 mg, 100 mg, or 125 mg equivalents of palbociclib free base

Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

2.5 mg, orally once daily

Arm title	Placebo plus Letrozole

Arm description:

Participants received letrozole 2.5 mg orally QD combined with placebo QD for 21 days of every-28-day cycle, followed by 7 days off treatment.

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

Dosage and administration details:	
Placebo was supplied as capsules containing 75 mg, 100 mg, or 125 mg equivalents of placebo free base	
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use
Dosage and administration details:	
2.5 mg, orally once daily	

Number of subjects in period 1	Palbociclib plus Letrozole	Placebo plus Letrozole
Started	444	222
Completed	0	0
Not completed	444	222
Adverse event, serious fatal	6	2
Study terminated by Sponsor	1	-
Global deterioration of health status	16	9
Adverse event, non-fatal	20	9
Other reasons	6	4
Ongoing at date of cutoff (26 Feb 2016)	205	61
Objective progression or relapse	172	125
Lost to follow-up	1	-
Subject refused continued treatment	12	9
Protocol deviation	5	3

Baseline characteristics

Reporting groups	
Reporting group title	Palbociclib plus Letrozole
Reporting group description:	
Participants received letrozole 2.5 milligram (mg) orally QD (once daily) combined with palbociclib 125 mg QD for 21 days of every-28-day cycle, followed by 7 days off treatment.	
Reporting group title	Placebo plus Letrozole
Reporting group description:	
Participants received letrozole 2.5 mg orally QD combined with placebo QD for 21 days of every-28-day cycle, followed by 7 days off treatment.	

Reporting group values	Palbociclib plus Letrozole	Placebo plus Letrozole	Total
Number of subjects	444	222	666
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)	263	141	404
From 65-84 years	181	81	262
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	61.7	60.6	
standard deviation	± 10.6	± 11.2	-
Gender, Male/Female Units: participants			
Female	444	222	666
Male	0	0	0

End points

End points reporting groups

Reporting group title	Palbociclib plus Letrozole
Reporting group description:	
Participants received letrozole 2.5 milligram (mg) orally QD (once daily) combined with palbociclib 125 mg QD for 21 days of every-28-day cycle, followed by 7 days off treatment.	
Reporting group title	Placebo plus Letrozole
Reporting group description:	
Participants received letrozole 2.5 mg orally QD combined with placebo QD for 21 days of every-28-day cycle, followed by 7 days off treatment.	
Subject analysis set title	Palbociclib plus Letrozole
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received letrozole 2.5 milligram (mg) orally QD (once daily) combined with palbociclib 125 mg QD or 21 days of every-28-day cycle, followed by 7 days off treatment.	
Subject analysis set title	Placebo plus Letrozole
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Participants received letrozole 2.5 mg orally QD combined with placebo QD for 21 days of every-28-day cycle,followed by 7 days off treatment.	

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 is defined as the time from the date of randomization to the date of the first documentation of objective tumor progression as per RECIST v.1.1 or death due to any cause in the absence of documented PD, whichever occurs first. If tumor progression data include more than 1 date, the first date will be used. PFS (in months) will be calculated as (first event 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 (up to approximately 2.5 years)	

End point values	Palbociclib plus Letrozole	Placebo plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	222		
Units: Months				
median (confidence interval 95%)	24.8 (22.1 to 99999)	14.5 (12.9 to 17.1)		

Statistical analyses

Statistical analysis title	Statistical Analysis for PFS
Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole

Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.000001 [1]
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.576
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.463
upper limit	0.718

Notes:

[1] - 1-sided p-value from the stratified log-rank test.

Secondary: Objective Response as assessed by the Investigator

End point title	Objective Response as assessed by the Investigator

End point description:

Objective Response (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 all randomized patients and randomized patients with measurable disease at baseline. Patients 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.

End point type	Secondary

End point timeframe:

From randomization until end of treatment (up to approximately 2.5 years)

End point values	Palbociclib plus Letrozole	Placebo plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	222		
Units: Percentage of participants				
number (confidence interval 95%)	46.4 (41.7 to 51.2)	38.3 (31.9 to 45)		

Statistical analyses

Statistical analysis title	Statistical Analysis for OR

Statistical analysis description:

Stratified analysis: Stratified by disease site (visceral vs non-visceral) per randomization.

Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole

Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0224 [2]
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.428
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.008
upper limit	2.03

Notes:

[2] - 1-sided p-value is from exact test.

Secondary: Objective Response: Patients with measurable disease at baseline as assessed by the Investigator

End point title	Objective Response: Patients with measurable disease at baseline as assessed by the Investigator

End point description:

Objective Response (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 all randomized patients and randomized patients with measurable disease at baseline. Patients 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.

End point type	Secondary

End point timeframe:

From randomization until end of treatment (up to approximately 2.5 years)

End point values	Palbociclib plus Letrozole	Placebo plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	338	171		
Units: Percentage of participants				
number (confidence interval 95%)	60.7 (55.2 to 65.9)	49.1 (41.4 to 56.9)		

Statistical analyses

Statistical analysis title	Statistical Analysis for OR

Statistical analysis description:

Stratified analysis: Stratified by disease site (visceral vs non-visceral) per randomization.

Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole

Number of subjects included in analysis	509
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009 [3]
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	1.594
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.08
upper limit	2.347

Notes:

[3] - 1-sided p-value is from exact test.

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 will be used. DR was calculated as [the date response ended (i.e. date of PD or death) – first CR or PR date + 1)]/30.4. DR would only be calculated for the subgroup of patients with an objective tumor response.

End point type	Secondary

End point timeframe:

From randomization until end of treatment (up to approximately 2.5 years)

End point values	Palbociclib plus Letrozole	Placebo plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	85		
Units: Months				
median (confidence interval 95%)	20.1 (19.3 to 28)	16.7 (13.8 to 22.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control (DC)/Clinical Benefit Response (CBR)

End point title	Disease Control (DC)/Clinical Benefit Response (CBR)

End point description:

DC is defined as the overall CR, PR, or stable disease (SD) ≥24 weeks according to the RECIST version 1.1; Appendix 1. Disease Control Rate (DCR) is defined as the proportion of participants with CR, PR, or SD ≥24 weeks relative to all randomized participants. Designation of best response of SD ≥24 weeks required the criteria to be met at least 24 weeks after randomization. Participants who do not have on-study radiographic tumor reevaluation, 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 achieving reaching a CR or PR and a best response of SD ≥24 weeks

was counted as non-responders in the assessment of DCR.

End point type	Secondary

End point timeframe:

From randomization until end of treatment (up to approximately 2.5 years)

End point values	Palbociclib plus Letrozole	Placebo plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	222		
Units: Percentage of participants				
number (confidence interval 95%)	85.8 (82.2 to 88.9)	71.2 (64.7 to 77)		

Statistical analyses

Statistical analysis title	Statistical Analysis for DC/CBR

Statistical analysis description:

Stratified analysis: Stratified by disease site (visceral, non-visceral) per randomization.

Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001 [4]
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	2.451
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.619
upper limit	3.722

Notes:

[4] - 1-sided p-value is from exact test.

Secondary: Tumor tissue biomarkers, including genes (eg, copy numbers of CCND1, CDKN2A), proteins (eg, Ki67, pRb), and RNA expression (eg, cdk4, cdk6): Protein biomarker analyses by using immunohistochemistry are presented

End point title	Tumor tissue biomarkers, including genes (eg, copy numbers of CCND1, CDKN2A), proteins (eg, Ki67, pRb), and RNA expression (eg, cdk4, cdk6): Protein biomarker analyses by using immunohistochemistry are presented

End point description:

PFS survival by biomarker status by Investigator assessment. Positive is defined as H-Score ≥1 and negative as H-Score <1. H-Score is calculated as the sum of the % of cells at each level of staining intensity (0, 1+, 2+, and 3+) multiplied by the staining intensity value: H-Score = (% at 0)*0 + (% at 1+)*1 + (% at 2+)*2 + (% at 3+)*3. H-Score values range from 0 to 300. ER stands for estrogen receptor and Rb stands for retinoblastoma susceptibility gene product.

End point type	Secondary

End point timeframe:
From randomization until end of treatment (up to approximately 24 Months)

End point values	Palbociclib plus Letrozole	Placebo plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	222		
Units: Months				
median (confidence interval 95%)				
ER Positive (N= 338, 166)	24.9 (22.2 to 99999)	16.3 (12.9 to 19.1)		
ER Negative (N= 40, 22)	15.6 (8.3 to 22)	5.4 (2.7 to 11.1)		
Rb Positive (N= 345, 167)	24.2 (21.4 to 25.7)	13.7 (11 to 16.5)		
Rb Negative (N= 29, 22)	99999 (11.4 to 99999)	18.5 (2.9 to 99999)		
Cyclin D1 Positive (N= 370, 179)	24.8 (21.5 to 27.6)	13.8 (11.3 to 16.8)		
Cyclin D1 Negative (N= 5, 10)	11.1 (2.2 to 23.9)	8.1 (0.4 to 99999)		
p16 Positive (N= 305, 161)	24.8 (21.5 to 99999)	13.8 (11.1 to 16.8)		
p16 Negative (N= 59, 25)	16.8 (11.1 to 24.9)	13.8 (8.1 to 99999)		
p16 H-Score<175 (N= 341, 177)	23.7 (19.6 to 25.7)	13.8 (11.2 to 16.8)		
p16 H-Score≥175 (N= 23, 9)	24.2 (11.1 to 99999)	5.6 (1.5 to 19.1)		
Ki67 ≤20% (N= 216, 102)	27.6 (24.2 to 99999)	16.8 (13.7 to 22)		
Ki67 >20% (N= 152, 83)	17.5 (13.8 to 22)	8.4 (5.6 to 13.6)		

Statistical analyses

Statistical analysis title	Statistical analysis for ER positive
Statistical analysis description: Statistical analysis for ER positive	
Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.571

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.443
upper limit	0.737

Statistical analysis title	Statistical analysis for ER Negative
Statistical analysis description: Statistical analysis for ER Negative	
Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.405
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.218
upper limit	0.751

Statistical analysis title	Statistical analysis for Rb Positive
Statistical analysis description: Statistical analysis for Rb Positive	
Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.531
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.416
upper limit	0.68

Statistical analysis title	Statistical analysis for Rb Negative
Statistical analysis description: Statistical analysis for Rb Negative	
Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole

Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3237
Method	Unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.675
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.308
upper limit	1.481

Statistical analysis title	Statistical analysis for Cyclin D1 Positive
Statistical analysis description:	
Statistical analysis for Cyclin D1 Positive	
Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.555
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.437
upper limit	0.705

Statistical analysis title	Statistical analysis for Cyclin D1 Negative
Statistical analysis description:	
Statistical analysis for Cyclin D1 Negative	
Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9964
Method	Unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.997
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.287
upper limit	3.461

Statistical analysis title	Statistical analysis for p16 Positive
Statistical analysis description: Statistical analysis for p16 Positive	
Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.518
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	0.67

Statistical analysis title	Statistical analysis for p16 Negative
Statistical analysis description: Statistical analysis for p16 Negative	
Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3221
Method	Unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.731
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.392
upper limit	1.364

Statistical analysis title	Statistical analysis for p16 HScore<175
Statistical analysis description: Statistical analysis for p16 HScore<175	
Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole

Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.581
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.455
upper limit	0.742

Statistical analysis title	Statistical analysis for p16 HScore≥175
Statistical analysis description: Statistical analysis for p16 HScore≥175	
Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0022
Method	Unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.255
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.65

Statistical analysis title	Statistical analysis for Ki67 ≤20%
Statistical analysis description: Statistical analysis for Ki67 ≤20%	
Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.379
upper limit	0.742

Statistical analysis title	Statistical analysis for Ki67 >20%
Statistical analysis description: Statistical analysis for Ki67 >20%	
Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0007
Method	Unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.569
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.409
upper limit	0.791

Secondary: Corrected QT interval (QTc) time-matched change from baseline on Cycle 1 Day 14

End point title	Corrected QT interval (QTc) time-matched change from baseline on Cycle 1 Day 14

End point description:

Triplicate 12-lead ECG measurements (each recording separated by approximately 2 minutes) were performed and sent to a central laboratory for blinded manual adjudication. The average was calculated. The time corresponding to beginning of depolarization to repolarization of the ventricles (QT interval) was adjusted for RR interval using QT and RR from each ECG by Fridericia's formula (QTcF = QT divided by cube root of RR), by Bazette's formula (QTcB = QT divided by square root of RR) and corrected QT interval according to study-specific criteria (QTcS). Time-matched change from baseline values were reported for QTc analysis population.

End point type	Secondary

End point timeframe:

Time-matched triplicate ECGs were collected at 0 (predose), 2, 4, 6 and 8 hours on Day 0 and on Cycle1 Day14

End point values	Palbociclib plus Letrozole	Placebo plus Letrozole		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	76	47		
Units: msec				
least squares mean (confidence interval 90%)				
QTcS at 0 hour	0.8 (-1.67 to 3.26)	2.95 (-0.19 to 6.1)		
QTcS at 2 hour	3.32 (0.79 to 5.85)	1.65 (-1.48 to 4.78)		
QTcS at 4 hour	2.76 (0.23 to 5.3)	1.74 (-1.39 to 4.87)		

QTcS at 6 hour	4.49 (1.96 to 7.02)	0.72 (-2.41 to 3.85)		
QTcS at 8 hour	0.94 (-1.6 to 3.48)	3.14 (0.01 to 6.27)		
QTcF at 0 hour	1.1 (-1.39 to 3.58)	3.06 (-0.11 to 6.23)		
QTcF at 2 hour	3.68 (1.12 to 6.23)	1.73 (-1.43 to 4.88)		
QTcF at 4 hour	2.86 (0.31 to 5.41)	1.54 (-1.62 to 4.7)		
QTcF at 6 hour	4.57 (2.01 to 7.12)	0.71 (-2.44 to 3.87)		
QTcF at 8 hour	1.21 (-1.36 to 3.77)	2.84 (-0.31 to 6)		
QTcB at 0 hour	-0.11 (-2.83 to 2.61)	2.78 (-0.69 to 6.25)		
QTcB at 2 hour	1.46 (-1.34 to 4.25)	0.83 (-2.63 to 4.28)		
QTcB at 4 hour	2.58 (-0.22 to 5.38)	2.47 (-0.98 to 5.92)		
QTcB at 6 hour	4.03 (1.24 to 6.83)	0.53 (-2.92 to 3.99)		
QTcB at 8 hour	-0.17 (-2.98 to 2.64)	4.14 (0.69 to 7.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Corrected QT interval (QTc)

End point title	Corrected QT interval (QTc)

End point description:

Triplicate 12-lead ECG measurements (each recording separated by approximately 2 minutes) were performed and sent to a central laboratory for blinded manual adjudication. The average was calculated. The time corresponding to beginning of depolarization to repolarization of the ventricles (QT interval) was adjusted for RR interval using QT and RR from each ECG by Fridericia's formula (QTcF = QT divided by cube root of RR), by Bazette's formula (QTcB = QT divided by square root of RR) and corrected QT interval according to study-specific criteria (QTcS). Percentage of participants with post-baseline maximum absolute values and maximum increase from baseline were summarized for the safety analysis population.

End point type	Secondary

End point timeframe:

For safety monitoring triplicate ECGs were obtained at 0 hour (pre-dose) on Day 1 of Cycle 1, Day 14 of Cycles 1 and Cycle 2, then on Day 1 of Cycles 4, 7, and 10. ECGs beyond Cycle 10 were performed as clinically indicated

End point values	Palbociclib plus Letrozole	Placebo plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	441	220		
Units: Percentage of participants				
number (not applicable)				
Maximum QTcS <450 msec	80.5	85.9		

Maximum QTcS 450-<480 msec	17.9	11.8		
Maximum QTcS 480-<500 msec	1.1	2.3		
Maximum QTcS ≥500 msec	0.5	0		
Maximum QTcF <450 msec	85.9	89.5		
Maximum QTcF 450-<480 msec	12.2	9.5		
Maximum QTcF 480-<500 msec	1.6	0.9		
Maximum QTcF ≥500 msec	0.2	0		
Maximum QTcB <450 msec	64.9	69.1		
Maximum QTcB 450-<480 msec	32.2	27.3		
Maximum QTcB 480-<500 msec	2.3	3.2		
Maximum QTcB ≥500 msec	0.7	0.5		
Maximum QTcS Change <30 msec	92.7	94.5		
Maximum QTcS 30≤Change <60 msec	6.6	5.5		
Maximum QTcS Change≥60 msec	0.7	0		
Maximum QTcF Change <30 msec	91.6	93.6		
Maximum QTcF 30≤Change <60 msec	7.9	6.4		
Maximum QTcF Change≥60 msec	0.5	0		
Maximum QTcB Change <30 msec	88.9	91.4		
Maximum QTcB 30≤Change <60 msec	10.2	8.2		
Maximum QTcB Change≥60 msec	0.9	0.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Plasma Trough Concentration (Ctrough) at Steady-State

End point title	Observed Plasma Trough Concentration (Ctrough) at Steady-State[5]

End point description:

Summary of Plasma Palbociclib Within-Patient Mean Steady-State Trough Concentrations.

End point type	Secondary

End point timeframe:

Day 14 of cycles 1 and 2

Notes:

[5] - 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: No descriptive statistic was available for the reporting arm placebo plus letrozole for the Secondary Endpoint: Observed Plasma Trough Concentration (Ctrough) at Steady-State.

End point values	Palbociclib plus Letrozole			
Subject group type	Reporting group			
Number of subjects analysed	423			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 14 (N= 395) Cycle 2 Day 14 (N= 401)	70.1 (± 59) 64.2 (± 82)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline Between Treatment Comparison in Euro Quality of Life (EQ-5D) Index

End point title	Change from Baseline Between Treatment Comparison in Euro Quality of Life (EQ-5D) Index

End point description:

The EuroQol EQ-5D is a brief self-administered health status instrument consisting of two parts. In the first part participants were asked to describe their health state on 5 dimensions (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with each dimension having 3 levels of function (1=no problem, 2=some problem, and 3=extreme problem). The scores on the 5 dimensions were summarized to create a single summary score, because the questions may be answered differently in different countries / regions due to different local customs and social perspectives. The summary score is called the summary index or the health utility value. The second part of EuroQoL EQ-5D is a visual analogue scale (VAS) in which the participants rate their overall health status using values from 0 (worst imaginable) to 100 (best imaginable). A positive change indicates improvement from baseline and a negative change indicates deterioration.

End point type	Secondary

End point timeframe:

From Baseline up to 2.5 years

End point values	Palbociclib plus Letrozole	Placebo plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	218		
Units: Units on a scale				
arithmetic mean (confidence interval 95%)	0.014 (0 to 0.03)	-0.01 (-0.03 to 0.01)		

Statistical analyses

Statistical analysis title	Statistical Analysis for EQ-5D
Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole
Number of subjects included in analysis	655
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0925
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.023

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.051

Secondary: Change from Baseline Between Treatment Comparison in Functional Assessment of Cancer therapy -Breast (FACT-B)

End point title	Change from Baseline Between Treatment Comparison in Functional Assessment of Cancer therapy -Breast (FACT-B)

End point description:

FACT is a modular approach to assess participant health-related quality of life using a 'core' set of questions (FACT-G) as well as a cancer site-specific module. The FACT-G is a 27-item compilation of general questions divided into 4 domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. The FACT-B consisted of the FACT-G (27-item) and a breast-specific module: a 10-item instrument designed to assess participant concerns relating to breast cancer. For all questions, participants were asked to respond to a five-level scale where 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, and 4=very much. FACT-B total score = Physical Well-Being + Social/Family Well-Being + Emotional Well-Being + Functional Well-Being + Breast Cancer Subscale.

End point type	Secondary

End point timeframe:

From Baseline up to 2.5 years

End point values	Palbociclib plus Letrozole	Placebo plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	439	218		
Units: Units on a scale				
arithmetic mean (confidence interval 95%)	-0.106 (-1.42 to 1.21)	0.219 (-1.68 to 2.12)		

Statistical analyses

Statistical analysis title	Statistical Analysis for FACT-B
Comparison groups	Palbociclib plus Letrozole v Placebo plus Letrozole
Number of subjects included in analysis	657
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7822
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-0.325
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.63
upper limit	1.98

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 participant randomization up to 28 days after last dose of study drug

End point values	Palbociclib plus Letrozole	Placebo plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	222		
Units: Percentage of Participants				
number (not applicable)				
Participants with AEs	98.9	95.5		
Participants with SAEs	19.6	12.6		
Participants with Grade 3 or 4 AEs	77.5	25.2		
Participants with Grade 5 AEs	2.3	1.8		
Permanently discontinued study due to AEs	2.5	1.8		
Permanently disc. palbociclib/placebo due to AEs	9.2	5.4		
Permanently discontinued letrozole due to AEs	6.1	5		
Temporarily disc. palbociclib/placebo due to AEs	74.8	15.8		
Temporarily discontinued letrozole due to AEs	17.3	9.9		
With palbociclib/placebo dose reduction due to AEs	36	1.4		

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 days after last dose of study medication.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	Placebo plus Letrozole
Reporting group description:	
Participants received letrozole 2.5 mg orally QD combined with placebo QD for 21 days of every-28-day cycle, followed by 7 days off treatment.	
Reporting group title	Palbociclib plus Letrozole
Reporting group description:	
Participants received letrozole 2.5 milligram (mg) orally QD (once daily) combined with palbociclib 125 mg QD for 21 days of every-28-day cycle, followed by 7 days off treatment.	

Serious adverse events	Placebo plus Letrozole	Palbociclib plus Letrozole	
Total subjects affected by serious adverse events			
subjects affected / exposed	28 / 222 (12.61%)	87 / 444 (19.59%)	
number of deaths (all causes)	6	12	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			

subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 222 (0.00%)	3 / 444 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian germ cell teratoma benign			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 222 (0.45%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 222 (0.45%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Device dislocation			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Disease progression			
subjects affected / exposed	0 / 222 (0.00%)	3 / 444 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 3	
General physical health deterioration			
subjects affected / exposed	1 / 222 (0.45%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 222 (0.45%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Puncture site pain			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 222 (0.00%)	3 / 444 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast haematoma			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterovaginal prolapse			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 222 (0.45%)	4 / 444 (0.90%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 222 (1.35%)	4 / 444 (0.90%)	
occurrences causally related to treatment / all	2 / 5	1 / 5	
deaths causally related to treatment / all	1 / 1	0 / 1	
Respiratory failure			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Tracheomalacia			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (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	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			

subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture displacement			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis radiation			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound secretion			

subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiovascular insufficiency			

subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cauda equina syndrome			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (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	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 222 (0.45%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			

subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic cerebral infarction			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
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			
Anaemia			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	0 / 222 (0.00%)	7 / 444 (1.58%)	
occurrences causally related to treatment / all	0 / 0	5 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Colitis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (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	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 222 (0.90%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			

subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 222 (0.00%)	3 / 444 (0.68%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stag horn calculus			
subjects affected / exposed	1 / 222 (0.45%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hypercalcaemia of malignancy			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperthyroidism			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Bone pain			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in jaw			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cellulitis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Clostridium difficile infection			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	2 / 222 (0.90%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Lower respiratory tract infection bacterial			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis bacterial			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pharyngitis streptococcal			

subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	2 / 222 (0.90%)	4 / 444 (0.90%)	
occurrences causally related to treatment / all	0 / 2	1 / 4	
deaths causally related to treatment / all	0 / 1	1 / 1	
Pyelonephritis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
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 / 222 (0.00%)	3 / 444 (0.68%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo plus Letrozole	Palbociclib plus Letrozole	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	206 / 222 (92.79%)	433 / 444 (97.52%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	68 / 222 (30.63%)	93 / 444 (20.95%)	
occurrences (all)	71	112	
Hypertension			
subjects affected / exposed	21 / 222 (9.46%)	28 / 444 (6.31%)	
occurrences (all)	29	55	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	26 / 222 (11.71%)	75 / 444 (16.89%)	
occurrences (all)	42	133	
Fatigue			
subjects affected / exposed	61 / 222 (27.48%)	166 / 444 (37.39%)	
occurrences (all)	84	281	
Influenza like illness			
subjects affected / exposed	10 / 222 (4.50%)	25 / 444 (5.63%)	
occurrences (all)	10	38	

Oedema peripheral			
subjects affected / exposed	14 / 222 (6.31%)	50 / 444 (11.26%)	
occurrences (all)	14	63	
Mucosal inflammation			
subjects affected / exposed	8 / 222 (3.60%)	41 / 444 (9.23%)	
occurrences (all)	10	78	
Pain			
subjects affected / exposed	20 / 222 (9.01%)	34 / 444 (7.66%)	
occurrences (all)	23	41	
Pyrexia			
subjects affected / exposed	19 / 222 (8.56%)	53 / 444 (11.94%)	
occurrences (all)	22	63	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	42 / 222 (18.92%)	111 / 444 (25.00%)	
occurrences (all)	53	163	
Dyspnoea			
subjects affected / exposed	30 / 222 (13.51%)	66 / 444 (14.86%)	
occurrences (all)	35	80	
Epistaxis			
subjects affected / exposed	14 / 222 (6.31%)	41 / 444 (9.23%)	
occurrences (all)	24	58	
Oropharyngeal pain			
subjects affected / exposed	7 / 222 (3.15%)	41 / 444 (9.23%)	
occurrences (all)	7	49	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	25 / 222 (11.26%)	36 / 444 (8.11%)	
occurrences (all)	28	42	
Depression			
subjects affected / exposed	20 / 222 (9.01%)	34 / 444 (7.66%)	
occurrences (all)	22	39	
Insomnia			
subjects affected / exposed	26 / 222 (11.71%)	66 / 444 (14.86%)	
occurrences (all)	32	80	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	9 / 222 (4.05%)	43 / 444 (9.68%)	
occurrences (all)	12	90	
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 222 (4.95%)	42 / 444 (9.46%)	
occurrences (all)	19	79	
Neutrophil count decreased			
subjects affected / exposed	7 / 222 (3.15%)	87 / 444 (19.59%)	
occurrences (all)	9	644	
Platelet count decreased			
subjects affected / exposed	1 / 222 (0.45%)	27 / 444 (6.08%)	
occurrences (all)	2	102	
Weight decreased			
subjects affected / exposed	10 / 222 (4.50%)	23 / 444 (5.18%)	
occurrences (all)	18	44	
White blood cell count decreased			
subjects affected / exposed	4 / 222 (1.80%)	72 / 444 (16.22%)	
occurrences (all)	7	397	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	11 / 222 (4.95%)	35 / 444 (7.88%)	
occurrences (all)	13	47	
Nervous system disorders			
Dizziness			
subjects affected / exposed	33 / 222 (14.86%)	63 / 444 (14.19%)	
occurrences (all)	38	78	
Dysgeusia			
subjects affected / exposed	11 / 222 (4.95%)	45 / 444 (10.14%)	
occurrences (all)	14	52	
Headache			
subjects affected / exposed	58 / 222 (26.13%)	95 / 444 (21.40%)	
occurrences (all)	94	138	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 222 (0.45%)	106 / 444 (23.87%)	
occurrences (all)	1	401	

Anaemia			
subjects affected / exposed	20 / 222 (9.01%)	103 / 444 (23.20%)	
occurrences (all)	40	265	
Neutropenia			
subjects affected / exposed	7 / 222 (3.15%)	294 / 444 (66.22%)	
occurrences (all)	13	2166	
Thrombocytopenia			
subjects affected / exposed	2 / 222 (0.90%)	44 / 444 (9.91%)	
occurrences (all)	3	108	
Eye disorders			
Lacrimation increased			
subjects affected / exposed	2 / 222 (0.90%)	25 / 444 (5.63%)	
occurrences (all)	5	28	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	12 / 222 (5.41%)	18 / 444 (4.05%)	
occurrences (all)	14	22	
Abdominal pain			
subjects affected / exposed	12 / 222 (5.41%)	50 / 444 (11.26%)	
occurrences (all)	19	70	
Abdominal pain upper			
subjects affected / exposed	17 / 222 (7.66%)	26 / 444 (5.86%)	
occurrences (all)	27	32	
Constipation			
subjects affected / exposed	34 / 222 (15.32%)	86 / 444 (19.37%)	
occurrences (all)	42	110	
Diarrhoea			
subjects affected / exposed	43 / 222 (19.37%)	116 / 444 (26.13%)	
occurrences (all)	78	269	
Dry mouth			
subjects affected / exposed	11 / 222 (4.95%)	25 / 444 (5.63%)	
occurrences (all)	17	31	
Dyspepsia			
subjects affected / exposed	27 / 222 (12.16%)	41 / 444 (9.23%)	
occurrences (all)	33	46	
Gastrooesophageal reflux disease			

subjects affected / exposed	7 / 222 (3.15%)	27 / 444 (6.08%)	
occurrences (all)	10	30	
Nausea			
subjects affected / exposed	57 / 222 (25.68%)	156 / 444 (35.14%)	
occurrences (all)	104	260	
Stomatitis			
subjects affected / exposed	13 / 222 (5.86%)	68 / 444 (15.32%)	
occurrences (all)	15	120	
Vomiting			
subjects affected / exposed	35 / 222 (15.77%)	69 / 444 (15.54%)	
occurrences (all)	58	123	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	35 / 222 (15.77%)	146 / 444 (32.88%)	
occurrences (all)	36	153	
Dry skin			
subjects affected / exposed	13 / 222 (5.86%)	55 / 444 (12.39%)	
occurrences (all)	13	77	
Pruritus			
subjects affected / exposed	8 / 222 (3.60%)	39 / 444 (8.78%)	
occurrences (all)	14	61	
Rash			
subjects affected / exposed	22 / 222 (9.91%)	61 / 444 (13.74%)	
occurrences (all)	26	99	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	75 / 222 (33.78%)	148 / 444 (33.33%)	
occurrences (all)	109	222	
Back pain			
subjects affected / exposed	48 / 222 (21.62%)	96 / 444 (21.62%)	
occurrences (all)	70	132	
Bone pain			
subjects affected / exposed	22 / 222 (9.91%)	38 / 444 (8.56%)	
occurrences (all)	26	59	
Muscle spasms			

subjects affected / exposed	12 / 222 (5.41%)	37 / 444 (8.33%)	
occurrences (all)	18	47	
Musculoskeletal chest pain			
subjects affected / exposed	9 / 222 (4.05%)	25 / 444 (5.63%)	
occurrences (all)	13	38	
Musculoskeletal pain			
subjects affected / exposed	16 / 222 (7.21%)	37 / 444 (8.33%)	
occurrences (all)	19	56	
Myalgia			
subjects affected / exposed	20 / 222 (9.01%)	53 / 444 (11.94%)	
occurrences (all)	27	64	
Neck pain			
subjects affected / exposed	10 / 222 (4.50%)	23 / 444 (5.18%)	
occurrences (all)	13	30	
Pain in extremity			
subjects affected / exposed	39 / 222 (17.57%)	68 / 444 (15.32%)	
occurrences (all)	56	91	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	22 / 222 (9.91%)	62 / 444 (13.96%)	
occurrences (all)	31	93	
Oral herpes			
subjects affected / exposed	3 / 222 (1.35%)	28 / 444 (6.31%)	
occurrences (all)	7	47	
Sinusitis			
subjects affected / exposed	7 / 222 (3.15%)	23 / 444 (5.18%)	
occurrences (all)	11	36	
Upper respiratory tract infection			
subjects affected / exposed	25 / 222 (11.26%)	59 / 444 (13.29%)	
occurrences (all)	31	82	
Urinary tract infection			
subjects affected / exposed	17 / 222 (7.66%)	52 / 444 (11.71%)	
occurrences (all)	34	75	
Metabolism and nutrition disorders			
Decreased appetite			

subjects affected / exposed occurrences (all)	20 / 222 (9.01%) 23	65 / 444 (14.64%) 91	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 October 2013	Amendment 1: For France only: Clarification of inclusion criterion #10
03 January 2014	Amendment 2: Clarification of inclusion criterion #10 and 4; Clarification of exclusion criterion #1 and 17; Added preliminary results; Added recommendation to take palbociclib with a meal; Added prohibition to take proton-pump inhibitors; Added recommendation to use local antacids as well as H2-receptor antagonist; Editorial changes were done.
21 March 2014	Amendment 3: Added ophthalmic procedures; Included preliminary results from a preclinical ocular study with palbociclib in rats; Clarified that safety related assessments must continue if participants continue study treatment beyond RECIST-defined disease progression; Changes done to align with updated protocol template; Electrocardiogram: Definition of of "evaluable" patient revised; Ocular Safety Assessment and Adverse Event Reporting: were added; sample size was revised; Section 15.1 and Appendix 6 FACT-B: updated; Appendix 8 was added.
18 September 2014	Amendment 4: Added prospective monitoring of hemoglobin A1c; Ocular Preclinical Date: Updated section to report emergent data findings from the 27-week rat toxicity study; updated study design to reflect Sponsor's decision to no longer require safety review by an internal oncology business unit safety data monitoring committee (IOBU-SDMC) for studies already monitored by an external data monitoring committee (E-DMC). Language related to cycle delay further defined to clearly state that any new cycle may only start if blinded study treatment can be resumed. Provided results from study A5481038 designed to investigate the effect of H2-receptor antagonists, proton pump inhibitors and local antacids; Editorial changes to differentiate between strong and moderate CYP3A inducers/inhibitors and to reflect current Sponsor protocol template.
02 December 2014	Amendment 5: Changed the interim analysis efficacy boundary from O'Brien-Fleming to Haybittle-Peto boundary to ensure that the study would only be stopped at the interim analysis if the primary analysis (PFS) results are statistically significant, and clinically meaningful and editorial changes to reflect current instructions for investigational product destruction at the end of the trial. Prohibited Medications: Strong/Moderate CYP3A inducers/inhibitors and proton-pump inhibitors are allowed for patients who permanently discontinue blinded therapy and continue on study with letrozole monotherapy only. Analysis of Primary Endpoint: Editorial change to clarify planned analyses.
07 April 2015	Amendment 6: Analysis Secondary Endpoints: Changes reflecting the collection of Patient Reported Outcome data during the post-progression follow-up period to assess potential impact of post-progression status on patient's quality of life and editorial changes to reflect current Sponsor's protocol template.
15 October 2015	Amendment 7 protocol language revise to reflect that collection of disease progression dates on subsequent anticancer therapy to better understand the potential influence of palbociclib response to subsequent anticancer therapies. Additional language was also added to clarify that the 7-day off treatment period in any given cycle should always be respected.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

For Overall Survival: The patients continue to be followed for survival and the final OS analysis will be performed when 390 deaths have been reported. OS should not be reported at this time because the OS data is still being followed.

Notes: