Clinical trial results:
Phase 1/2, Open-Label, Randomized Study of the Safety, Efficacy, and Pharmacokinetics of Letrozole Plus PD 0332991 (Oral CDK 4/6 Inhibitor) and Letrozole Single Agent for the First-Line Treatment of ER Positive, HER2 Negative Advanced Breast Cancer in Postmenopausal Women

Summary

EudraCT number	2008-002392-27
Trial protocol	IE HU DE FR IT ES GB
Global end of trial date	20 December 2017

Results information

Result version number	v1 (current)
This version publication date	01 December 2018
First version publication date	01 December 2018

Trial information

Trial identification

Sponsor protocol code	A5481003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00721409
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 18007181021, 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	Final
Date of interim/final analysis	05 July 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	20 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

For Phase 1: To assess the safety and tolerability of palbociclib in combination with letrozole in postmenopausal women with Estrogen Receptor (ER)-positive, Human Epidermal Growth Factor Receptor 2 (HER2)-negative advanced breast cancer. For Phase 2: To assess the effect of palbociclib plus letrozole and of letrozole alone on progression-free survival (PFS) in the first-line treatment of ER-positive, HER2-negative advanced breast cancer in postmenopausal women.

Protection of trial subjects:

The study was conducted in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 September 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	86 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 43
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Hungary: 26
Country: Number of subjects enrolled	Ireland: 18
Country: Number of subjects enrolled	Italy: 3
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	South Africa: 1
Country: Number of subjects enrolled	Korea, Republic of: 5
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Ukraine: 24
Worldwide total number of subjects	177
EEA total number of subjects	89

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)	96
From 65 to 84 years	80
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

This Phase 1/2, open-label, randomized study enrolled a total of 12 subjects at 3 sites in the United States for Phase 1. Phase 1 subjects received Palbociclib + Letrozole. In Phase 2, a total of 165 subjects were randomized (84 in Palbociclib plus Letrozole arm and 81 in Letrozole alone arm) at 50 sites in 12 countries.

Pre-assignment

Screening details:

Phase 2 portion has 2 parts. Phase 2, Part 1 – ER positive, HER2 negative postmenopausal women with advanced breast cancer. Phase 2, Part 2- ER positive, HER2 negative postmenopausal women with tumors demonstrating CCND1 gene amplification and/or loss of CDKN2A gene.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Phase 1 (Palbociclib + Letrozole)

Arm description:

In Cycle 1 (3 weeks), subjects received single agent Palbociclib 125 milligrams per day (mg/d) orally for 2 weeks followed by 1 week off treatment. In Cycles 2 and beyond (4 weeks each), subjects received Letrozole 2.5 mg/d in a continuous regimen plus Palbociclib 125 mg/d orally for 3 weeks followed by 1 week 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 125 milligram (mg) was administered orally, once in a day, up to 2 weeks followed by 1 week off treatment in Cycle 1. In Cycle 2 and beyond, Palbociclib 125 mg was administered orally once in a day for 3 weeks followed by 1 week off treatment. Cycle 1 was of 3 weeks and beyond that each cycle was of 4 weeks.

Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Letrozole 2.5 mg was administered orally, once in a day, up to 3 weeks followed by 1 week off treatment from Cycle 2 and beyond.

Arm title	Phase 2 (Palbociclib + Letrozole)

Arm description:

All subjects who were randomized to Letrozole plus Palbociclib in both Phase 2 part 1 (Ph2P1) and Phase 2 part 2 (Ph2P2) are combined and presented. In Ph2P1 and Ph2P2, the subjects received Palbociclib 125 mg/d orally for 3 weeks followed by 1 week off treatment and Letrozole 2.5 mg/d orally in a continuous regimen.

Arm type	Experimental

Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Letrozole 2.5 mg was administered orally, once in a day, up to 3 weeks followed by 1 week off treatment from Cycle 2 and beyond.

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 125 mg was administered orally, once in a day, up to 2 weeks followed by 1 week off treatment in Cycle 1. In Cycle 2 and beyond, Palbociclib 125 mg was administered orally once in a day for 3 weeks followed by 1 week off treatment. Cycle 1 was of 3 weeks and beyond that each cycle was of 4 weeks.

Arm title	Phase 2 (Letrozole)

Arm description:

All subjects who were randomized to receive Letrozole alone in both Phase 2 part 1 (Ph2P1) and Phase 2 part 2 (Ph2P2) are combined and presented. This was considered as control arm. Letrozole 2.5 mg/d was administered orally in a continuous regimen.

Arm type	Experimental
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Letrozole 2.5 mg was administered orally, once in a day, up to 3 weeks followed by 1 week off treatment from Cycle 2 and beyond.

Number of subjects in period 1	Phase 1 (Palbociclib + Letrozole)	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)
Started	12	84	81
Treated	12	83	77
Completed	0	2	2
Not completed	12	82	79
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	1	6	5
Global deterioration of health status	2	6	3
Adverse event, non-fatal	-	13	2
Reason not specified	1	-	2
Objective progression or relapse	8	55	62
Lost to follow-up	-	-	1
Randomized not Treated	-	1	4

Baseline characteristics

Reporting groups	
Reporting group title	Phase 1 (Palbociclib + Letrozole)
Reporting group description:	
In Cycle 1 (3 weeks), subjects received single agent Palbociclib 125 milligrams per day (mg/d) orally for 2 weeks followed by 1 week off treatment. In Cycles 2 and beyond (4 weeks each), subjects received Letrozole 2.5 mg/d in a continuous regimen plus Palbociclib 125 mg/d orally for 3 weeks followed by 1 week off treatment.	
Reporting group title	Phase 2 (Palbociclib + Letrozole)
Reporting group description:	
All subjects who were randomized to Letrozole plus Palbociclib in both Phase 2 part 1 (Ph2P1) and Phase 2 part 2 (Ph2P2) are combined and presented. In Ph2P1 and Ph2P2, the subjects received Palbociclib 125 mg/d orally for 3 weeks followed by 1 week off treatment and Letrozole 2.5 mg/d orally in a continuous regimen.	
Reporting group title	Phase 2 (Letrozole)
Reporting group description:	
All subjects who were randomized to receive Letrozole alone in both Phase 2 part 1 (Ph2P1) and Phase 2 part 2 (Ph2P2) are combined and presented. This was considered as control arm. Letrozole 2.5 mg/d was administered orally in a continuous regimen.	

Reporting group values	Phase 1 (Palbociclib + Letrozole)	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)
Number of subjects	12	84	81
Age, Customized Units: Subjects			
<18 Years	0	0	0
18-44 Years	1	2	4
45-64 Years	6	45	38
>= 65 Years	5	37	39
Age continuous Units: years			
arithmetic mean	61.7	62.7	63.0
standard deviation	± 9.65	± 10.19	± 9.16
Sex: Female, Male Units: Subjects			
Female	12	84	81
Male	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	6	4
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	1	1
White	11	76	72
More than one race	0	0	0
Unknown or Not Reported	1	1	4

Reporting group values	Total		
Number of subjects	177		

Age, Customized Units: Subjects			
<18 Years	0		
18-44 Years	7		
45-64 Years	89		
>= 65 Years	81		
Age continuous Units: years arithmetic mean standard deviation	 -		
Sex: Female, Male Units: Subjects			
Female	177		
Male	0		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	10		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	2		
White	159		
More than one race	0		
Unknown or Not Reported	6		

End points

End points reporting groups

Reporting group title	Phase 1 (Palbociclib + Letrozole)

Reporting group description:

In Cycle 1 (3 weeks), subjects received single agent Palbociclib 125 milligrams per day (mg/d) orally for 2 weeks followed by 1 week off treatment. In Cycles 2 and beyond (4 weeks each), subjects received Letrozole 2.5 mg/d in a continuous regimen plus Palbociclib 125 mg/d orally for 3 weeks followed by 1 week off treatment.

Reporting group title	Phase 2 (Palbociclib + Letrozole)

Reporting group description:

All subjects who were randomized to Letrozole plus Palbociclib in both Phase 2 part 1 (Ph2P1) and Phase 2 part 2 (Ph2P2) are combined and presented. In Ph2P1 and Ph2P2, the subjects received Palbociclib 125 mg/d orally for 3 weeks followed by 1 week off treatment and Letrozole 2.5 mg/d orally in a continuous regimen.

Reporting group title	Phase 2 (Letrozole)

Reporting group description:

All subjects who were randomized to receive Letrozole alone in both Phase 2 part 1 (Ph2P1) and Phase 2 part 2 (Ph2P2) are combined and presented. This was considered as control arm. Letrozole 2.5 mg/d was administered orally in a continuous regimen.

Subject analysis set title	Ph2P1 (Palbociclib + Letrozole)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects were randomized to receive Letrozole plus Palbociclib. Palbociclib 125 mg/d orally for 3 weeks followed by 1 week off treatment and Letrozole 2.5 mg/d orally in a continuous regimen.

Subject analysis set title	Ph2P1 (Letrozole)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects were randomized to receive Letrozole alone in Phase 2 Part 1. Letrozole 2.5 mg/d was administered orally in a continuous regimen.

Subject analysis set title	Ph2P2 (Palbociclib + Letrozole)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects were randomized to receive Letrozole plus Palbociclib in Phase 2 Part 2. Palbociclib 125 mg/d orally for 3 weeks followed by 1 week off treatment and Letrozole 2.5 mg/d orally in a continuous regimen.

Subject analysis set title	Ph2P2 (Letrozole)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Subjects were randomized to receive Letrozole alone in Phase 2 Part 2. Letrozole 2.5 mg/d was administered orally in a continuous regimen.

Subject analysis set title	Palbociclib alone (Cycle 1 Day 14)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In Cycle 1 (3 weeks), subjects received single agent Palbociclib 125 mg/d orally for 2 weeks followed by 1 week off treatment.

Subject analysis set title	Palbociclib + Letrozole (Cycle 2 Day 14)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

In Cycles 2 and beyond (4 weeks each), subjects received Letrozole 2.5 mg/d in a continuous regimen plus Palbociclib 125 mg/d orally for 3 weeks followed by 1 week off treatment.

Subject analysis set title	Letrozole alone (Cycle 2 Day 28)
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received daily 2.5 mg doses of Letrozole alone.

Primary: Number of Subjects With Treatment-Emergent Adverse Events (TEAEs; All Causalities) at Phase 1

End point title	Number of Subjects With Treatment-Emergent Adverse Events (TEAEs; All Causalities) at Phase 1[1][2]

End point description:

AE: any untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. AEs included both serious and non-serious AEs. SAE: AE resulting in any of following outcomes/deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment emergent AE: events occurred between first dose of study drug and up to 28 days after last dose (up to 55 months) that were absent before treatment or worsened relative to pre-treatment state. AEs graded as per the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Subjects with AE of grade 3, 4 and grade 5 reported as Grade 3: Severe, Grade 4: Life threatening, Grade 5: Death related to AE. Safety analysis set: subjects who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline up to 28 days after last dose of study drug (for a maximum of 55 months)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided'

[2] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 1 (Palbociclib + Letrozole)			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: subjects				
Subjects with AEs	12			
Subjects with SAEs	2			
Subjects with Grade 3 or 4 AEs	11			
Subjects with Grade 5 AEs	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects With Treatment-Related Adverse Events at Phase 1

End point title	Number of Subjects With Treatment-Related Adverse Events at Phase 1[3][4]

End point description:

AE: any untoward medical occurrence in subject who received study drug. AEs included both serious and non-serious AEs. SAE: AE resulting in any of following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment emergent AEs: events occurred between first dose of study drug and up to 28 days after last dose (up to 55 months) that were absent before treatment or that worsened relative to pre-treatment state. Treatment related AEs: AEs with causality related to treatment. Relatedness to drug was assessed by the investigator. AEs graded according to the CTCAE version 3.0. Number of subjects with AE of grade 3, 4 and 5 were reported as Grade 3: Severe, Grade 4: Life threatening, Grade 5: Death related to AE. Safety analysis set: subjects who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Baseline up to 28 days after last dose of study drug (for a maximum of 55 months)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided'

[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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 1 (Palbociclib + Letrozole)			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: subjects				
Subjects with AEs	12			
Subjects with SAEs	0			
Subjects with Grade 3 or 4 AEs	11			
Subjects with Grade 5 AEs	0			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Dose Limiting Toxicities (DLT) at Phase 1

End point title	Number of Subjects with Dose Limiting Toxicities (DLT) at Phase 1[5][6]

End point description:

DLT: any of following TEAEs occurred during second cycle of treatment and possibly attributable to combination of Letrozole+Palbociclib- 1:Grade 4 hematologic toxicity (including platelets less than [<] 25,000 per microliter [/mcL], absolute neutrophil count [ANC] <500/mcL). 2:Grade 3 neutropenia associated with a documented infection or fever greater than and equal to (>=) 38.5 degree Celsius (°C). 3:Grade >=3 non-hematologic toxicities, except those that have not been maximally treated (eg, nausea, vomiting, diarrhea, hypertension). 4:Delay by >=1 week in receiving next scheduled dose of either study treatment due to persisting treatment-related toxicities (platelet count <50,000/mcL; ANC <1,000/mcL; nonhematologic toxicities of Grade >=3 severity). 5:Inability to deliver at least 80 percent (%) of planned Palbociclib or Letrozole doses during Cycle 2 due to toxicity possibly attributable to study treatment. Safety analysis set: subjects who received at least 1 dose of study drug.

End point type	Primary

End point timeframe:

Cycle 2 (4 weeks)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As the endpoint is descriptive in nature, no statistical analysis is provided'

[6] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 1 (Palbociclib + Letrozole)			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: subjects				
Grade 4 Neutropenia	2			
<80% of doses due to elevated creatinine	1			

Statistical analyses

No statistical analyses for this end point

Primary: Progression-Free Survival (PFS) at Phase 2 - Investigator Assessment

End point title	Progression-Free Survival (PFS) at Phase 2 - Investigator Assessment[7]

End point description:

PFS was defined as the time from randomization (or the first dose of study treatment for non-randomized studies) to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first. PFS calculated as (weeks or months) = (first event date minus randomization or the first dose date plus 1) divided by 7 (or 30.44 if in months). PFS is usually characterized by the median, 25% percentile, 75% percentile and their 95% confidence intervals (CIs). Intent-to-Treat (ITT) population included randomized subjects from Phase 2, where subjects were classified according to the randomized treatment regardless of what treatment, if any, was received. Here, "99999" represents data was not available as upper limit of confidence interval was not reached.

End point type	Primary

End point timeframe:

From randomization date to date of first documentation of progression or death (assessed up to 41 months)

Notes:

[7] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)	Ph2P1 (Palbociclib + Letrozole)	Ph2P1 (Letrozole)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	84	81	34	32
Units: Months				
median (confidence interval 95%)	20.2 (13.8 to 27.5)	10.2 (5.7 to 12.6)	26.1 (11.2 to 99999)	5.7 (2.6 to 10.5)

End point values	Ph2P2 (Palbociclib + Letrozole)	Ph2P2 (Letrozole)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	49		
Units: Months				
median (confidence interval 95%)	18.1 (13.1 to 27.5)	11.1 (7.1 to 16.4)		

Statistical analyses

Statistical analysis title	Phase2(Palbociclib+Letrozole)vs.Phase2(Letrozole)

Statistical analysis description:

The primary hypothesis to be tested was H0: λ=1 versus. HA: λ<1, where λ was the Palbociclib plus Letrozole: Letrozole alone HR. HR < 1 indicates a reduction in hazard rate in favor of Palbociclib + Letrozole. Stratified analysis was presented above.

Comparison groups	Phase 2 (Palbociclib + Letrozole) v Phase 2 (Letrozole)
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0004 [8]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.488
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.319
upper limit	0.748

Notes:

[8] - 1-sided p-value from the log-rank test stratified by stratification factors per randomization and Part.

Statistical analysis title	Ph2P1(Palbociclib+Letrozole)vsPh2P1(Letrozole)

Statistical analysis description:

The primary hypothesis to be tested was H0: λ=1 versus. HA: λ<1, where λ was the Palbociclib plus Letrozole: Letrozole alone HR. A HR < 1 indicates a reduction in hazard rate in favor of Palbociclib + Letrozole. Unstratified analysis was presented above.

Comparison groups	Ph2P1 (Palbociclib + Letrozole) v Ph2P1 (Letrozole)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [9]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.299
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.156
upper limit	0.572

Notes:

[9] - 1-sided p-value from the log-rank test.

Statistical analysis title	Ph2P2(Palbociclib+Letrozole)vsPh2P2(Letrozole)

Statistical analysis description:

The primary hypothesis to be tested was H0: λ=1 versus. HA: λ<1, where λ was the Palbociclib plus Letrozole: Letrozole alone HR. A HR < 1 indicates a reduction in hazard rate in favor of Palbociclib + Letrozole. Unstratified analysis was presented above.

Comparison groups	Ph2P2 (Palbociclib + Letrozole) v Ph2P2 (Letrozole)
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0046 [10]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.508
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.303
upper limit	0.853

Notes:

[10] - 1-sided p-value from the log-rank test.

Secondary: Objective Response Rate - Percentage of Subjects with Confirmed Objective Tumor Response at Phase 1

End point title	Objective Response Rate - Percentage of Subjects with Confirmed Objective Tumor Response at Phase 1[11]

End point description:

Percentage of subjects with objective response based assessment of confirmed complete response (CR) or confirmed partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST). Confirmed responses are those that persist on repeat imaging study at least 4 weeks after initial documentation of response. Per RECIST v1.0: CR defined as disappearance of all target lesions and non-target lesions. PR defined as >=30% decrease in sum of the longest diameters (LD) of the target lesions taking as a reference the baseline sum LD according to RECIST associated to non-progressive disease response for non target lesions. Efficacy analysis set included all enrolled subjects with disease under study, adequate baseline disease assessment, and who started study treatment.

End point type	Secondary

End point timeframe:

From Baseline up to 55 months

Notes:

[11] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 1 (Palbociclib + Letrozole)			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of subjects				
number (confidence interval 95%)	33.3 (9.9 to 65.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinical Benefit Response (CBR) at Phase 1

End point title	Percentage of Subjects With Clinical Benefit Response (CBR) at Phase 1[12]

End point description:

CBR was defined as a confirmed CR, confirmed PR, or stable disease (SD) for at least 24 weeks on study according to RECIST. Confirmed responses are those that persisted on repeat imaging >= 4 weeks after initial response. Efficacy analysis set included all enrolled subjects with disease under study, adequate baseline disease assessment, and who started study treatment.

End point type	Secondary

End point timeframe:

From Baseline up to 55 months

Notes:

[12] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 1 (Palbociclib + Letrozole)			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: percentage of subjects				
number (confidence interval 95%)	83.3 (51.6 to 97.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Plasma Palbociclib Steady-State Pharmacokinetic Parameter Following Palbociclib Alone and in Combination With Letrozole: Area Under the Plasma Concentration-Time Curve From Time 0 to 24 Hours (AUC24) at Phase 1

End point title	Summary of Plasma Palbociclib Steady-State Pharmacokinetic Parameter Following Palbociclib Alone and in Combination With Letrozole: Area Under the Plasma Concentration-Time Curve From Time 0 to 24 Hours (AUC24) at Phase 1

End point description:

On Cycle 1 Day 14, plasma pharmacokinetic samples were collected prior to and 1, 2, 4, 8, 12 and 24 hours after Palbociclib dosing. On Cycle 2 Day 14, plasma pharmacokinetic samples for Palbociclib and Letrozole were collected prior to and 1, 2, 4, 8, 12 and 24 hours after Palbociclib and Letrozole dosing. The pharmacokinetic parameter analysis set consisted of all subjects treated who had at least 1 of the pharmacokinetic parameters of primary interest.

End point type	Secondary

End point timeframe:

Cycle 1 Day 14, and Cycle 2 Day 14

End point values	Palbociclib alone (Cycle 1 Day 14)	Palbociclib + Letrozole (Cycle 2 Day 14)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: nanogram*hour per milliliter (ng*hr/mL)				
geometric mean (geometric coefficient of variation)	1982 (± 29)	1933 (± 31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Plasma Palbociclib Steady-State Pharmacokinetic Parameter Following Palbociclib Alone and in Combination With Letrozole: Maximum Observed Plasma Concentration (Cmax) at Phase 1

End point title	Summary of Plasma Palbociclib Steady-State Pharmacokinetic Parameter Following Palbociclib Alone and in Combination With Letrozole: Maximum Observed Plasma Concentration (Cmax) at Phase 1

End point description:

On Cycle 1 Day 14, plasma pharmacokinetic samples were collected prior to and 1, 2, 4, 8, 12, 24, 48, 96 and 120 hours after Palbociclib dosing. On Cycle 2 Day 14, plasma pharmacokinetic samples for Palbociclib and letrozole were collected prior to and 1, 2, 4, 8, 12 and 24 hours after Palbociclib and letrozole dosing. The pharmacokinetic parameter analysis set consisted of all subjects treated who had at least 1 of the pharmacokinetic parameters of primary interest.

End point type	Secondary

End point timeframe:

Cycle 1 Day 14, and Cycle 2 Day 14

End point values	Palbociclib alone (Cycle 1 Day 14)	Palbociclib + Letrozole (Cycle 2 Day 14)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: nanogram per milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)	115.8 (± 28)	108.4 (± 29)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Plasma Palbociclib Steady-State Pharmacokinetic Parameter Following Palbociclib Alone and in Combination With Letrozole: Time to Maximum Plasma Concentration (Tmax) at Phase 1

End point title	Summary of Plasma Palbociclib Steady-State Pharmacokinetic Parameter Following Palbociclib Alone and in Combination With Letrozole: Time to Maximum Plasma Concentration (Tmax) at Phase 1

End point description:

On Cycle 1 Day 14, plasma pharmacokinetic samples were collected prior to and 1, 2, 4, 8, 12, 24, 48, 96 and 120 hours after Palbociclib dosing. On Cycle 2 Day 14, plasma pharmacokinetic samples for Palbociclib and letrozole were collected prior to and 1, 2, 4, 8, 12 and 24 hours after Palbociclib and letrozole dosing. The pharmacokinetic parameter analysis set consisted of all subjects treated who had at least 1 of the pharmacokinetic parameters of primary interest.

End point type	Secondary

End point timeframe:

Cycle 1 Day 14, and Cycle 2 Day 14

End point values	Palbociclib alone (Cycle 1 Day 14)	Palbociclib + Letrozole (Cycle 2 Day 14)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: Hour				
median (full range (min-max))	7.92 (2.17 to 8.20)	7.92 (2.00 to 8.08)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Plasma Palbociclib Steady-State Pharmacokinetic Parameter Following Palbociclib Alone and in Combination With Letrozole: Terminal Plasma Half-Life (t1/2) at Phase 1

End point title	Summary of Plasma Palbociclib Steady-State Pharmacokinetic Parameter Following Palbociclib Alone and in Combination With Letrozole: Terminal Plasma Half-Life (t1/2) at Phase 1

End point description:

On Cycle 1 Day 14, plasma pharmacokinetic samples were collected prior to and 1, 2, 4, 8, 12, 24, 48, 96 and 120 hours after Palbociclib dosing. On Cycle 2 Day 14, plasma pharmacokinetic samples for Palbociclib and letrozole were collected prior to and 1, 2, 4, 8, 12 and 24 hours after Palbociclib and letrozole dosing. The pharmacokinetic parameter analysis set consisted of all subjects treated who had at least 1 of the pharmacokinetic parameters of primary interest.

End point type	Secondary

End point timeframe:

Cycle 1 Day 14, and Cycle 2 Day 14

End point values	Palbociclib alone (Cycle 1 Day 14)	Palbociclib + Letrozole (Cycle 2 Day 14)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: Hour				
arithmetic mean (standard deviation)	28.81 (± 5.0462)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Plasma Palbociclib Steady-State Pharmacokinetic Parameter Following Palbociclib Alone and in Combination With Letrozole: Apparent Clearance (CL/F) at Phase 1

End point title	Summary of Plasma Palbociclib Steady-State Pharmacokinetic Parameter Following Palbociclib Alone and in Combination With Letrozole: Apparent Clearance (CL/F) at Phase 1

End point description:

On Cycle 1 Day 14, plasma pharmacokinetic samples were collected prior to and 1, 2, 4, 8, 12, 24, 48, 96 and 120 hours after Palbociclib dosing. On Cycle 2 Day 14, plasma pharmacokinetic samples for Palbociclib and letrozole were collected prior to and 1, 2, 4, 8, 12 and 24 hours after Palbociclib and letrozole dosing. The pharmacokinetic parameter analysis set consisted of all subjects treated who had at least 1 of the pharmacokinetic parameters of primary interest.

End point type	Secondary

End point timeframe:

Cycle 1 Day 14, and Cycle 2 Day 14

End point values	Palbociclib alone (Cycle 1 Day 14)	Palbociclib + Letrozole (Cycle 2 Day 14)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: Liter per hour (L/hr)				
geometric mean (geometric coefficient of variation)	63.08 (± 29)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Plasma Palbociclib Steady-State Pharmacokinetic Parameter Following Palbociclib Alone and in Combination With Letrozole: Apparent Volume of Distribution (Vz/F) at Phase 1

End point title	Summary of Plasma Palbociclib Steady-State Pharmacokinetic Parameter Following Palbociclib Alone and in Combination With

	Letrozole: Apparent Volume of Distribution (Vz/F) at Phase 1

End point description:

On Cycle 1 Day 14, plasma pharmacokinetic samples were collected prior to and 1, 2, 4, 8, 12, 24, 48, 96 and 120 hours after Palbociclib dosing. On Cycle 2 Day 14, plasma pharmacokinetic samples for Palbociclib and letrozole were collected prior to and 1, 2, 4, 8, 12 and 24 hours after Palbociclib and letrozole dosing. The pharmacokinetic parameter analysis set consisted of all subjects treated who had at least 1 of the pharmacokinetic parameters of primary interest.

End point type	Secondary

End point timeframe:

Cycle 1 Day 14, and Cycle 2 Day 14

End point values	Palbociclib alone (Cycle 1 Day 14)	Palbociclib + Letrozole (Cycle 2 Day 14)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: Liter				
geometric mean (geometric coefficient of variation)	2583 (± 26)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Plasma Letrozole Pharmacokinetic Parameter Following Letrozole Alone and in Combination With Palbociclib: AUC24 at Phase 1

End point title	Summary of Plasma Letrozole Pharmacokinetic Parameter Following Letrozole Alone and in Combination With Palbociclib: AUC24 at Phase 1

End point description:

On Cycle 2 Day 14, plasma pharmacokinetic samples for Palbociclib and letrozole were collected prior to and 1, 2, 4, 8, 12 and 24 hours after Palbociclib and letrozole dosing. On Cycle 2 Day 28, plasma pharmacokinetic samples were collected prior to and 1, 2, 4, 8, 12, and 24 hours after letrozole dosing. The pharmacokinetic parameter analysis set consisted of all subjects treated who had at least 1 of the pharmacokinetic parameters of primary interest.

End point type	Secondary

End point timeframe:

Cycle 2 Day 14, Cycle 2 Day 28

End point values	Palbociclib + Letrozole (Cycle 2 Day 14)	Letrozole alone (Cycle 2 Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)	1739 (± 30)	1936 (± 35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Plasma Letrozole Pharmacokinetic Parameter Following Letrozole Alone and in Combination With Palbociclib: Cmax at Phase 1

End point title	Summary of Plasma Letrozole Pharmacokinetic Parameter Following Letrozole Alone and in Combination With Palbociclib: Cmax at Phase 1

End point description:

On Cycle 2 Day 14, plasma pharmacokinetic samples for Palbociclib and letrozole were collected prior to and 1, 2, 4, 8, 12 and 24 hours after Palbociclib and letrozole dosing. On Cycle 2 Day 28, plasma pharmacokinetic samples were collected prior to and 1, 2, 4, 8, 12, and 24 hours after letrozole dosing. The pharmacokinetic parameter analysis set consisted of all subjects treated who had at least 1 of the pharmacokinetic parameters of primary interest.

End point type	Secondary

End point timeframe:

Cycle 2 Day 14, and Cycle 2 Day 28

End point values	Palbociclib + Letrozole (Cycle 2 Day 14)	Letrozole alone (Cycle 2 Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	94.95 (± 27)	104.0 (± 31)		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Plasma Letrozole Pharmacokinetic Parameter Following Letrozole Alone and in Combination With Palbociclib: Tmax at Phase 1

End point title	Summary of Plasma Letrozole Pharmacokinetic Parameter Following Letrozole Alone and in Combination With Palbociclib: Tmax at Phase 1

End point description:

On Cycle 2 Day 14, plasma pharmacokinetic samples for Palbociclib and letrozole were collected prior to and 1, 2, 4, 8, 12 and 24 hours after Palbociclib and letrozole dosing. On Cycle 2 Day 28, plasma pharmacokinetic samples were collected prior to and 1, 2, 4, 8, 12, and 24 hours after letrozole dosing. The pharmacokinetic parameter analysis set consisted of all subjects treated who had at least 1 of the pharmacokinetic parameters of primary interest.

End point type	Secondary

End point timeframe:

Cycle 2 Day 14, and Cycle 2 Day 28

End point values	Palbociclib + Letrozole (Cycle 2 Day 14)	Letrozole alone (Cycle 2 Day 28)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	12	12		
Units: Hour				
median (full range (min-max))	2.00 (0.833 to 4.13)	1.04 (0.00 to 4.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Increase From Baseline in Corrected QT (QTc) Interval at Phase 1

End point title	Number of Subjects With Increase From Baseline in Corrected QT (QTc) Interval at Phase 1[13]

End point description:

Triplicate 12-lead ECG measurements (each recording separated by approximately 2 minutes) were performed and 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). Subjects with maximum increase from baseline of 30 to < 60 msec(borderline) and >=60 msec (prolonged) were summarized. Safety analysis set: subjects who received at least 1 dose of study drug.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 prior to dosing, Cycle 1 Day 14 (2, 4 [prior to meal], 8, 24, 48, and 96 hours after dosing of Palbociclib), Cycle 2 Day 1 and Day 14 (prior to and 4 hours after dosing of letrozole)

Notes:

[13] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 1 (Palbociclib + Letrozole)			
Subject group type	Reporting group			
Number of subjects analysed	12			
Units: subjects				
QTcB - Change <30	9			
QTcB - 30 <= change <60	3			
QTcB - Change >=60	0			
QTcF - Change <30	11			
QTcF - 30 <= change <60	1			
QTcF - Change >=60	0			

QTcS - Change <30	8			
QTcS - 30 <= change <60	4			
QTcS - Change >=60	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Overall survival (OS) at Phase 2

End point title	Overall survival (OS) at Phase 2[14]

End point description:

Time in weeks or months from randomization to date of death due to any cause. OS was calculated as (the death date or last known alive date (if death date unavailable) minus the date of randomization plus 1) divided by 7 or 30.44 if in months. ITT population included randomized subjects from Phase 2, where subjects were classified according to the randomized treatment regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

From randomization until death (assessed up to 86 months)

Notes:

[14] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)	Ph2P1 (Palbociclib + Letrozole)	Ph2P1 (Letrozole)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	84	81	34	32
Units: Months				
median (confidence interval 95%)	37.5 (31.4 to 47.8)	34.5 (27.4 to 42.6)	37.5 (27.6 to 58.8)	33.3 (26.0 to 54.3)

End point values	Ph2P2 (Palbociclib + Letrozole)	Ph2P2 (Letrozole)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	49		
Units: Months				
median (confidence interval 95%)	35.1 (28.1 to 47.8)	35.7 (26.6 to 46.7)		

Statistical analyses

Statistical analysis title	Phase2(Palbociclib+Letrozole)vsPhase2(Letrozole)

Statistical analysis description:

Stratified analysis was presented above. HR was assuming proportional hazards, HR < 1 indicated a

reduction in hazard rate in favor of Palbociclib + Letrozole.

Comparison groups	Phase 2 (Palbociclib + Letrozole) v Phase 2 (Letrozole)
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2812 [15]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.897
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.623
upper limit	1.294

Notes:

[15] - 1-sided p-value from the log-rank test stratified by Part (α = 0.10).

Statistical analysis title	Ph2P1(Palbociclib+Letrozole)vsPh2P1(Letrozole)
Statistical analysis description:	
Unstratified analysis was presented above.	
Comparison groups	Ph2P1 (Palbociclib + Letrozole) v Ph2P1 (Letrozole)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2803 [16]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.837
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.458
upper limit	1.527

Notes:

[16] - 1-sided p-value from the unstratified log-rank test (α=0.10).

Statistical analysis title	Ph2P2(Palbociclib+Letrozole)vsPh2P2(Letrozole)
Statistical analysis description:	
Unstratified analysis was presented above.	
Comparison groups	Ph2P2 (Palbociclib + Letrozole) v Ph2P2 (Letrozole)
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3875 [17]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.935

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.59
upper limit	1.48

Notes:

[17] - 1-sided p-value from the unstratified log-rank test (α=0.10).

Secondary: Objective Response Rate - Percentage of Subjects With Confirmed Objective Response at Phase 2- Investigator Assessment

End point title	Objective Response Rate - Percentage of Subjects With Confirmed Objective Response at Phase 2- Investigator Assessment[18]

End point description:

Percentage of subjects with objective response based assessment of confirmed CR or PR according to RECIST. Confirmed responses are those that persist on repeat imaging study at least 4 weeks after initial documentation of response. Per RECIST v1.0, CR defined as disappearance of all target lesions and non-target lesions. PR defined as >=30% decrease in sum of the longest diameters (LD) of the target lesions taking as a reference the baseline sum LD according to RECIST associated to non-progressive disease response for non target lesions. ITT population included randomized subjects from Phase 2, where subjects were classified according to the randomized treatment regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

From randomization up to 41 months

Notes:

[18] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)	Ph2P1 (Palbociclib + Letrozole)	Ph2P1 (Letrozole)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	84	81	34	32
Units: Percentage of subjects				
number (confidence interval 95%)	42.9 (32.1 to 54.1)	33.3 (23.2 to 44.7)	44.1 (27.2 to 62.1)	25.0 (11.5 to 43.4)

End point values	Ph2P2 (Palbociclib + Letrozole)	Ph2P2 (Letrozole)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	49		
Units: Percentage of subjects				
number (confidence interval 95%)	42.0 (28.2 to 56.8)	38.8 (25.2 to 53.8)		

Statistical analyses

Statistical analysis title	Phase2(Palbociclib+Letrozole)vsPhase2(Letrozole)

Statistical analysis description:

Objective Response CI was calculated using the exact Clopper-Pearson method. The stratified analysis presented above was based on CMH test stratified by Part. An Odds Ratio >1 means better response in favor of Palbociclib + Letrozole arm.

Comparison groups	Phase 2 (Palbociclib + Letrozole) v Phase 2 (Letrozole)
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1347 [19]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.76
upper limit	2.97

Notes:

[19] - 1-sided p-value is from the stratified exact test (1-sided, α =0.10)

Statistical analysis title	Ph2P1(Palbociclib+Letrozole)vsPh2P1(Letrozole)

Statistical analysis description:

Unstratified analysis was presented above. Exact CI was based on Clopper-Pearson method.

Comparison groups	Ph2P1 (Palbociclib + Letrozole) v Ph2P1 (Letrozole)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0849 [20]
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	2.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	7.84

Notes:

[20] - Chi-square test was used (1-sided, α=0.10)

Statistical analysis title	Ph2P2(Palbociclib+Letrozole)vsPh2P2(Letrozole)

Statistical analysis description:

Unstratified analysis was presented above. Exact CI was based on Clopper-Pearson method.

Comparison groups	Ph2P2 (Palbociclib + Letrozole) v Ph2P2 (Letrozole)
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4515 [21]
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.14

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	2.76

Notes:

[21] - Chi-square test was used (1-sided, α=0.10)

Secondary: Objective Response Rate - Percentage of Subjects with Confirmed Objective Response in Subjects With Measurable Disease at Phase 2- Investigator Assessment

End point title	Objective Response Rate - Percentage of Subjects with Confirmed Objective Response in Subjects With Measurable Disease at Phase 2- Investigator Assessment[22]

End point description:

Percentage of subjects with objective response based on assessment of confirmed CR or PR as per RECIST. CR: those that persist on repeat imaging study at least 4 weeks after initial documentation of response. CR: disappearance of all target and non-target lesions. PR: >=30% decrease in sum of LD of target lesions reference to baseline sum LD as per RECIST associated to non-progressive disease response for non target lesions. Measurable disease: lesions accurately measured in at least 1 dimension (longest diameter to be recorded) as >=20 mm with conventional techniques or as >=10-16 mm with spiral computer tomography scan. Clinical lesions considered measurable when they were superficial (eg, skin nodules, palpable lymph nodes). ITT population: randomized subjects from Phase 2, classified according to randomized treatment regardless of what treatment, if any, was received. Here, "number of subjects analyzed" signifies number of subjects evaluable for this endpoint for each arm.

End point type	Secondary

End point timeframe:

From randomization up to 41 months

Notes:

[22] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)	Ph2P1 (Palbociclib + Letrozole)	Ph2P1 (Letrozole)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	65	66	27	23
Units: Percentage of subjects				
number (confidence interval 95%)	55.4 (42.5 to 67.7)	39.4 (27.6 to 52.2)	55.6 (35.3 to 74.5)	34.8 (16.4 to 57.3)

End point values	Ph2P2 (Palbociclib + Letrozole)	Ph2P2 (Letrozole)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	43		
Units: Percentage of subjects				
number (confidence interval 95%)	55.3 (38.3 to 71.4)	41.9 (27.0 to 57.9)		

Statistical analyses

Statistical analysis title	Phase2(Palbociclib+Letrozole)vsPhase2(Letrozole)

Statistical analysis description:

Objective Response CI was calculated using the exact Clopper-Pearson method. The stratified analysis presented above was based on CMH test stratified by Part. An Odds Ratio >1 means better response in favor of palbociclib + letrozole arm.

Comparison groups	Phase 2 (Palbociclib + Letrozole) v Phase 2 (Letrozole)
Number of subjects included in analysis	131
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0471 [23]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	1.93
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.91
upper limit	4.08

Notes:

[23] - 1-sided p-value is from the stratified exact test (1-sided, α =0.10)

Statistical analysis title	Ph2P1(Palbociclib+Letrozole)vsPh2P1(Letrozole)

Statistical analysis description:

Unstratified analysis was presented above. Exact CI was based on Clopper-Pearson method.

Comparison groups	Ph2P1 (Palbociclib + Letrozole) v Ph2P1 (Letrozole)
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.118 [24]
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	2.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	8.66

Notes:

[24] - Chi-square test was used (1-sided, α=0.10)

Statistical analysis title	Ph2P2(Palbociclib+Letrozole)vsPh2P2(Letrozole)

Statistical analysis description:

Unstratified analysis was presented above. Exact CI was based on Clopper-Pearson method.

Comparison groups	Ph2P2 (Palbociclib + Letrozole) v Ph2P2 (Letrozole)

Number of subjects included in analysis	64
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1631 [25]
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	1.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	4.54

Notes:

[25] - Chi-square test was used (1-sided, α=0.10)

Secondary: Duration of Response at Phase 2 - Investigator Assessment

End point title	Duration of Response at Phase 2 - Investigator Assessment[26]

End point description:

Time in months from randomization or (start of study treatment for non-randomized studies) to first documentation of objective tumor progression. Time to progression was calculated as (first event date or last known progression-free date minus the date of randomization [or first dose of study medication for non-randomized studies] plus 1) divided by 30.44. Tumor progression was determined from oncologic assessment data (where data meet the criteria for progressive disease [PD] per RECIST). ITT population included randomized subjects from Phase 2, where subjects were classified according to the randomized treatment regardless of what treatment, if any, was received. Here, "number of subjects analyzed" signifies number of subjects evaluable for this endpoint for each arm and "99999" represents data not available as upper limit of confidence interval was not reached.

End point type	Secondary

End point timeframe:

From randomization up to 41 months

Notes:

[26] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)	Ph2P1 (Palbociclib + Letrozole)	Ph2P1 (Letrozole)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	36	27	15	8
Units: Months				
median (confidence interval 95%)	20.3 (13.4 to 25.8)	11.1 (9.3 to 31.6)	20.9 (6.2 to 25.8)	10.8 (3.7 to 31.6)

End point values	Ph2P2 (Palbociclib + Letrozole)	Ph2P2 (Letrozole)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	19		
Units: Months				
median (confidence interval 95%)	20.2 (13.0 to 99999)	14.8 (7.4 to 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With CBR at Phase 2 - Investigator Assessment

End point title	Number of Subjects With CBR at Phase 2 - Investigator Assessment[27]

End point description:

CBR was defined as a confirmed complete response (CR), confirmed partial response (PR), or stable disease (SD) for at least 24 weeks on study according to RECIST. ITT population included randomized subjects from Phase 2, where subjects were classified according to the randomized treatment regardless of what treatment, if any, was received.

End point type	Secondary

End point timeframe:

From randomization up to 41 months

Notes:

[27] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)	Ph2P1 (Palbociclib + Letrozole)	Ph2P1 (Letrozole)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	84	81	34	32
Units: Percentage of subjects				
number (confidence interval 95%)	81.0 (70.9 to 88.7)	58.0 (46.5 to 68.9)	76.5 (58.8 to 89.3)	43.8 (26.4 to 62.3)

End point values	Ph2P2 (Palbociclib + Letrozole)	Ph2P2 (Letrozole)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	49		
Units: Percentage of subjects				
number (confidence interval 95%)	84.0 (70.9 to 92.8)	67.3 (52.5 to 80.1)		

Statistical analyses

Statistical analysis title	Phase2(Palbociclib+Letrozole)vsPhase2(Letrozole)

Statistical analysis description:

CBR CI was calculated using the exact Clopper-Pearson method. The stratified analysis presented above

was based on CMH test stratified by Part. An Odds Ratio >1 means better response in favor of palbociclib + letrozole arm.

Comparison groups	Phase 2 (Palbociclib + Letrozole) v Phase 2 (Letrozole)
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0009 [28]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	3.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.48
upper limit	6.98

Notes:

[28] - 1-sided p-value is from the stratified exact test (1-sided, α =0.10).

Statistical analysis title	Ph2P1(Palbociclib+Letrozole)vsPh2P1(Letrozole)
Statistical analysis description:	
Unstratified analysis was presented above. Exact CI was based on Clopper-Pearson method.	
Comparison groups	Ph2P1 (Palbociclib + Letrozole) v Ph2P1 (Letrozole)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0065 [29]
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	4.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.3
upper limit	13.9

Notes:

[29] - Chi-square test was used (1-sided, α=0.10)

Statistical analysis title	Ph2P2(Palbociclib+Letrozole)vsPh2P2(Letrozole)
Statistical analysis description:	
Unstratified analysis was presented above. Exact CI was based on Clopper-Pearson method.	
Comparison groups	Ph2P2 (Palbociclib + Letrozole) v Ph2P2 (Letrozole)
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0442 [30]
Method	Chi-squared
Parameter estimate	Odds ratio (OR)
Point estimate	2.55

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.89
upper limit	7.7

Notes:

[30] - Chi-square test was used (1-sided, α=0.10)

Secondary: Time to Tumor Progression (TTP) at Phase 2-Investigator Assessment

End point title	Time to Tumor Progression (TTP) at Phase 2-Investigator Assessment[31]

End point description:

Time in months from randomization or (start of study treatment for non-randomized studies) to first documentation of objective tumor progression. Time to progression was calculated as (first event date or last known progression-free date minus the date of randomization [or first dose of study medication for non-randomized studies] plus 1) divided by 30.44. Tumor progression was determined from oncologic assessment data (where data meet the criteria for progressive disease [PD] per RECIST). ITT population included randomized subjects from Phase 2, where subjects were classified according to the randomized treatment regardless of what treatment, if any, was received. Here, "99999" represents data not available as upper limit of confidence interval was not reached.

End point type	Secondary

End point timeframe:

From randomization up to 41 months

Notes:

[31] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)	Ph2P1 (Palbociclib + Letrozole)	Ph2P1 (Letrozole)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	84	81	34	32
Units: Months				
median (confidence interval 95%)	20.2 (13.8 to 27.5)	10.2 (5.7 to 12.6)	26.1 (11.2 to 99999)	5.7 (2.6 to 10.5)

End point values	Ph2P2 (Palbociclib + Letrozole)	Ph2P2 (Letrozole)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	49		
Units: Months				
median (confidence interval 95%)	18.8 (13.1 to 27.5)	11.1 (7.1 to 16.4)		

Statistical analyses

Statistical analysis title	Phase2(Palbociclib+Letrozole)vsPhase2(Letrozole)

Statistical analysis description:

Kaplan-Meier method was applied for median and 95% CI. HR was based on assuming proportional hazards, HR < 1 indicates a reduction in hazard rate in favor of palbociclib + letrozole.

Comparison groups	Phase 2 (Palbociclib + Letrozole) v Phase 2 (Letrozole)
Number of subjects included in analysis	165
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [32]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.399
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.265
upper limit	0.601

Notes:

[32] - 1-sided p-value is from the stratified log-rank test (α =0.10).

Statistical analysis title	Ph2P1(Palbociclib+Letrozole)vsPh2P1(Letrozole)

Statistical analysis description:

Unstratified analysis was presented above. Kaplan-Meier method was applied for median and 95% CI.

Comparison groups	Ph2P1 (Palbociclib + Letrozole) v Ph2P1 (Letrozole)
Number of subjects included in analysis	66
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [33]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.299
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.156
upper limit	0.572

Notes:

[33] - 1-sided p-value is from unstratified log-rank test (α=0.10).

Statistical analysis title	Ph2P2(Palbociclib+Letrozole)vsPh2P2(Letrozole)

Statistical analysis description:

Unstratified analysis was presented above. Kaplan-Meier method was applied for median and 95% CI.

Comparison groups	Ph2P2 (Palbociclib + Letrozole) v Ph2P2 (Letrozole)
Number of subjects included in analysis	99
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.003 [34]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.486

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.288
upper limit	0.822

Notes:

[34] - 1-sided p-value is from unstratified log-rank test (α=0.10).

Secondary: Change from Baseline in Modified Brief Pain Inventory in Pain Severity Scale (mBPI-sf) Questionnaire at Phase 2

End point title	Change from Baseline in Modified Brief Pain Inventory in Pain Severity Scale (mBPI-sf) Questionnaire at Phase 2[35]

End point description:

The mBPI-sf is a validated and reliable self-report questionnaire which consists of 13 questions that assess the severity and impact of pain on daily function. The 13 items of the questionnaire make up two scales and two single items. The scales include the 4-item Pain Severity Scale (worst pain, least pain, average pain, and pain right now) and the 7-item Pain Interference Scale (general activity, mood, walking ability, normal work and relations with other people, sleep, and enjoyment of life). Each item of the pain severity and pain interference scales are based on a 11-point numeric rating scale from 0 ("no pain" or "does not interfere") to 10 ("pain as bad as you can imagine" or "completely interferes"). Patient reported outcome evaluable subjects: who had received at least 1 dose of study medication, had baseline data, and at least one post-baseline measurement. Here, "number of subjects analyzed" signifies number of subjects evaluable for this endpoint for each arm.

End point type	Secondary

End point timeframe:

Baseline, Month 41

Notes:

[35] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)	Ph2P1 (Palbociclib + Letrozole)	Ph2P1 (Letrozole)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	76	74	29	27
Units: Units on a scale				
arithmetic mean (standard error)				
Pain at its worst in the last 24 hours	0.6 (± 0.42)	0.1 (± 0.42)	0.2 (± 0.60)	0.0 (± 0.89)
Pain at its least in the last 24 hours	0.4 (± 0.27)	0.4 (± 0.27)	0.3 (± 0.31)	0.7 (± 0.50)
Pain on the average	0.2 (± 0.33)	0.2 (± 0.34)	-0.1 (± 0.48)	0.2 (± 0.64)
Pain right now	0.3 (± 0.35)	0.1 (± 0.36)	0.1 (± 0.31)	0.3 (± 0.66)
Pain Severity Scale	0.4 (± 0.29)	0.2 (± 0.32)	0.0 (± 0.36)	0.3 (± 0.62)

End point values	Ph2P2 (Palbociclib + Letrozole)	Ph2P2 (Letrozole)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	47		
Units: Units on a scale				
arithmetic mean (standard error)				
Pain at its worst in the last 24 hours	1.2 (± 0.55)	0.1 (± 0.43)		

Pain at its least in the last 24 hours	0.5 (± 0.40)	0.2 (± 0.31)		
Pain on the average	0.4 (± 0.45)	0.3 (± 0.40)		
Pain right now	0.3 (± 0.55)	0.0 (± 0.43)		
Pain Severity Scale	0.6 (± 0.41)	0.1 (± 0.36)		

Statistical analyses

Statistical analysis title	Phase2(Palbociclib+Letrozole)vsPhase2(Letrozole)
Statistical analysis description:	
Statistical analysis presented above is for Pain Severity Scale.	
Comparison groups	Phase 2 (Palbociclib + Letrozole) v Phase 2 (Letrozole)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.69 [36]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1

Notes:

[36] - P-values are based on 2-sample t-test.

Statistical analysis title	Ph2P1(Palbociclib+Letrozole)vsPh2P1(Letrozole)
Statistical analysis description:	
Statistical analysis presented above is for Pain Severity Scale.	
Comparison groups	Ph2P1 (Palbociclib + Letrozole) v Ph2P1 (Letrozole)
Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7125 [37]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.8
upper limit	1.2

Notes:

[37] - P-values are based on 2-sample t-test.

Statistical analysis title	Ph2P2(Palbociclib+Letrozole)vsPh2P2(Letrozole)

Statistical analysis description:

Statistical analysis presented above is for Pain Severity Scale.

Comparison groups	Ph2P2 (Palbociclib + Letrozole) v Ph2P2 (Letrozole)
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4012 [38]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	1.5

Notes:

[38] - P-values are based on 2-sample t-test.

Secondary: Change from Baseline in Modified Brief Pain Inventory in Pain Interference Scale (mBPI-sf) Questionnaire at Phase 2

End point title	Change from Baseline in Modified Brief Pain Inventory in Pain Interference Scale (mBPI-sf) Questionnaire at Phase 2[39]

End point description:

The mBPI-sf is a validated and reliable self-report questionnaire which consists of 13 questions that assess the severity and impact of pain on daily function. The 13 items of the questionnaire make up two scales and two single items. The scales include the 4-item Pain Severity Scale (worst pain, least pain, average pain, and pain right now) and the 7-item Pain Interference Scale (general activity, mood, walking ability, normal work and relations with other people, sleep, and enjoyment of life). Each item of the pain severity and pain interference scales are based on a 11-point numeric rating scale from 0 ("no pain" or "does not interfere") to 10 ("pain as bad as you can imagine" or "completely interferes"). Patient reported outcome evaluable subjects: who had received at least 1 dose of study medication, had baseline data, and at least one post-baseline measurement. Here, "number of subjects analyzed" signifies number of subjects evaluable for this endpoint for each arm.

End point type	Secondary

End point timeframe:

Baseline, Month 41

Notes:

[39] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)	Ph2P1 (Palbociclib + Letrozole)	Ph2P1 (Letrozole)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	76	74	29	27
Units: Units on a scale				
arithmetic mean (standard error)				
General Activity	1.1 (± 0.40)	0.2 (± 0.31)	1.0 (± 0.66)	0.2 (± 0.58)
Mood	0.8 (± 0.50)	0.2 (± 0.36)	0.6 (± 0.72)	-0.2 (± 0.62)
Walking ability	0.8 (± 0.46)	0.1 (± 0.35)	1.0 (± 0.55)	0.3 (± 0.63)
Normal work	0.7 (± 0.48)	0.3 (± 0.39)	1.0 (± 0.53)	0.2 (± 0.74)
Relations	0.8 (± 0.32)	0.8 (± 0.32)	0.6 (± 0.34)	0.6 (± 0.60)
Sleep	0.6 (± 0.43)	0.3 (± 0.35)	0.1 (± 0.53)	0.5 (± 0.63)
Enjoyment of life	0.8 (± 0.46)	0.6 (± 0.41)	0.4 (± 0.34)	0.2 (± 0.69)
Pain Interference Scale	0.8 (± 0.34)	0.4 (± 0.30)	0.7 (± 0.42)	0.3 (± 0.56)

End point values	Ph2P2 (Palbociclib + Letrozole)	Ph2P2 (Letrozole)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	47	47		
Units: Units on a scale				
arithmetic mean (standard error)				
General Activity	1.2 (± 0.51)	0.3 (± 0.37)		
Mood	1.0 (± 0.69)	0.4 (± 0.44)		
Walking ability	0.7 (± 0.67)	0.0 (± 0.43)		
Normal work	0.5 (± 0.71)	0.4 (± 0.45)		
Relations	0.9 (± 0.47)	0.8 (± 0.37)		
Sleep	0.9 (± 0.61)	0.1 (± 0.42)		
Enjoyment of life	1.1 (± 0.71)	0.8 (± 0.52)		
Pain Interference Scale	0.9 (± 0.48)	0.4 (± 0.36)		

Statistical analyses

Statistical analysis title	Phase2(Palbociclib+Letrozole)vsPhase2(Letrozole)
Statistical analysis description:	
Statistical analysis presented above is for Pain Interference Scale.	
Comparison groups	Phase 2 (Palbociclib + Letrozole) v Phase 2 (Letrozole)
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3346 [40]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5
upper limit	1.3

Notes:

[40] - P-values are based on 2-sample t-test.

Statistical analysis title	Ph2P1(Palbociclib+Letrozole)vsPh2P1(Letrozole)
Statistical analysis description:	
Statistical analysis presented above is for Pain Interference Scale.	
Comparison groups	Ph2P1 (Palbociclib + Letrozole) v Ph2P1 (Letrozole)

Number of subjects included in analysis	56
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.563 [41]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	1.9

Notes:

[41] - P-values are based on 2-sample t-test.

Statistical analysis title	Ph2P2(Palbociclib+Letrozole)vsPh2P2(Letrozole)

Statistical analysis description:

Statistical analysis presented above is for Pain Severity Scale.

Comparison groups	Ph2P2 (Palbociclib + Letrozole) v Ph2P2 (Letrozole)
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4427 [42]
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7
upper limit	1.6

Notes:

[42] - P-values are based on 2-sample t-test.

Secondary: Presence or Absence of Tumor Tissue Biomarkers at Phase 2 - p16/INK4A, CCND1

End point title	Presence or Absence of Tumor Tissue Biomarkers at Phase 2 - p16/INK4A, CCND1

End point description:

Tissue samples were used for retrospective biomarker analyses. For Phase 2 Part 2, the tissue samples were sent to a central laboratory for the assessment of subject selection biomarkers. For Phase 2 Part 1, the assessment of the biomarkers (CCND1 amplification and/or loss of p16) were performed retrospectively from the available samples. Copy number analysis set included subjects who had at least 1 of the biomarker assessments. Here, "number of subjects analyzed" signifies number of subjects evaluable for this endpoint for each arm.

End point type	Secondary

End point timeframe:

Screening visit (<= 28 days prior to dosing)

End point values	Ph2P1 (Palbociclib + Letrozole)	Ph2P1 (Letrozole)	Ph2P2 (Palbociclib + Letrozole)	Ph2P2 (Letrozole)
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	22	24	50	48
Units: Subjects				
CCND1>=1.5	12	9	39	44
p16/INK4A<0.8	0	2	19	12
CCND1>=1.5 and p16/INK4A<0.8	0	2	8	8

Statistical analyses

No statistical analyses for this end point

Secondary: Presence or Absence of Tumor Tissue Biomarkers at Phase 2 - Ki67

End point title	Presence or Absence of Tumor Tissue Biomarkers at Phase 2 - Ki67[43]

End point description:

Frequency of tumor tissue biomarker Ki67 was evaluated in across treatment groups. Ki67 analysis set included subjects who had a Ki67 protein biomarker assessment. Here, "number of subjects analyzed" signifies number of subjects evaluable for this endpoint for each arm.

End point type	Secondary

End point timeframe:

Screening visit (<= 28 days prior to dosing)

Notes:

[43] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)	Ph2P1 (Palbociclib + Letrozole)	Ph2P1 (Letrozole)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	74	71	24	26
Units: Subjects				
<=20%	26	31	7	16
>20%	48	40	17	10

End point values	Ph2P2 (Palbociclib + Letrozole)	Ph2P2 (Letrozole)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	45		
Units: Subjects				
<=20%	19	15		
>20%	31	30		

Statistical analyses

No statistical analyses for this end point

Secondary: Presence or Absence of Tumor Tissue Biomarkers at Phase 2 - Tumor Retinoblastoma (RB) and CyclinD1

End point title	Presence or Absence of Tumor Tissue Biomarkers at Phase 2 - Tumor Retinoblastoma (RB) and CyclinD1[44]

End point description:

Presence or absence of tumor RB and CyclinD1 were evaluated. The following definitions of expression applied in the below table: Positive: any expression >0 and Negative: any expression=0. Protein biomarkers analysis set included all subjects who had at least protein biomarker assessment. Here, "number of subjects analyzed" signifies number of subjects evaluable for this endpoint for each arm.

End point type	Secondary

End point timeframe:

Screening visit (<= 28 days prior to dosing)

Notes:

[44] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)	Ph2P1 (Palbociclib + Letrozole)	Ph2P1 (Letrozole)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	45	35	12	16
Units: Subjects				
CyclinD1 - Positive	41	32	10	16
CyclinD1 - Negative	3	3	2	0
RB - Positive	41	32	10	16
RB - Negative	2	2	2	0

End point values	Ph2P2 (Palbociclib + Letrozole)	Ph2P2 (Letrozole)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	33	19		
Units: Subjects				
CyclinD1 - Positive	31	16		
CyclinD1 - Negative	1	3		
RB - Positive	31	16		
RB - Negative	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Copy Number for CCND1 (CCND1/CEP11) and p16/INK4A (p16/CEP9) at Phase 2

End point title	Summary of Copy Number for CCND1 (CCND1/CEP11) and p16/INK4A (p16/CEP9) at Phase 2[45]

End point description:

Gene copy number for CCND1 (CCND1/CEP11) and p16/INK4A (p16/CEP9) were evaluated. This analysis was done for Phase 2 combined group. Copy number analysis set included all subjects who had at least one copy number assessment. Here, "number of subjects analyzed" signifies number of subjects evaluable for this endpoint for each arm.

End point type	Secondary

End point timeframe:

Screening visit (<= 28 days prior to dosing)

Notes:

[45] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	72		
Units: Copy number				
arithmetic mean (standard deviation)				
CCND1	2.76 (± 1.875)	2.73 (± 1.559)		
p16/INK4A	0.83 (± 0.224)	0.87 (± 0.173)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Tumor Expression of CYP19A1 and CCND1 Genotypes at Phase 2

End point title	Percentage of Subjects With Tumor Expression of CYP19A1 and CCND1 Genotypes at Phase 2[46]

End point description:

One 2-mL blood specimen was collected for the analysis of germline polymorphism in CYP19A1 and CCND1 genes. A single nucleotide polymorphism (SNP) rs4646 as defined in the National Center for Biotechnology Information (NCBI) database in the aromatase gene (CYP19A1) was analyzed. A germline polymorphism G/A870 (rs9344) in the CCND1 gene was analyzed. Polymorphism analysis set included subjects who had at least 1 polymorphism assessment. Here, "number of subjects analyzed" signifies number of subjects evaluable for this endpoint for each arm.

End point type	Secondary

End point timeframe:

Screening visit (<= 28 days prior to dosing)

Notes:

[46] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)	Ph2P1 (Palbociclib + Letrozole)	Ph2P1 (Letrozole)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	76	74	30	28
Units: Percentage of subjects				
number (not applicable)				
CYP19A1 - A/A Genotype	7.9	5.4	10.0	10.7
CYP19A1 - C/A Genotype	34.2	36.5	33.3	42.9
CYP19A1 - C/C Genotype	57.9	58.1	56.7	46.4
CCND1 - A/A Genotype	26.3	28.4	33.3	39.3
CCND1 - G/A Genotype	47.4	47.3	43.3	42.9
CCND1 - G/G Genotype	26.3	24.3	23.3	17.9

End point values	Ph2P2 (Palbociclib + Letrozole)	Ph2P2 (Letrozole)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	46	46		
Units: Percentage of subjects				
number (not applicable)				
CYP19A1 - A/A Genotype	6.5	2.2		
CYP19A1 - C/A Genotype	34.8	32.6		
CYP19A1 - C/C Genotype	58.7	65.2		
CCND1 - A/A Genotype	21.7	21.7		
CCND1 - G/A Genotype	50.0	50.0		
CCND1 - G/G Genotype	28.3	28.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with TEAEs (All Causalities) at Phase 2

End point title	Number of Subjects with TEAEs (All Causalities) at Phase 2[47]

End point description:

AE: any untoward medical occurrence in subject who received study drug without regard to possibility of causal relationship. AEs included both serious and non-serious AEs. SAE: AE resulting in any of following outcomes/deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Treatment emergent AE: events occurred between first dose of study drug and up to 28 days after last dose (up to 86 months) that were absent before treatment or worsened relative to

pre-treatment state. AEs graded as per the CTCAE version 3.0. Subjects with AE of grade 3, 4 and grade 5 reported as Grade 3: Severe, Grade 4: Life threatening, Grade 5: Death related to AE. All treated as treated set included all treated subjects classified by treatment actually received.

End point type	Secondary

End point timeframe:

Baseline up to 28 days after last dose of study drug (for a maximum of 86 months)

Notes:

[47] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)	Ph2P1 (Palbociclib + Letrozole)	Ph2P1 (Letrozole)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	83	77	33	29
Units: Subjects				
Subjects with AEs	83	66	33	25
Subjects with SAEs	22	6	10	2
Subjects with Grade 3 or 4 AEs	70	19	29	5
Subjects with Grade 5 AEs	1	0	0	0

End point values	Ph2P2 (Palbociclib + Letrozole)	Ph2P2 (Letrozole)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	48		
Units: Subjects				
Subjects with AEs	50	41		
Subjects with SAEs	12	4		
Subjects with Grade 3 or 4 AEs	41	14		
Subjects with Grade 5 AEs	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment-Related Adverse Events at Phase 2

End point title	Number of Subjects with Treatment-Related Adverse Events at Phase 2[48]

End point description:

AE: any untoward medical occurrence in subject who received study drug. AEs included both serious and non-serious AEs. SAE: AE resulting in any of following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. TEAEs: events occurred between first dose of study drug and up to 28 days after last dose (up to 86 months) that were absent before treatment or that worsened relative to pre-treatment state. Treatment related AEs: AEs with causality related to treatment. Relatedness to drug was assessed by the investigator. AEs graded according to the CTCAE version 3.0. Number of subjects with AE of grade 3, 4 and 5 were reported as Grade 3: Severe, Grade 4: Life threatening, Grade 5: Death related to AE. All treated as treated set included all treated subjects classified by treatment actually received.

End point type	Secondary

End point timeframe:

Baseline up to 28 days after last dose of study drug (for a maximum of 86 months)

Notes:

[48] - 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: Only arms which are applicable to the endpoint are reported.

End point values	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)	Ph2P1 (Palbociclib + Letrozole)	Ph2P1 (Letrozole)
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	83	77	33	29
Units: Subjects				
Subjects with AEs	78	33	32	13
Subjects with SAEs	1	0	0	0
Subjects with Grade 3 or 4 AEs	57	2	25	0
Subjects with Grade 5 AEs	0	0	0	0

End point values	Ph2P2 (Palbociclib + Letrozole)	Ph2P2 (Letrozole)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	50	48		
Units: Subjects				
Subjects with AEs	46	20		
Subjects with SAEs	1	0		
Subjects with Grade 3 or 4 AEs	32	2		
Subjects with Grade 5 AEs	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 28 days after last dose of study drug (for a maximum of 86 months)

Adverse event reporting additional description:

An event may be categorized as serious in one subject and non serious in another, or 1 subject may experience both event. All treatment emergent AEs and SAEs were collected and reported. The same event may appear as both AE and SAE. Analysis was done on subjects who received at least one dose of study drug.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Phase 1 (Palbociclib + Letrozole)

Reporting group description:

In Cycle 1 (3 weeks), subjects received single agent palbociclib 125 mg/d orally for 2 weeks followed by 1 week off treatment. In Cycles 2 and beyond (4 weeks each), subjects received letrozole 2.5 mg/d in a continuous regimen plus Palbociclib 125 mg/d orally for 3 weeks followed by 1 week off treatment.

Reporting group title	Phase 2 (Palbociclib + Letrozole)

Reporting group description:

All participants who were randomized to letrozole plus palbociclib in both Phase 2 part 1 (Ph2P1) and Phase 2 part 2 (Ph2P2) are combined and presented. In Ph2P1 and Ph2P2, the participants received palbociclib 125 mg/d orally for 3 weeks followed by 1 week off treatment and letrozole 2.5 mg/d orally in a continuous regimen.

Reporting group title	Phase 2 (Letrozole)

Reporting group description:

All participants who were randomized to receive letrozole alone in both Phase 2 part 1 (Ph2P1) and Phase 2 part 2 (Ph2P2) are combined and presented. This was considered as control arm. Letrozole 2.5 mg/d was administered orally in a continuous regimen.

Reporting group title	Ph2P1 (Palbociclib + Letrozole)

Reporting group description:

All participants were randomized to receive Letrozole plus Palbociclib. Palbociclib 125 mg/d orally for 3 weeks followed by 1 week off treatment and Letrozole 2.5 mg/d orally in a continuous regimen.

Reporting group title	Ph2P1 (Letrozole)

Reporting group description:

Participants were randomized to receive Letrozole alone. Letrozole 2.5 mg/d was administered orally in a continuous regimen. This was considered as control arm.

Reporting group title	Ph2P2 (Palbociclib + Letrozole)

Reporting group description:

Participants were randomized to receive Letrozole plus Palbociclib. Palbociclib 125 mg/d orally for 3 weeks followed by 1 week off treatment and Letrozole 2.5 mg/d orally in a continuous regimen.

Reporting group title	Ph2P2 (Letrozole)

Reporting group description:

Participants were randomized to receive Letrozole. Letrozole 2.5 mg/d was administered orally in a continuous regimen. This was considered as control arm.

Serious adverse events	Phase 1 (Palbociclib + Letrozole)	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 12 (16.67%)	22 / 83 (26.51%)	6 / 77 (7.79%)
number of deaths (all causes)	0	3	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fallopian tube cancer			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			
subjects affected / exposed	0 / 12 (0.00%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pain			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			

subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fractured sacrum			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			

subjects affected / exposed	0 / 12 (0.00%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 12 (0.00%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 12 (0.00%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Neuralgia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain stem infarction			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			

subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 12 (0.00%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal achalasia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			

subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	0 / 12 (0.00%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal disorder			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral obstruction			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 12 (0.00%)	2 / 83 (2.41%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bone pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 12 (0.00%)	2 / 83 (2.41%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Erysipelas			
subjects affected / exposed	0 / 12 (0.00%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			

subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastoiditis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Ph2P1 (Palbociclib + Letrozole)	Ph2P1 (Letrozole)	Ph2P2 (Palbociclib + Letrozole)
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 33 (30.30%)	2 / 29 (6.90%)	12 / 50 (24.00%)
number of deaths (all causes)	1	0	2
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fallopian tube cancer			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Plasma cell myeloma			

subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Disease progression			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pain			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			

subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fractured sacrum			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper limb fracture			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Neuralgia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain stem infarction			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis ischaemic			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorder			

subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oesophageal achalasia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Subcutaneous emphysema			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Nephrolithiasis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal disorder			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urethral obstruction			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	2 / 50 (4.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Osteonecrosis of jaw			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Erysipelas			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gangrene			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal bacteraemia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Campylobacter infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective exacerbation of chronic			

obstructive airways disease			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mastoiditis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Ph2P2 (Letrozole)		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 48 (8.33%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fallopian tube cancer			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Plasma cell myeloma			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Disease progression			

subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pain				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pulmonary embolism				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Aspartate aminotransferase increased				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Blood alkaline phosphatase increased				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gamma-glutamyltransferase increased				

subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Fractured sacrum			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hip fracture			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Upper limb fracture			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Neuralgia			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Brain stem infarction			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis ischaemic			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorder			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Oesophageal achalasia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Vomiting				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastritis				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Inguinal hernia				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
Subcutaneous emphysema				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Nephrolithiasis				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal disorder				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Urethral obstruction				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Acute kidney injury				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bone pain			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Arthralgia			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Osteonecrosis of jaw			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gangrene			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Influenza			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pneumonia				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Staphylococcal bacteraemia				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Campylobacter infection				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infective exacerbation of chronic obstructive airways disease				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Mastoiditis				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Phase 1 (Palbociclib + Letrozole)	Phase 2 (Palbociclib + Letrozole)	Phase 2 (Letrozole)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	83 / 83 (100.00%)	57 / 77 (74.03%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			

subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences (all)	1	3	0
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 12 (0.00%)	2 / 83 (2.41%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Hot flush			
subjects affected / exposed	3 / 12 (25.00%)	19 / 83 (22.89%)	11 / 77 (14.29%)
occurrences (all)	5	21	12
Hypertension			
subjects affected / exposed	0 / 12 (0.00%)	6 / 83 (7.23%)	5 / 77 (6.49%)
occurrences (all)	0	6	7
Lymphoedema			
subjects affected / exposed	0 / 12 (0.00%)	4 / 83 (4.82%)	0 / 77 (0.00%)
occurrences (all)	0	4	0
Peripheral vascular disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Phlebitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 12 (8.33%)	11 / 83 (13.25%)	4 / 77 (5.19%)
occurrences (all)	1	14	4
Chest pain			
subjects affected / exposed	0 / 12 (0.00%)	3 / 83 (3.61%)	4 / 77 (5.19%)
occurrences (all)	0	4	4
Facial pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Fatigue			
subjects affected / exposed	10 / 12 (83.33%)	34 / 83 (40.96%)	18 / 77 (23.38%)
occurrences (all)	20	70	29
Influenza like illness			

subjects affected / exposed	1 / 12 (8.33%)	5 / 83 (6.02%)	2 / 77 (2.60%)
occurrences (all)	1	7	2
Mucosal inflammation			
subjects affected / exposed	0 / 12 (0.00%)	7 / 83 (8.43%)	2 / 77 (2.60%)
occurrences (all)	0	12	2
Non-cardiac chest pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Oedema peripheral			
subjects affected / exposed	2 / 12 (16.67%)	6 / 83 (7.23%)	8 / 77 (10.39%)
occurrences (all)	2	8	11
Pain			
subjects affected / exposed	2 / 12 (16.67%)	3 / 83 (3.61%)	3 / 77 (3.90%)
occurrences (all)	3	3	3
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	9 / 83 (10.84%)	2 / 77 (2.60%)
occurrences (all)	0	10	2
Temperature intolerance			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Chills			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
Face oedema			
subjects affected / exposed	1 / 12 (8.33%)	2 / 83 (2.41%)	1 / 77 (1.30%)
occurrences (all)	1	2	1
Peripheral swelling			
subjects affected / exposed	1 / 12 (8.33%)	4 / 83 (4.82%)	2 / 77 (2.60%)
occurrences (all)	1	4	2
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	2 / 12 (16.67%)	1 / 83 (1.20%)	1 / 77 (1.30%)
occurrences (all)	3	2	1
Reproductive system and breast disorders			

Breast discomfort			
subjects affected / exposed	0 / 12 (0.00%)	2 / 83 (2.41%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Breast pain			
subjects affected / exposed	0 / 12 (0.00%)	2 / 83 (2.41%)	4 / 77 (5.19%)
occurrences (all)	0	3	4
Pelvic pain			
subjects affected / exposed	1 / 12 (8.33%)	2 / 83 (2.41%)	2 / 77 (2.60%)
occurrences (all)	1	2	3
Vaginal discharge			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Vulvovaginal pruritus			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 12 (25.00%)	12 / 83 (14.46%)	8 / 77 (10.39%)
occurrences (all)	6	21	13
Dyspnoea			
subjects affected / exposed	5 / 12 (41.67%)	14 / 83 (16.87%)	7 / 77 (9.09%)
occurrences (all)	7	20	8
Epistaxis			
subjects affected / exposed	0 / 12 (0.00%)	9 / 83 (10.84%)	1 / 77 (1.30%)
occurrences (all)	0	12	1
Nasal congestion			
subjects affected / exposed	2 / 12 (16.67%)	2 / 83 (2.41%)	0 / 77 (0.00%)
occurrences (all)	2	3	0
Oropharyngeal pain			
subjects affected / exposed	1 / 12 (8.33%)	9 / 83 (10.84%)	1 / 77 (1.30%)
occurrences (all)	1	15	1
Rhinitis allergic			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	1 / 77 (1.30%)
occurrences (all)	1	1	1
Rhinorrhoea			

subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
Sinus congestion			
subjects affected / exposed	3 / 12 (25.00%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences (all)	3	1	0
Snoring			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Lower respiratory tract congestion			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 12 (8.33%)	2 / 83 (2.41%)	4 / 77 (5.19%)
occurrences (all)	2	2	5
Depression			
subjects affected / exposed	3 / 12 (25.00%)	4 / 83 (4.82%)	5 / 77 (6.49%)
occurrences (all)	3	4	5
Insomnia			
subjects affected / exposed	3 / 12 (25.00%)	8 / 83 (9.64%)	6 / 77 (7.79%)
occurrences (all)	3	9	7
Mood altered			
subjects affected / exposed	1 / 12 (8.33%)	4 / 83 (4.82%)	1 / 77 (1.30%)
occurrences (all)	2	7	1
Sleep disorder			
subjects affected / exposed	0 / 12 (0.00%)	3 / 83 (3.61%)	1 / 77 (1.30%)
occurrences (all)	0	3	1
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	6 / 83 (7.23%)	1 / 77 (1.30%)
occurrences (all)	0	8	1
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	6 / 83 (7.23%)	1 / 77 (1.30%)
occurrences (all)	0	11	1
Blood alkaline phosphatase increased			

subjects affected / exposed	0 / 12 (0.00%)	8 / 83 (9.64%)	3 / 77 (3.90%)
occurrences (all)	0	10	3
Blood creatinine increased			
subjects affected / exposed	2 / 12 (16.67%)	4 / 83 (4.82%)	5 / 77 (6.49%)
occurrences (all)	7	4	5
Blood phosphorus decreased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 83 (2.41%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	4 / 83 (4.82%)	1 / 77 (1.30%)
occurrences (all)	0	14	1
Red blood cell count decreased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 83 (2.41%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Weight decreased			
subjects affected / exposed	2 / 12 (16.67%)	4 / 83 (4.82%)	1 / 77 (1.30%)
occurrences (all)	2	5	1
White blood cell count decreased			
subjects affected / exposed	0 / 12 (0.00%)	2 / 83 (2.41%)	0 / 77 (0.00%)
occurrences (all)	0	5	0
Weight increased			
subjects affected / exposed	0 / 12 (0.00%)	3 / 83 (3.61%)	6 / 77 (7.79%)
occurrences (all)	0	5	9
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 12 (16.67%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences (all)	2	1	0
Thermal burn			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
Fall			
subjects affected / exposed	0 / 12 (0.00%)	7 / 83 (8.43%)	3 / 77 (3.90%)
occurrences (all)	0	14	3
Periorbital haemorrhage			

subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Skin abrasion			
subjects affected / exposed	1 / 12 (8.33%)	2 / 83 (2.41%)	0 / 77 (0.00%)
occurrences (all)	1	2	0
Skin injury			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 12 (25.00%)	10 / 83 (12.05%)	3 / 77 (3.90%)
occurrences (all)	3	15	4
Dysgeusia			
subjects affected / exposed	1 / 12 (8.33%)	6 / 83 (7.23%)	0 / 77 (0.00%)
occurrences (all)	1	7	0
Headache			
subjects affected / exposed	4 / 12 (33.33%)	12 / 83 (14.46%)	8 / 77 (10.39%)
occurrences (all)	5	21	10
Memory impairment			
subjects affected / exposed	1 / 12 (8.33%)	2 / 83 (2.41%)	1 / 77 (1.30%)
occurrences (all)	1	2	1
Neuropathy peripheral			
subjects affected / exposed	2 / 12 (16.67%)	9 / 83 (10.84%)	4 / 77 (5.19%)
occurrences (all)	3	11	4
Paraesthesia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	2 / 77 (2.60%)
occurrences (all)	1	1	2
Sciatica			
subjects affected / exposed	1 / 12 (8.33%)	2 / 83 (2.41%)	0 / 77 (0.00%)
occurrences (all)	1	2	0
Sinus headache			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Syncope			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0

Radicular pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 12 (0.00%)	3 / 83 (3.61%)	0 / 77 (0.00%)
occurrences (all)	0	6	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 12 (33.33%)	29 / 83 (34.94%)	3 / 77 (3.90%)
occurrences (all)	19	90	7
Leukopenia			
subjects affected / exposed	8 / 12 (66.67%)	36 / 83 (43.37%)	3 / 77 (3.90%)
occurrences (all)	70	172	4
Lymphopenia			
subjects affected / exposed	0 / 12 (0.00%)	3 / 83 (3.61%)	0 / 77 (0.00%)
occurrences (all)	0	3	0
Neutropenia			
subjects affected / exposed	11 / 12 (91.67%)	62 / 83 (74.70%)	4 / 77 (5.19%)
occurrences (all)	144	621	20
Thrombocytopenia			
subjects affected / exposed	3 / 12 (25.00%)	16 / 83 (19.28%)	2 / 77 (2.60%)
occurrences (all)	16	62	3
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	2 / 77 (2.60%)
occurrences (all)	1	1	2
Ear pain			
subjects affected / exposed	0 / 12 (0.00%)	2 / 83 (2.41%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Lacrimation increased			
subjects affected / exposed	2 / 12 (16.67%)	3 / 83 (3.61%)	0 / 77 (0.00%)
occurrences (all)	3	3	0
Visual impairment			

subjects affected / exposed	1 / 12 (8.33%)	4 / 83 (4.82%)	1 / 77 (1.30%)
occurrences (all)	1	4	1
Cataract			
subjects affected / exposed	1 / 12 (8.33%)	2 / 83 (2.41%)	0 / 77 (0.00%)
occurrences (all)	2	2	0
Presbyopia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	2 / 77 (2.60%)
occurrences (all)	1	0	2
Abdominal distension			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	2 / 77 (2.60%)
occurrences (all)	1	0	2
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	7 / 83 (8.43%)	4 / 77 (5.19%)
occurrences (all)	0	8	4
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	2 / 83 (2.41%)	4 / 77 (5.19%)
occurrences (all)	0	4	4
Constipation			
subjects affected / exposed	3 / 12 (25.00%)	13 / 83 (15.66%)	7 / 77 (9.09%)
occurrences (all)	4	20	10
Diarrhoea			
subjects affected / exposed	6 / 12 (50.00%)	18 / 83 (21.69%)	9 / 77 (11.69%)
occurrences (all)	10	31	10
Dry mouth			
subjects affected / exposed	1 / 12 (8.33%)	3 / 83 (3.61%)	4 / 77 (5.19%)
occurrences (all)	1	3	4
Dyspepsia			
subjects affected / exposed	3 / 12 (25.00%)	4 / 83 (4.82%)	2 / 77 (2.60%)
occurrences (all)	4	6	2
Flatulence			
subjects affected / exposed	0 / 12 (0.00%)	2 / 83 (2.41%)	1 / 77 (1.30%)
occurrences (all)	0	2	1

Food poisoning			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	1 / 77 (1.30%)
occurrences (all)	1	1	1
Chronic gastritis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	1 / 77 (1.30%)
occurrences (all)	3	1	1
Gingival pain			
subjects affected / exposed	1 / 12 (8.33%)	4 / 83 (4.82%)	0 / 77 (0.00%)
occurrences (all)	1	4	0
Mouth ulceration			
subjects affected / exposed	1 / 12 (8.33%)	2 / 83 (2.41%)	1 / 77 (1.30%)
occurrences (all)	1	2	1
Nausea			
subjects affected / exposed	6 / 12 (50.00%)	25 / 83 (30.12%)	11 / 77 (14.29%)
occurrences (all)	8	48	13
Stomatitis			
subjects affected / exposed	2 / 12 (16.67%)	10 / 83 (12.05%)	2 / 77 (2.60%)
occurrences (all)	2	44	2
Rectal haemorrhage			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Toothache			
subjects affected / exposed	1 / 12 (8.33%)	6 / 83 (7.23%)	2 / 77 (2.60%)
occurrences (all)	1	6	2
Vomiting			
subjects affected / exposed	3 / 12 (25.00%)	15 / 83 (18.07%)	3 / 77 (3.90%)
occurrences (all)	4	27	3
Oral disorder			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
Gastritis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 83 (1.20%)	4 / 77 (5.19%)
occurrences (all)	0	1	5

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 12 (8.33%)	18 / 83 (21.69%)	2 / 77 (2.60%)
occurrences (all)	1	20	3
Dermatitis contact			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Dry skin			
subjects affected / exposed	2 / 12 (16.67%)	6 / 83 (7.23%)	4 / 77 (5.19%)
occurrences (all)	2	7	4
Hyperhidrosis			
subjects affected / exposed	0 / 12 (0.00%)	4 / 83 (4.82%)	1 / 77 (1.30%)
occurrences (all)	0	4	1
Ingrown hair			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Nail disorder			
subjects affected / exposed	1 / 12 (8.33%)	5 / 83 (6.02%)	1 / 77 (1.30%)
occurrences (all)	1	5	1
Pain of skin			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
Pruritus			
subjects affected / exposed	0 / 12 (0.00%)	5 / 83 (6.02%)	2 / 77 (2.60%)
occurrences (all)	0	11	3
Rash			
subjects affected / exposed	3 / 12 (25.00%)	7 / 83 (8.43%)	4 / 77 (5.19%)
occurrences (all)	3	8	5
Skin disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Skin swelling			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Swelling face			

subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
Night sweats			
subjects affected / exposed	1 / 12 (8.33%)	3 / 83 (3.61%)	1 / 77 (1.30%)
occurrences (all)	1	4	1
Erythema			
subjects affected / exposed	0 / 12 (0.00%)	3 / 83 (3.61%)	3 / 77 (3.90%)
occurrences (all)	0	3	6
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	3 / 12 (25.00%)	4 / 83 (4.82%)	2 / 77 (2.60%)
occurrences (all)	3	4	2
Pollakiuria			
subjects affected / exposed	1 / 12 (8.33%)	4 / 83 (4.82%)	1 / 77 (1.30%)
occurrences (all)	1	5	1
Incontinence			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Thyroid mass			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 12 (41.67%)	22 / 83 (26.51%)	14 / 77 (18.18%)
occurrences (all)	12	49	29
Back pain			
subjects affected / exposed	3 / 12 (25.00%)	17 / 83 (20.48%)	13 / 77 (16.88%)
occurrences (all)	3	25	15
Bone pain			
subjects affected / exposed	0 / 12 (0.00%)	10 / 83 (12.05%)	3 / 77 (3.90%)
occurrences (all)	0	15	4
Joint swelling			

subjects affected / exposed	2 / 12 (16.67%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences (all)	3	1	0
Muscle spasms			
subjects affected / exposed	0 / 12 (0.00%)	5 / 83 (6.02%)	3 / 77 (3.90%)
occurrences (all)	0	6	3
Musculoskeletal chest pain			
subjects affected / exposed	2 / 12 (16.67%)	3 / 83 (3.61%)	3 / 77 (3.90%)
occurrences (all)	2	4	5
Musculoskeletal pain			
subjects affected / exposed	1 / 12 (8.33%)	9 / 83 (10.84%)	5 / 77 (6.49%)
occurrences (all)	1	19	7
Myalgia			
subjects affected / exposed	1 / 12 (8.33%)	6 / 83 (7.23%)	3 / 77 (3.90%)
occurrences (all)	1	8	3
Osteonecrosis of jaw			
subjects affected / exposed	1 / 12 (8.33%)	3 / 83 (3.61%)	0 / 77 (0.00%)
occurrences (all)	1	3	0
Pain in extremity			
subjects affected / exposed	3 / 12 (25.00%)	9 / 83 (10.84%)	7 / 77 (9.09%)
occurrences (all)	4	18	8
Spinal pain			
subjects affected / exposed	0 / 12 (0.00%)	5 / 83 (6.02%)	3 / 77 (3.90%)
occurrences (all)	0	5	3
Temporomandibular joint syndrome			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Arthropathy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Muscular weakness			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	1 / 77 (1.30%)
occurrences (all)	1	1	1
Limb discomfort			
subjects affected / exposed	0 / 12 (0.00%)	0 / 83 (0.00%)	2 / 77 (2.60%)
occurrences (all)	0	0	2
Osteoporosis			

subjects affected / exposed	0 / 12 (0.00%)	2 / 83 (2.41%)	1 / 77 (1.30%)
occurrences (all)	0	2	1
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 12 (0.00%)	5 / 83 (6.02%)	0 / 77 (0.00%)
occurrences (all)	0	6	0
Bronchitis			
subjects affected / exposed	1 / 12 (8.33%)	3 / 83 (3.61%)	2 / 77 (2.60%)
occurrences (all)	1	5	2
Cystitis			
subjects affected / exposed	0 / 12 (0.00%)	3 / 83 (3.61%)	1 / 77 (1.30%)
occurrences (all)	0	3	1
Diverticulitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 83 (0.00%)	2 / 77 (2.60%)
occurrences (all)	0	0	2
Ear infection			
subjects affected / exposed	0 / 12 (0.00%)	3 / 83 (3.61%)	0 / 77 (0.00%)
occurrences (all)	0	3	0
Gastroenteritis viral			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	1 / 77 (1.30%)
occurrences (all)	1	1	1
Herpes zoster			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	1 / 77 (1.30%)
occurrences (all)	3	1	1
Influenza			
subjects affected / exposed	1 / 12 (8.33%)	8 / 83 (9.64%)	1 / 77 (1.30%)
occurrences (all)	1	10	1
Localised infection			
subjects affected / exposed	2 / 12 (16.67%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
Nasopharyngitis			
subjects affected / exposed	1 / 12 (8.33%)	12 / 83 (14.46%)	7 / 77 (9.09%)
occurrences (all)	3	16	11
Oral herpes			
subjects affected / exposed	1 / 12 (8.33%)	3 / 83 (3.61%)	0 / 77 (0.00%)
occurrences (all)	2	5	0

Pneumonia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	2 / 77 (2.60%)
occurrences (all)	1	1	2
Sinusitis			
subjects affected / exposed	2 / 12 (16.67%)	2 / 83 (2.41%)	2 / 77 (2.60%)
occurrences (all)	3	3	2
Skin infection			
subjects affected / exposed	2 / 12 (16.67%)	2 / 83 (2.41%)	1 / 77 (1.30%)
occurrences (all)	2	3	1
Tooth infection			
subjects affected / exposed	2 / 12 (16.67%)	2 / 83 (2.41%)	0 / 77 (0.00%)
occurrences (all)	2	2	0
Upper respiratory tract infection			
subjects affected / exposed	3 / 12 (25.00%)	12 / 83 (14.46%)	2 / 77 (2.60%)
occurrences (all)	8	15	2
Urinary tract infection			
subjects affected / exposed	2 / 12 (16.67%)	9 / 83 (10.84%)	5 / 77 (6.49%)
occurrences (all)	2	15	5
Herpes simplex			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	1 / 77 (1.30%)
occurrences (all)	1	2	1
Gingivitis			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences (all)	2	1	0
Rhinitis			
subjects affected / exposed	2 / 12 (16.67%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences (all)	2	1	0
Cellulitis			
subjects affected / exposed	0 / 12 (0.00%)	2 / 83 (2.41%)	2 / 77 (2.60%)
occurrences (all)	0	2	5
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 12 (25.00%)	17 / 83 (20.48%)	5 / 77 (6.49%)
occurrences (all)	5	18	5
Diabetes mellitus			

subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Hyperkalaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 12 (0.00%)	4 / 83 (4.82%)	2 / 77 (2.60%)
occurrences (all)	0	5	2
Hypokalaemia			
subjects affected / exposed	1 / 12 (8.33%)	2 / 83 (2.41%)	1 / 77 (1.30%)
occurrences (all)	1	2	1
Hyponatraemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 83 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Hyperuricaemia			
subjects affected / exposed	0 / 12 (0.00%)	3 / 83 (3.61%)	2 / 77 (2.60%)
occurrences (all)	0	3	2
Dehydration			
subjects affected / exposed	1 / 12 (8.33%)	1 / 83 (1.20%)	0 / 77 (0.00%)
occurrences (all)	1	1	0

Non-serious adverse events	Ph2P1 (Palbociclib + Letrozole)	Ph2P1 (Letrozole)	Ph2P2 (Palbociclib + Letrozole)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 33 (100.00%)	22 / 29 (75.86%)	50 / 50 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	3
Vascular disorders			
Haematoma			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Hot flush			
subjects affected / exposed	9 / 33 (27.27%)	5 / 29 (17.24%)	10 / 50 (20.00%)
occurrences (all)	10	6	11
Hypertension			

subjects affected / exposed	1 / 33 (3.03%)	2 / 29 (6.90%)	5 / 50 (10.00%)
occurrences (all)	1	2	5
Lymphoedema			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	2 / 50 (4.00%)
occurrences (all)	2	0	2
Peripheral vascular disorder			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Phlebitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	9 / 50 (18.00%)
occurrences (all)	2	0	12
Chest pain			
subjects affected / exposed	0 / 33 (0.00%)	2 / 29 (6.90%)	3 / 50 (6.00%)
occurrences (all)	0	2	4
Facial pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	14 / 33 (42.42%)	7 / 29 (24.14%)	20 / 50 (40.00%)
occurrences (all)	31	14	39
Influenza like illness			
subjects affected / exposed	3 / 33 (9.09%)	1 / 29 (3.45%)	2 / 50 (4.00%)
occurrences (all)	5	1	2
Mucosal inflammation			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	5 / 50 (10.00%)
occurrences (all)	5	0	7
Non-cardiac chest pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Oedema peripheral			

subjects affected / exposed	3 / 33 (9.09%)	5 / 29 (17.24%)	3 / 50 (6.00%)
occurrences (all)	5	6	3
Pain			
subjects affected / exposed	1 / 33 (3.03%)	2 / 29 (6.90%)	2 / 50 (4.00%)
occurrences (all)	1	2	2
Pyrexia			
subjects affected / exposed	8 / 33 (24.24%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences (all)	9	0	1
Temperature intolerance			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Face oedema			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Peripheral swelling			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	2 / 50 (4.00%)
occurrences (all)	2	0	2
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 33 (3.03%)	1 / 29 (3.45%)	0 / 50 (0.00%)
occurrences (all)	2	1	0
Reproductive system and breast disorders			
Breast discomfort			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Breast pain			
subjects affected / exposed	2 / 33 (6.06%)	3 / 29 (10.34%)	0 / 50 (0.00%)
occurrences (all)	3	3	0
Pelvic pain			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Vaginal discharge			

subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal pruritus			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 33 (27.27%)	4 / 29 (13.79%)	3 / 50 (6.00%)
occurrences (all)	18	4	3
Dyspnoea			
subjects affected / exposed	4 / 33 (12.12%)	3 / 29 (10.34%)	10 / 50 (20.00%)
occurrences (all)	9	3	11
Epistaxis			
subjects affected / exposed	4 / 33 (12.12%)	0 / 29 (0.00%)	5 / 50 (10.00%)
occurrences (all)	6	0	6
Nasal congestion			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	3	0	0
Oropharyngeal pain			
subjects affected / exposed	5 / 33 (15.15%)	0 / 29 (0.00%)	4 / 50 (8.00%)
occurrences (all)	10	0	5
Rhinitis allergic			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Rhinorrhoea			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Sinus congestion			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Snoring			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Lower respiratory tract congestion			

subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 33 (6.06%)	4 / 29 (13.79%)	0 / 50 (0.00%)
occurrences (all)	2	5	0
Depression			
subjects affected / exposed	2 / 33 (6.06%)	4 / 29 (13.79%)	2 / 50 (4.00%)
occurrences (all)	2	4	2
Insomnia			
subjects affected / exposed	4 / 33 (12.12%)	3 / 29 (10.34%)	4 / 50 (8.00%)
occurrences (all)	4	3	5
Mood altered			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	2 / 50 (4.00%)
occurrences (all)	3	0	4
Sleep disorder			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	3 / 33 (9.09%)	1 / 29 (3.45%)	3 / 50 (6.00%)
occurrences (all)	5	1	3
Aspartate aminotransferase increased			
subjects affected / exposed	2 / 33 (6.06%)	1 / 29 (3.45%)	4 / 50 (8.00%)
occurrences (all)	6	1	5
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 33 (6.06%)	2 / 29 (6.90%)	6 / 50 (12.00%)
occurrences (all)	4	2	6
Blood creatinine increased			
subjects affected / exposed	1 / 33 (3.03%)	3 / 29 (10.34%)	3 / 50 (6.00%)
occurrences (all)	1	3	3
Blood phosphorus decreased			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Gamma-glutamyltransferase increased			

subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	2 / 50 (4.00%)
occurrences (all)	12	0	2
Red blood cell count decreased			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Weight decreased			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	4 / 50 (8.00%)
occurrences (all)	0	1	5
White blood cell count decreased			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	5	0	0
Weight increased			
subjects affected / exposed	1 / 33 (3.03%)	2 / 29 (6.90%)	2 / 50 (4.00%)
occurrences (all)	1	2	4
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Thermal burn			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	4 / 33 (12.12%)	0 / 29 (0.00%)	3 / 50 (6.00%)
occurrences (all)	7	0	7
Periorbital haemorrhage			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Skin abrasion			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Skin injury			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Nervous system disorders			

Dizziness			
subjects affected / exposed	3 / 33 (9.09%)	3 / 29 (10.34%)	7 / 50 (14.00%)
occurrences (all)	3	4	12
Dysgeusia			
subjects affected / exposed	4 / 33 (12.12%)	0 / 29 (0.00%)	2 / 50 (4.00%)
occurrences (all)	5	0	2
Headache			
subjects affected / exposed	6 / 33 (18.18%)	3 / 29 (10.34%)	6 / 50 (12.00%)
occurrences (all)	14	4	7
Memory impairment			
subjects affected / exposed	1 / 33 (3.03%)	1 / 29 (3.45%)	1 / 50 (2.00%)
occurrences (all)	1	1	1
Neuropathy peripheral			
subjects affected / exposed	6 / 33 (18.18%)	2 / 29 (6.90%)	3 / 50 (6.00%)
occurrences (all)	8	2	3
Paraesthesia			
subjects affected / exposed	0 / 33 (0.00%)	2 / 29 (6.90%)	1 / 50 (2.00%)
occurrences (all)	0	2	1
Sciatica			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Sinus headache			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Syncope			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Radicular pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	6
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	13 / 33 (39.39%)	0 / 29 (0.00%)	16 / 50 (32.00%)
occurrences (all)	55	0	35
Leukopenia			
subjects affected / exposed	16 / 33 (48.48%)	1 / 29 (3.45%)	20 / 50 (40.00%)
occurrences (all)	127	1	45
Lymphopenia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences (all)	2	0	1
Neutropenia			
subjects affected / exposed	26 / 33 (78.79%)	1 / 29 (3.45%)	36 / 50 (72.00%)
occurrences (all)	373	1	248
Thrombocytopenia			
subjects affected / exposed	8 / 33 (24.24%)	1 / 29 (3.45%)	8 / 50 (16.00%)
occurrences (all)	49	2	13
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Ear pain			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Lacrimation increased			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	2 / 50 (4.00%)
occurrences (all)	1	0	2
Visual impairment			
subjects affected / exposed	1 / 33 (3.03%)	1 / 29 (3.45%)	3 / 50 (6.00%)
occurrences (all)	1	1	3
Cataract			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Presbyopia			

subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Abdominal distension			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	7 / 33 (21.21%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	8	0	0
Abdominal pain upper			
subjects affected / exposed	1 / 33 (3.03%)	1 / 29 (3.45%)	1 / 50 (2.00%)
occurrences (all)	3	1	1
Constipation			
subjects affected / exposed	8 / 33 (24.24%)	4 / 29 (13.79%)	5 / 50 (10.00%)
occurrences (all)	11	5	9
Diarrhoea			
subjects affected / exposed	9 / 33 (27.27%)	2 / 29 (6.90%)	9 / 50 (18.00%)
occurrences (all)	19	2	12
Dry mouth			
subjects affected / exposed	2 / 33 (6.06%)	2 / 29 (6.90%)	1 / 50 (2.00%)
occurrences (all)	2	2	1
Dyspepsia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	3 / 50 (6.00%)
occurrences (all)	1	0	5
Flatulence			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Food poisoning			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Chronic gastritis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0

Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 33 (3.03%)	1 / 29 (3.45%)	0 / 50 (0.00%)
occurrences (all)	1	1	0
Gingival pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	4 / 50 (8.00%)
occurrences (all)	0	0	4
Mouth ulceration			
subjects affected / exposed	2 / 33 (6.06%)	1 / 29 (3.45%)	0 / 50 (0.00%)
occurrences (all)	2	1	0
Nausea			
subjects affected / exposed	12 / 33 (36.36%)	7 / 29 (24.14%)	13 / 50 (26.00%)
occurrences (all)	22	9	26
Stomatitis			
subjects affected / exposed	5 / 33 (15.15%)	1 / 29 (3.45%)	5 / 50 (10.00%)
occurrences (all)	20	1	24
Rectal haemorrhage			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Toothache			
subjects affected / exposed	1 / 33 (3.03%)	1 / 29 (3.45%)	5 / 50 (10.00%)
occurrences (all)	1	1	5
Vomiting			
subjects affected / exposed	9 / 33 (27.27%)	2 / 29 (6.90%)	6 / 50 (12.00%)
occurrences (all)	13	2	14
Oral disorder			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Gastritis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 29 (6.90%)	1 / 50 (2.00%)
occurrences (all)	0	2	1
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	8 / 33 (24.24%)	1 / 29 (3.45%)	10 / 50 (20.00%)
occurrences (all)	9	2	11
Dermatitis contact			

subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	2 / 33 (6.06%)	1 / 29 (3.45%)	4 / 50 (8.00%)
occurrences (all)	3	1	4
Hyperhidrosis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	3 / 50 (6.00%)
occurrences (all)	1	0	3
Ingrown hair			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Nail disorder			
subjects affected / exposed	3 / 33 (9.09%)	0 / 29 (0.00%)	2 / 50 (4.00%)
occurrences (all)	3	0	2
Pain of skin			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	4 / 50 (8.00%)
occurrences (all)	1	0	10
Rash			
subjects affected / exposed	3 / 33 (9.09%)	1 / 29 (3.45%)	4 / 50 (8.00%)
occurrences (all)	3	2	5
Skin disorder			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Skin swelling			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Swelling face			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Night sweats			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	2 / 50 (4.00%)
occurrences (all)	2	0	2
Erythema			

subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	3 / 50 (6.00%)
occurrences (all)	0	2	3
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	2 / 33 (6.06%)	2 / 29 (6.90%)	2 / 50 (4.00%)
occurrences (all)	2	2	2
Pollakiuria			
subjects affected / exposed	4 / 33 (12.12%)	1 / 29 (3.45%)	0 / 50 (0.00%)
occurrences (all)	5	1	0
Incontinence			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Thyroid mass			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 33 (27.27%)	5 / 29 (17.24%)	13 / 50 (26.00%)
occurrences (all)	23	8	26
Back pain			
subjects affected / exposed	6 / 33 (18.18%)	5 / 29 (17.24%)	11 / 50 (22.00%)
occurrences (all)	9	6	16
Bone pain			
subjects affected / exposed	6 / 33 (18.18%)	2 / 29 (6.90%)	4 / 50 (8.00%)
occurrences (all)	11	2	4
Joint swelling			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Muscle spasms			
subjects affected / exposed	1 / 33 (3.03%)	2 / 29 (6.90%)	4 / 50 (8.00%)
occurrences (all)	1	2	5
Musculoskeletal chest pain			

subjects affected / exposed	1 / 33 (3.03%)	2 / 29 (6.90%)	2 / 50 (4.00%)
occurrences (all)	1	2	3
Musculoskeletal pain			
subjects affected / exposed	3 / 33 (9.09%)	3 / 29 (10.34%)	6 / 50 (12.00%)
occurrences (all)	10	3	9
Myalgia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	4 / 50 (8.00%)
occurrences (all)	4	0	4
Osteonecrosis of jaw			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
Pain in extremity			
subjects affected / exposed	3 / 33 (9.09%)	1 / 29 (3.45%)	6 / 50 (12.00%)
occurrences (all)	5	1	13
Spinal pain			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	4 / 50 (8.00%)
occurrences (all)	1	0	4
Temporomandibular joint syndrome			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Arthropathy			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Muscular weakness			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Limb discomfort			
subjects affected / exposed	0 / 33 (0.00%)	2 / 29 (6.90%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Osteoporosis			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	3 / 50 (6.00%)
occurrences (all)	2	0	4

Bronchitis			
subjects affected / exposed	3 / 33 (9.09%)	1 / 29 (3.45%)	0 / 50 (0.00%)
occurrences (all)	5	1	0
Cystitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	3 / 50 (6.00%)
occurrences (all)	0	0	3
Diverticulitis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 29 (6.90%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Ear infection			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences (all)	2	0	1
Gastroenteritis viral			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Herpes zoster			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Influenza			
subjects affected / exposed	4 / 33 (12.12%)	1 / 29 (3.45%)	4 / 50 (8.00%)
occurrences (all)	5	1	5
Localised infection			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	7 / 33 (21.21%)	3 / 29 (10.34%)	5 / 50 (10.00%)
occurrences (all)	8	4	8
Oral herpes			
subjects affected / exposed	3 / 33 (9.09%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	5	0	0
Pneumonia			
subjects affected / exposed	0 / 33 (0.00%)	2 / 29 (6.90%)	1 / 50 (2.00%)
occurrences (all)	0	2	1
Sinusitis			
subjects affected / exposed	1 / 33 (3.03%)	2 / 29 (6.90%)	1 / 50 (2.00%)
occurrences (all)	1	2	2

Skin infection			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	3	0	0
Tooth infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Upper respiratory tract infection			
subjects affected / exposed	8 / 33 (24.24%)	2 / 29 (6.90%)	4 / 50 (8.00%)
occurrences (all)	11	2	4
Urinary tract infection			
subjects affected / exposed	6 / 33 (18.18%)	3 / 29 (10.34%)	3 / 50 (6.00%)
occurrences (all)	12	3	3
Herpes simplex			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	2	0	0
Gingivitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 50 (2.00%)
occurrences (all)	0	0	1
Rhinitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Cellulitis			
subjects affected / exposed	2 / 33 (6.06%)	1 / 29 (3.45%)	0 / 50 (0.00%)
occurrences (all)	2	2	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	9 / 33 (27.27%)	2 / 29 (6.90%)	8 / 50 (16.00%)
occurrences (all)	9	2	9
Diabetes mellitus			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Hyperkalaemia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			

subjects affected / exposed	2 / 33 (6.06%)	1 / 29 (3.45%)	2 / 50 (4.00%)
occurrences (all)	3	1	2
Hypokalaemia			
subjects affected / exposed	1 / 33 (3.03%)	1 / 29 (3.45%)	1 / 50 (2.00%)
occurrences (all)	1	1	1
Hyponatraemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 50 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	3 / 50 (6.00%)
occurrences (all)	0	1	3
Dehydration			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Ph2P2 (Letrozole)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	35 / 48 (72.92%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Tumour pain			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Hot flush			
subjects affected / exposed	6 / 48 (12.50%)		
occurrences (all)	6		
Hypertension			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	5		
Lymphoedema			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Peripheral vascular disorder			

subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Phlebitis			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	4		
Chest pain			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Facial pain			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Fatigue			
subjects affected / exposed	11 / 48 (22.92%)		
occurrences (all)	15		
Influenza like illness			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Mucosal inflammation			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Non-cardiac chest pain			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Oedema peripheral			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	5		
Pain			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Pyrexia			

subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Temperature intolerance			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Chills			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Face oedema			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Peripheral swelling			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Breast discomfort			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Breast pain			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Pelvic pain			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	3		
Vaginal discharge			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Vulvovaginal pruritus			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	9		
Dyspnoea			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	5		
Epistaxis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Nasal congestion			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Oropharyngeal pain			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Sinus congestion			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Snoring			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Lower respiratory tract congestion			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Depression			

subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Insomnia				
subjects affected / exposed	3 / 48 (6.25%)			
occurrences (all)	4			
Mood altered				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Sleep disorder				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Aspartate aminotransferase increased				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Blood alkaline phosphatase increased				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Blood creatinine increased				
subjects affected / exposed	2 / 48 (4.17%)			
occurrences (all)	2			
Blood phosphorus decreased				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Gamma-glutamyltransferase increased				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Red blood cell count decreased				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Weight decreased				

subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
White blood cell count decreased			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Weight increased			
subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	7		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Thermal burn			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Fall			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Periorbital haemorrhage			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Skin abrasion			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Skin injury			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Dysgeusia			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Headache			

subjects affected / exposed	5 / 48 (10.42%)		
occurrences (all)	6		
Memory impairment			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Neuropathy peripheral			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Paraesthesia			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Sciatica			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Sinus headache			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Syncope			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Radicular pain			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	7		
Leukopenia			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	3		
Lymphopenia			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		

Neutropenia			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	19		
Thrombocytopenia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Ear pain			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Lacrimation increased			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Visual impairment			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Cataract			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Presbyopia			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	2		
Abdominal distension			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Abdominal pain			

subjects affected / exposed	4 / 48 (8.33%)			
occurrences (all)	4			
Abdominal pain upper				
subjects affected / exposed	3 / 48 (6.25%)			
occurrences (all)	3			
Constipation				
subjects affected / exposed	3 / 48 (6.25%)			
occurrences (all)	5			
Diarrhoea				
subjects affected / exposed	7 / 48 (14.58%)			
occurrences (all)	8			
Dry mouth				
subjects affected / exposed	2 / 48 (4.17%)			
occurrences (all)	2			
Dyspepsia				
subjects affected / exposed	2 / 48 (4.17%)			
occurrences (all)	2			
Flatulence				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Food poisoning				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Chronic gastritis				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Gingival pain				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Mouth ulceration				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Nausea				

subjects affected / exposed	4 / 48 (8.33%)		
occurrences (all)	4		
Stomatitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Rectal haemorrhage			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Oral disorder			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Gastritis			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Dermatitis contact			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Dry skin			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Hyperhidrosis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Ingrown hair			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		

Nail disorder subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		
Pain of skin subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0		
Pruritus subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 3		
Rash subjects affected / exposed occurrences (all)	3 / 48 (6.25%) 3		
Skin disorder subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0		
Skin swelling subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0		
Swelling face subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0		
Night sweats subjects affected / exposed occurrences (all)	1 / 48 (2.08%) 1		
Erythema subjects affected / exposed occurrences (all)	2 / 48 (4.17%) 4		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0		
Pollakiuria subjects affected / exposed occurrences (all)	0 / 48 (0.00%) 0		
Incontinence			

subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Thyroid mass			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	9 / 48 (18.75%)		
occurrences (all)	21		
Back pain			
subjects affected / exposed	8 / 48 (16.67%)		
occurrences (all)	9		
Bone pain			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	2		
Joint swelling			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Muscle spasms			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	3		
Musculoskeletal pain			
subjects affected / exposed	2 / 48 (4.17%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Osteonecrosis of jaw			

subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Pain in extremity			
subjects affected / exposed	6 / 48 (12.50%)		
occurrences (all)	7		
Spinal pain			
subjects affected / exposed	3 / 48 (6.25%)		
occurrences (all)	3		
Temporomandibular joint syndrome			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Arthropathy			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Muscular weakness			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Limb discomfort			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Osteoporosis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		
Bronchitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Diverticulitis			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		

Ear infection				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Gastroenteritis viral				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Herpes zoster				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Influenza				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Localised infection				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Nasopharyngitis				
subjects affected / exposed	4 / 48 (8.33%)			
occurrences (all)	7			
Oral herpes				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Pneumonia				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Sinusitis				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Skin infection				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Tooth infection				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Upper respiratory tract infection				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			

Urinary tract infection				
subjects affected / exposed	2 / 48 (4.17%)			
occurrences (all)	2			
Herpes simplex				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Gingivitis				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Rhinitis				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Cellulitis				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	3			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	3 / 48 (6.25%)			
occurrences (all)	3			
Diabetes mellitus				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Hyperkalaemia				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Hypocalcaemia				
subjects affected / exposed	1 / 48 (2.08%)			
occurrences (all)	1			
Hypokalaemia				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Hyponatraemia				
subjects affected / exposed	0 / 48 (0.00%)			
occurrences (all)	0			
Hyperuricaemia				

subjects affected / exposed	1 / 48 (2.08%)		
occurrences (all)	1		
Dehydration			
subjects affected / exposed	0 / 48 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 July 2009	Due to the possible effect of administration of a high-fat meal on PD 0332991 exposure, a new guideline was added for subjects to fast from 1 hour before to 2 hours after administration of PD 0332991 on non-serial PK days. The list of prohibited drugs that might interact with CYP3A4 was updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported