



Clinical trial results:

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

Summary

EudraCT number	2012-004601-27
Trial protocol	DE BE IE FR GB ES HU IT PL
Global end of trial date	09 November 2023

Results information

Result version number	v2 (current)
This version publication date	06 November 2024
First version publication date	16 December 2016
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	A5481008
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01740427
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 May 2024
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	09 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that the combination of PD-0332991 with letrozole was superior to placebo plus letrozole in prolonging progression-free survival (PFS) in postmenopausal women with estrogen receptor (ER)-positive/ human epidermal growth factor receptor 2 (HER2)-negative ER (+)/HER2 (-) advanced breast cancer (ABC) who had not received any prior systemic anti-cancer therapies for their advanced/metastatic disease.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

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

Notes:

Population of trial subjects

Subjects enrolled per country

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

Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	United States: 197
Worldwide total number of subjects	666
EEA total number of subjects	190

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	404
From 65 to 84 years	255
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

A total of 666 participants were randomised at 239 centers in 19 countries.

Pre-assignment

Screening details:

The study consisted of a screening visit within 28 days before randomization, an active treatment phase, divided in cycles of 28 days each, and a post-treatment follow-up period during which survival and new anti-cancer therapy information was collected every 6 months (+/-7 days) from the last dose of study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Palbociclib Plus Letrozole

Arm description:

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

Arm type	Experimental
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2.5 mg orally, QD.

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

Dosage and administration details:

125 mg orally, QD for 21 days.

Arm title	Placebo Plus Letrozole
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Arm description:

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

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

Dosage and administration details:

2.5 mg orally, QD.

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

Dosage and administration details:

Orally, QD for 21 days.

Number of subjects in period 1	Palbociclib Plus Letrozole	Placebo Plus Letrozole
Started	444	222
Completed	0	0
Not completed	444	222
Adverse event, serious fatal	10	3
Adverse event, non-fatal	32	9
Objective Progression or Relapse	286	172
Participant Refused Continued Treatment	27	15
Site Terminated by Sponsor	1	-
Lost to follow-up	3	-
Global Deterioration of Health Status	28	12
Protocol deviation	5	3
Unspecified reasons	52	8

Baseline characteristics

Reporting groups

Reporting group title	Palbociclib Plus Letrozole
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Reporting group description:

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

Reporting group title	Placebo Plus Letrozole
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Reporting group description:

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

Reporting group values	Palbociclib Plus Letrozole	Placebo Plus Letrozole	Total
Number of subjects	444	222	666
Age categorical Units: Participants			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	263	141	404
From 65-84 years	176	79	255
85 years and over	5	2	7
Age Continuous Units: years			
arithmetic mean	61.7	60.6	
standard deviation	± 10.6	± 11.2	-
Sex: Female, Male Units: Participants			
Female	444	222	666
Male	0	0	0

End points

End points reporting groups

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

Primary: Progression-Free Survival (PFS) as Assessed by the Investigator

End point title	Progression-Free Survival (PFS) as Assessed by the Investigator
End point description: PFS=time from date of randomisation to date of 1st documentation of objective tumor progression per Response Evaluation Criteria In Solid Tumors Criteria (RECIST v1.1)/death in absence of progressive disease(PD).If tumor progression data include more than 1 date,1st date will be used.PFS=(1st event date–randomisation date+1)/30.4.Progression=using RECIST v1.1,20% increase in sum of diameters of target measurable lesions above smallest sum observed(over baseline if no decrease in sum is observed during therapy),with minimum absolute increase of 5mm,unequivocal progression of pre-existing non-target lesions,appearance of new lesions.Intent to treat(ITT)population/full analysis set:randomised participants,with drug assignment designated according to initial randomisation,regardless whether participants received medication/received different drug from that to which they were randomised.99999=value was not available as there wasn't enough PD events in treatment group at time of analysis.	
End point type	Primary
End point timeframe: From randomisation date to date of first documentation of progression OR death (up to approximately 2.5 years)	

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

Statistical analyses

Statistical analysis title	Palbociclib + Letrozole vs Placebo + Letrozole
Comparison groups	Palbociclib Plus Letrozole v Placebo Plus Letrozole

Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 ^[1]
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.576
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.463
upper limit	0.718

Notes:

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

Secondary: Objective Response as Assessed by the Investigator

End point title	Objective Response as Assessed by the Investigator
End point description:	
OR defined as overall complete response (CR)/partial response (PR) according to RECIST v1.1. Objective Response Rate (ORR) is defined as proportion of participants with CR/PR relative to all randomised participants with measurable disease at baseline. Participants who do not have on-study radiographic tumor re-evaluation, who received anti-tumor treatment, or who died, progressed/ dropped out for any reason prior to reaching CR/PR were counted as non-responders in assessment of ORR. Per RECIST v1.1, CR: Complete disappearance of target lesions with exception of nodal disease. All target nodes must decrease to normal size (short axis <10mm). PR: ≥30% decrease under baseline of sum of diameters of all target measurable lesions. Short diameter is used in sum for target nodes, while longest diameter is used in sum for all other target lesions. Stable Disease: neither sufficient shrinkage nor increase to qualify for disease progression. ITT population or full analysis set was analysed.	
End point type	Secondary
End point timeframe:	
From randomisation until end of treatment (up to approximately 2.5 years)	

End point values	Palbociclib Plus Letrozole	Placebo Plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	222		
Units: Percentage of participants				
number (confidence interval 95%)	46.4 (41.7 to 51.2)	38.3 (31.9 to 45.0)		

Statistical analyses

Statistical analysis title	Palbociclib +Letrozole vs Placebo + Letrozole
Statistical analysis description:	
Stratified analysis: Stratified by disease site (visceral vs non-visceral) per randomization.	
Comparison groups	Palbociclib Plus Letrozole v Placebo Plus Letrozole

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

Notes:

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

Secondary: Objective Response: Participants With Measurable Disease at Baseline as Assessed by the Investigator

End point title	Objective Response: Participants With Measurable Disease at Baseline as Assessed by the Investigator
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End point description:

OR is defined as overall CR or PR according to RECIST v1.1. ORR is defined as proportion of participants with CR or PR relative to all randomised participants with measurable disease at baseline. Participants who do not have on-study radiographic tumor re-evaluation, who received anti-tumor treatment, or who died, progressed/ dropped out for any reason prior to reaching a CR or PR were counted as non-responders in the assessment of ORR. Per RECIST v1.1, CR: Complete disappearance of target lesions with exception of nodal disease. All target nodes must decrease to normal size (short axis <10mm). PR: $\geq 30\%$ decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in sum for target nodes, while the longest diameter is used in the sum for all other target lesions. Stable Disease (SD): neither sufficient shrinkage nor increase to qualify for disease progression. ITT population or full analysis set was analysed.

End point type	Secondary
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End point timeframe:

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

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

Statistical analyses

Statistical analysis title	Palbociclib + Letrozole vs Placebo + Letrozole
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Statistical analysis description:

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

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

Notes:

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

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

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

DC = overall CR, PR, stable disease (SD) ≥ 24 weeks according to RECIST version 1.1. Disease Control Rate (DCR) = participants with CR, PR, or SD ≥ 24 weeks relative to all randomised participants. Participants who don't have on-study radiographic tumor reevaluation, who received anti-tumor treatment, best response of SD ≥ 24 weeks, who died, progressed, dropped out for any reason prior to achieving reaching CR/PR and best response of SD ≥ 24 weeks was counted as non-responders in DCR. Per RECIST v1.1, CR: Complete disappearance of target lesions with exception of nodal disease. All target nodes must decrease to normal size (short axis $< 10\text{mm}$). PR: $\geq 30\%$ decrease under baseline of sum of diameters of all target measurable lesions. Short diameter is used in sum for target nodes, while longest diameter is used in sum for all other target lesions. SD: neither sufficient shrinkage nor increase to qualify for disease progression. ITT population or full analysis set was analysed.

End point type	Secondary
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End point timeframe:

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

End point values	Palbociclib Plus Letrozole	Placebo Plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	222		
Units: Percentage of participants				
number (confidence interval 95%)	85.8 (82.2 to 88.9)	71.2 (64.7 to 77.0)		

Statistical analyses

Statistical analysis title	Palbociclib + Letrozole vs Placebo + Letrozole
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Statistical analysis description:

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

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

Notes:

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

Secondary: Duration of Response (DR)

End point title	Duration of Response (DR)
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End point description:

DR is defined as time from first documentation of objective tumor response (CR or PR) to first documentation of disease progression or to death due to any cause, whichever occurs first. If tumor progression data included more than 1 date, first date will be used. DR was calculated as [date response ended (i.e. date of PD or death) – first CR or PR date + 1]/30.4. DR would only be calculated for the subgroup of participants with an objective tumor response. Per RECIST v1.1, CR: Complete disappearance of target lesions with exception of nodal disease. All target nodes must decrease to normal size (short axis <10mm). PR: ≥30% decrease under baseline of sum of diameters of all target measurable lesions. Short diameter is used in sum for target nodes, while longest diameter is used in sum for all other target lesions. Stable Disease (SD): neither sufficient shrinkage nor increase to qualify for disease progression. ITT population or full analysis set was analysed.

End point type	Secondary
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End point timeframe:

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

End point values	Palbociclib Plus Letrozole	Placebo Plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	206	85		
Units: Months				
median (confidence interval 95%)	20.1 (19.3 to 28.0)	16.7 (13.8 to 22.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS by Tumor tissue Biomarkers Status, Including Genes (eg, Copy Numbers of CCND1, CDKN2A), Proteins (eg, Ki67, pRb), and RNA Expression (eg, cdk4, cdk6)

End point title	PFS by Tumor tissue Biomarkers Status, Including Genes (eg, Copy Numbers of CCND1, CDKN2A), Proteins (eg, Ki67, pRb), and RNA Expression (eg, cdk4, cdk6)
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End point description:

PFS by biomarker status by Investigator assessment. Progression by RECIST v1.1 = 20% increase in sum of longest diameter of target lesions, or measurable increase in non-target lesion, or appearance of new lesions. Positive = H-Score ≥ 1 and negative = H-Score < 1 . H-Score was calculated as sum of the % of cells at each level of staining intensity (0, 1+, 2+, and 3+) multiplied by staining intensity value: H-Score = (% at 0)*0 + (% at 1+)*1 + (% at 2+)*2 + (% at 3+)*3. H-Score values range from 0 to 300. ER stands for estrogen receptor and Rb stands for retinoblastoma susceptibility gene product. ITT population or full analysis set included all participants who were randomised, with study medication, regardless of whether participants received study medication or received a different drug from that to which they were randomised. Here "Number Analysed (n)" signifies number of participants evaluable for specified rows. 99999 indicates insufficient number of participants with events.

End point type	Secondary
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End point timeframe:

From randomisation until end of treatment (up to approximately 24 Months)

End point values	Palbociclib Plus Letrozole	Placebo Plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	222		
Units: Months				
median (confidence interval 95%)				
ER Positive (n=338, 166)	24.9 (22.2 to 99999)	16.3 (12.9 to 19.1)		
ER Negative (n=40, 22)	15.6 (8.3 to 22.0)	5.4 (2.7 to 11.1)		
Rb Positive (n=345, 167)	24.2 (21.4 to 25.7)	13.7 (11.0 to 16.5)		
Rb Negative (n=29, 22)	99999 (11.4 to 99999)	18.5 (2.9 to 99999)		
Cyclin D1 Positive (n=370, 179)	24.8 (21.5 to 27.6)	13.8 (11.3 to 16.8)		
Cyclin D1 Negative (n=5, 10)	11.1 (2.2 to 23.9)	8.1 (0.4 to 99999)		
p16 Positive (n=305, 161)	24.8 (21.5 to 99999)	13.8 (11.1 to 16.8)		
p16 Negative (n=59, 25)	16.8 (11.1 to 24.9)	13.8 (8.1 to 99999)		
p16 H-Score<175 (n=341, 177)	23.7 (19.6 to 25.7)	13.8 (11.2 to 16.8)		
p16 H-Score ≥ 175 (n=23, 9)	24.2 (11.1 to 99999)	5.6 (1.5 to 19.1)		
Ki67 $\leq 20\%$ (n=216, 102)	27.6 (24.2 to 99999)	16.8 (13.7 to 22.0)		
Ki67 $>20\%$ (n=152, 83)	17.5 (13.8 to 22.0)	8.4 (5.6 to 13.6)		

Statistical analyses

Statistical analysis title	Palbociclib + Letrozole vs Placebo + Letrozole
Statistical analysis description:	
Statistical analysis for ER positive	
Comparison groups	Palbociclib Plus Letrozole v Placebo Plus Letrozole

Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.571
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.443
upper limit	0.737

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

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

Statistical analysis title	Palbociclib + Letrozole vs Placebo + Letrozole
Statistical analysis description:	
Statistical analysis for Rb Negative	
Comparison groups	Palbociclib Plus Letrozole v Placebo Plus Letrozole
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3237
Method	Unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.675
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.308
upper limit	1.481

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

Statistical analysis title	Palbociclib + Letrozole vs Placebo + Letrozole
Statistical analysis description:	
Statistical analysis for Cyclin D1 Negative	
Comparison groups	Palbociclib Plus Letrozole v Placebo Plus Letrozole

Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.9964
Method	Unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.997
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.287
upper limit	3.461

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

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

Statistical analysis title	Palbociclib + Letrozole vs Placebo + Letrozole
Statistical analysis description:	
Statistical analysis for p16 HScore<175	
Comparison groups	Palbociclib Plus Letrozole v Placebo Plus Letrozole
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.581
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.455
upper limit	0.742

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

Statistical analysis title	Palbociclib + Letrozole vs Placebo + Letrozole
Statistical analysis description:	
Statistical analysis for Ki67 <= 20%	
Comparison groups	Palbociclib Plus Letrozole v Placebo Plus Letrozole

Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0002
Method	Unstratified log-rank test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.379
upper limit	0.742

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

Secondary: Corrected QT interval (QTc) Time-Matched Change From Baseline on Cycle 1 Day 14

End point title	Corrected QT interval (QTc) Time-Matched Change From Baseline on Cycle 1 Day 14
End point description: <p>Triplicate 12-lead ECG measurements (each recording separated by approximately 2 minutes) were performed and sent to a central laboratory for blinded manual adjudication. The average was calculated. The time corresponding to beginning of depolarisation to repolarisation of the ventricles (QT interval) was adjusted for RR interval using QT and RR from each ECG by Fridericia's formula ($QTcF = QT$ divided by cube root of RR), by Bazette's formula ($QTcB = QT$ divided by square root of RR) and corrected QT interval according to study-specific criteria (QTcS). Time-matched change from baseline values were reported for QTc analysis population. QTc analysis set is a subset of as treated (AT) population who were in Group 1; their QTc was used to study the effect of palbociclib on QT interval via serial triplicate ECGs with PK draws; and who had ≥ 1 pair of time-matched Day 0 and palbociclib postdose (Cycle1 Day 14) measurements.</p>	
End point type	Secondary
End point timeframe: <p>Time-matched triplicate ECGs were collected at 0 (predose), 2, 4, 6 and 8 hours on Day 0 and on Cycle1 Day 14</p>	

End point values	Palbociclib Plus Letrozole	Placebo Plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	76	47		
Units: Millisecond (msec)				
least squares mean (confidence interval 90%)				
QTcS at 0 hour	0.80 (-1.67 to 3.26)	2.95 (-0.19 to 6.10)		
QTcS at 2 hour	3.32 (0.79 to 5.85)	1.65 (-1.48 to 4.78)		
QTcS at 4 hour	2.76 (0.23 to 5.30)	1.74 (-1.39 to 4.87)		
QTcS at 6 hour	4.49 (1.96 to 7.02)	0.72 (-2.41 to 3.85)		
QTcS at 8 hour	0.94 (-1.60 to 3.48)	3.14 (0.01 to 6.27)		
QTcF at 0 hour	1.10 (-1.39 to 3.58)	3.06 (-0.11 to 6.23)		
QTcF at 2 hour	3.68 (1.12 to 6.23)	1.73 (-1.43 to 4.88)		
QTcF at 4 hour	2.86 (0.31 to 5.41)	1.54 (-1.62 to 4.70)		
QTcF at 6 hour	4.57 (2.01 to 7.12)	0.71 (-2.44 to 3.87)		
QTcF at 8 hour	1.21 (-1.36 to 3.77)	2.84 (-0.31 to 6.00)		
QTcB at 0 hour	-0.11 (-2.83 to 2.61)	2.78 (-0.69 to 6.25)		
QTcB at 2 hour	1.46 (-1.34 to 4.25)	0.83 (-2.63 to 4.28)		
QTcB at 4 hour	2.58 (-0.22 to 5.38)	2.47 (-0.98 to 5.92)		
QTcB at 6 hour	4.03 (1.24 to 6.83)	0.53 (-2.92 to 3.99)		
QTcB at 8 hour	-0.17 (-2.98 to 2.64)	4.14 (0.69 to 7.59)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Corrected QT interval (QTc)

End point title	Percentage of Participants With Corrected QT interval (QTc)
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End point description:

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

received at least 1 dose of study medication, with treatment assignments designated according to actual study treatment received.

End point type	Secondary
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End point timeframe:

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

End point values	Palbociclib Plus Letrozole	Placebo Plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	441	220		
Units: Percentage of participants				
number (not applicable)				
Maximum QTcS <450 msec	80.5	85.9		
Maximum QTcS 450-<480 msec	17.9	11.8		
Maximum QTcS 480-<500 msec	1.1	2.3		
Maximum QTcS ≥500 msec	0.5	0		
Maximum QTcF <450 msec	85.9	89.5		
Maximum QTcF 450-<480 msec	12.2	9.5		
Maximum QTcF 480-<500 msec	1.6	0.9		
Maximum QTcF ≥500 msec	0.2	0		
Maximum QTcB <450 msec	64.9	69.1		
Maximum QTcB 450-<480 msec	32.2	27.3		
Maximum QTcB 480-<500 msec	2.3	3.2		
Maximum QTcB ≥500 msec	0.7	0.5		
Maximum QTcS Change <30 msec	92.7	94.5		
Maximum QTcS 30≤Change <60 msec	6.6	5.5		
Maximum QTcS Change≥60 msec	0.7	0		
Maximum QTcF Change <30 msec	91.6	93.6		
Maximum QTcF 30≤Change <60 msec	7.9	6.4		
Maximum QTcF Change≥60 msec	0.5	0		
Maximum QTcB Change <30 msec	88.9	91.4		
Maximum QTcB 30≤Change <60 msec	10.2	8.2		
Maximum QTcB Change≥60 msec	0.9	0.5		

Statistical analyses

No statistical analyses for this end point

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

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

FACT is modular approach to assess participant health-related quality of life using 'core' set of questions (FACT-G) as well as cancer site-specific module. FACT-G is 27-item compilation of general questions divided into 4 domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being. FACT-B consisted of FACT-G (27-item) and breast-specific module: 10-item

instrument designed to assess participant concerns relating to breast cancer. For all questions, participants were asked to respond to five-level scale where 0=not at all, 1=little bit, 2=somewhat, 3=quite a bit, and 4=very much. FACT-B total score = Physical Well-Being + Social/Family Well-Being + Emotional Well-Being + Functional Well-Being + Breast Cancer Subscale. As each item ranges from 0-4, the range of possible scores is 0-144, with 0=worst possible score and 144=best. PRO Analysis Set is subset of ITT participants, who had both baseline and at least one follow-up PRO assessment.

End point type	Secondary
End point timeframe:	
From Baseline up to 2.5 years	

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

Statistical analyses

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

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

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

The EuroQol EQ-5D is a 6-item instrument designed to assess health status in terms of a single index value or utility score. It contains 5 descriptors of current health state (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) with each dimension having 3 levels of function (1=no problem, 2=some problem, and 3=extreme problem). The scores on the 5 descriptors are summarised to create a single summary score. An overall utility score is calculated based on these domains, with a range score from 0 (worse health scenario) to a maximum of 1.0 (best health scenario). Patient Reported Outcome (PRO) Analysis Set was a subset of ITT participants, who had both baseline and at least one follow-up PRO assessment.

End point type	Secondary
End point timeframe:	
From Baseline up to 2.5 years	

End point values	Palbociclib Plus Letrozole	Placebo Plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	437	218		
Units: Units on a scale				
arithmetic mean (confidence interval 95%)	0.014 (0.00 to 0.03)	-0.010 (-0.03 to 0.01)		

Statistical analyses

Statistical analysis title	Palbociclib + Letrozole vs Placebo + Letrozole
Comparison groups	Palbociclib Plus Letrozole v Placebo Plus Letrozole
Number of subjects included in analysis	655
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0925
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	0.023
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.004
upper limit	0.051

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

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

Summary of plasma palbociclib within-participant mean steady-state trough concentrations. Pharmacokinetic analysis set was a subset of AT participants, who were treated with Palbociclib and had at least one measured plasma concentration. Here "number of participants analysed (n)" signifies number of participants evaluable for specified rows.

End point type	Secondary
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End point timeframe:

0 hour (predose) on Day 14 of cycles 1 and 2

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint was summarized for specified reporting arms only.

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

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs): All Causalities

End point title	Percentage of Participants With Treatment-Emergent Adverse Events (TEAEs): All Causalities
End point description:	
<p>AE: any untoward medical occurrence in clinical investigation participant administered product/medical device; event need not necessarily have causal relationship with treatment/usage. SAE: any untoward medical occurrence at any dose resulted in death; life-threatening; required hospitalisation; resulted in persistent/significant disability/congenital anomaly/birth defect. TEAE: events that occurred between first dose of study drug up to 28 days after last dose that were absent before treatment/that worsened relative to pretreatment state. Severity was graded by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.0 as Grade 1=mild, Grade 2=moderate, Grade 3=severe, Grade 4=life-threatening, Grade 5=death related to AE. Discontinuation included permanent, temporary discontinuation and dose reduction due to AEs. AT population=participants who received 1 dose of study medication, with treatment assignments designated according to actual study treatment received.</p>	
End point type	Secondary
End point timeframe:	
From date of randomization up to 28 days after last dose of study drug (final analysis till study completion, approximately up to 10.51 years)	

End point values	Palbociclib Plus Letrozole	Placebo Plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	222		
Units: Percentage of participants				
number (not applicable)				
Participants with AEs	99.1	96.4		
Participants with SAEs	28.2	17.1		
Participants with Grade 3 or 4 AEs	83.1	30.2		
Participants with Grade 5 AEs	3.6	2.3		
Permanently discontinued study due to AEs	4.1	2.3		
Permanently disc. palbociclib/placebo due to AEs	14.4	6.3		
Permanently discontinued letrozole due to AEs	9.2	5.9		

Temporarily disc. palbociclib/placebo due to AEs	79.7	17.1		
Temporarily discontinued letrozole due to AEs	23.0	11.3		
With palbociclib/placebo dose reduction due to AEs	41.9	2.3		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS): Primary Analysis

End point title	Overall Survival (OS): Primary Analysis
End point description:	
OS was defined as the time from date of randomisation to date of death due to any cause. Participants without survival data beyond the date of their last follow-up were censored on the last date they were known to be alive. Data for this endpoint was reported at primary analysis. ITT population or full analysis set included all participants who were randomised, with study medication, regardless of whether participants received study medication or received a different drug from that to which they were randomised.	
End point type	Secondary
End point timeframe:	
From date of randomisation until death due to any cause or censored (assessed up to data cut-off date of 15-Nov-2021, approximately 8.7 years)	

End point values	Palbociclib Plus Letrozole	Placebo Plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	222		
Units: Months				
median (confidence interval 95%)	53.9 (49.8 to 60.8)	51.2 (43.7 to 58.9)		

Statistical analyses

Statistical analysis title	Palbociclib + Letrozole vs Placebo + Letrozole
Comparison groups	Palbociclib Plus Letrozole v Placebo Plus Letrozole
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.33775 ^[6]
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.956

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.777
upper limit	1.177

Notes:

[6] - 1-sided p-value from the stratified log-rank test.

Secondary: Overall Survival (OS): Final Analysis

End point title	Overall Survival (OS): Final Analysis
End point description:	
OS was defined as the time from date of randomisation to date of death due to any cause. Participants without survival data beyond the date of their last follow-up were censored on the last date they were known to be alive. Data for this endpoint was reported at final analysis. ITT population or full analysis set included all participants who were randomised, with study medication, regardless of whether participants received study medication or received a different drug from that to which they were randomised.	
End point type	Secondary
End point timeframe:	
From date of randomisation until death due to any cause or censored (final analysis till study completion, approximately up to 10.51 years)	

End point values	Palbociclib Plus Letrozole	Placebo Plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	222		
Units: Months				
median (confidence interval 95%)	53.8 (49.8 to 59.2)	49.8 (42.3 to 56.4)		

Statistical analyses

Statistical analysis title	Palbociclib + Letrozole vs Placebo + Letrozole
Comparison groups	Palbociclib Plus Letrozole v Placebo Plus Letrozole
Number of subjects included in analysis	666
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.208706 ^[7]
Method	Stratified Log Rank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.921
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.755
upper limit	1.124

Notes:

[7] - 1-sided p-value from the stratified log-rank test.

Secondary: Survival Probability at 1 Year, 2 Year and 3 Year

End point title	Survival Probability at 1 Year, 2 Year and 3 Year
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End point description:

One, two or three-year survival probability was defined as the probability of survival 1 year, 2 or 3 years after the date of randomisation. The survival probability was estimated using the Kaplan-Meier method and 2-sided 95% confidence interval (CI) was calculated using the product limit method. ITT population or full analysis set included all participants who were randomised, with study medication, regardless of whether participants received study medication or received a different drug from that to which they were randomised.

End point type	Secondary
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End point timeframe:

1, 2 and 3 years after randomisation

End point values	Palbociclib Plus Letrozole	Placebo Plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	222		
Units: Percent probability				
number (confidence interval 95%)				
1 year survival probability	92.7 (89.8 to 94.7)	94.9 (91.0 to 97.2)		
2 year survival probability	78.4 (74.1 to 82.0)	82.5 (76.6 to 87.0)		
3 year survival probability	69.8 (65.1 to 73.9)	65.0 (58.0 to 71.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Laboratory Abnormalities by Maximum Common Terminology Criteria for Adverse Events (CTCAE) Grade

End point title	Number of Participants with Laboratory Abnormalities by Maximum Common Terminology Criteria for Adverse Events (CTCAE) Grade
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End point description:

Laboratory abnormalities included anemia, hemoglobin increased, neutrophils (absolute), platelets, white blood cells, alanine aminotransferase (ALT), alkaline phosphatase, aspartate aminotransferase (AST), bilirubin (total), creatinine, hypercalcemia, hyperkalemia, hypermagnesemia, hyponatremia, hypoalbuminemia, hypocalcemia, hypokalemia, hypomagnesemia and hyponatremia. Laboratory abnormalities were graded by CTCAE version (v) 4.0 as Grade 1 = mild, Grade 2 = moderate, Grade 3 = severe and Grade 4 = life-threatening. Categories with at least 1 non-zero data values were reported. AT population included all participants who received at least 1 dose of study medication, with treatment assignments designated according to actual study treatment received. Here, "Number of Participants Analysed" signifies participants evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

From randomisation up to 28 days after last dose of study drug (assessed up to analysis date of 15-Nov-2021, approximately 8.7 years)

End point values	Palbociclib Plus Letrozole	Placebo Plus Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	444	221		
Units: Participants				
Anemia: Grade 1-2	328	90		
Anemia: Grade 3	30	6		
Hemoglobin Increased: Grade 1-2	14	25		
Hemoglobin Increased: Grade 3	1	0		
Neutrophils (Absolute): Grade 1-2	109	42		
Neutrophils (Absolute): Grade 3	254	2		
Neutrophils (Absolute): Grade 4	60	1		
Platelets: Grade 1-2	289	32		
Platelets: Grade 3	6	0		
Platelets: Grade 4	1	0		
White Blood Cells: Grade 1-2	248	57		
White Blood Cells: Grade 3	177	0		
White Blood Cells: Grade 4	6	0		
ALT: Grade 1-2	222	76		
ALT: Grade 3	16	0		
ALT: Grade 4	1	0		
Alkaline Phosphatase: Grade 1-2	174	95		
Alkaline Phosphatase: Grade 3	7	0		
AST: Grade 1-2	260	82		
AST: Grade 3	23	2		
Bilirubin (Total): Grade 1-2	33	11		
Bilirubin (Total): Grade 3	3	0		
Creatinine: Grade 1-2	418	201		
Creatinine: Grade 3	8	0		
Creatinine: Grade 4	2	0		
Hypercalcemia: Grade 1-2	111	54		
Hypercalcemia: Grade 3	1	2		
Hyperkalemia: Grade 1-2	118	51		
Hyperkalemia: Grade 3	6	1		
Hyperkalemia: Grade 4	2	0		
Hypermagnesemia: Grade 1-2	71	26		
Hypermagnesemia: Grade 3	9	6		
Hypermagnesemia: Grade 4	2	0		
Hypernatremia: Grade 1-2	94	35		
Hypernatremia: Grade 3	8	1		
Hypoalbuminemia: Grade 1-2	118	42		
Hypoalbuminemia: Grade 3	2	0		
Hypocalcemia: Grade 1-2	158	48		
Hypocalcemia: Grade 3	4	1		
Hypocalcemia: Grade 4	3	0		
Hypokalemia: Grade 1-2	105	32		
Hypokalemia: Grade 3	11	2		
Hypomagnesemia: Grade 1-2	127	41		

Hypomagnesemia: Grade 3	1	0		
Hypomagnesemia: Grade 4	2	0		
Hyponatremia: Grade 1-2	107	44		
Hyponatremia: Grade 3	11	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the date of randomization up to 28 days after last dose of study medication (final analysis till study completion, approximately up to 10.8 years)

Adverse event reporting additional description:

Same event may appear as non-SAE and SAE but are distinct events. Event may be an SAE in 1 participant and non-SAE in other, or participant may have both non-SAE and SAE. AT population included all participants who received at least 1 dose of study medication, with treatment assignments designated according to actual study treatment received.

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	26.1
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Reporting groups

Reporting group title	Placebo Plus Letrozole
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Reporting group description:

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

Reporting group title	Palbociclib Plus Letrozole
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Reporting group description:

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

Serious adverse events	Placebo Plus Letrozole	Palbociclib Plus Letrozole	
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 222 (17.12%)	125 / 444 (28.15%)	
number of deaths (all causes)	6	16	
number of deaths resulting from adverse events	5	16	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute leukaemia			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervix carcinoma			

subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial cancer			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 222 (0.00%)	3 / 444 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian germ cell teratoma benign			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papillary thyroid cancer			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder cancer			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Breast cancer metastatic			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastric cancer			

subjects affected / exposed	1 / 222 (0.45%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung adenocarcinoma			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 222 (0.45%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic arteriosclerosis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral embolism			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	1 / 222 (0.45%)	3 / 444 (0.68%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Disease progression			
subjects affected / exposed	0 / 222 (0.00%)	4 / 444 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 4	
General physical health deterioration			
subjects affected / exposed	1 / 222 (0.45%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 222 (0.45%)	3 / 444 (0.68%)	
occurrences causally related to treatment / all	1 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Puncture site pain			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 222 (0.00%)	4 / 444 (0.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			

subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incarcerated hernia			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Serositis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Mucosal inflammation			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Breast haematoma			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterovaginal prolapse			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 222 (0.45%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 222 (0.45%)	5 / 444 (1.13%)	
occurrences causally related to treatment / all	0 / 1	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 222 (1.35%)	4 / 444 (0.90%)	
occurrences causally related to treatment / all	2 / 5	1 / 5	
deaths causally related to treatment / all	1 / 1	0 / 1	
Respiratory failure			
subjects affected / exposed	1 / 222 (0.45%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Tracheomalacia			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			

subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchial hyperreactivity			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea exertional			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Emphysema			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrothorax			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Organic brain syndrome			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			

Device dislocation			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Neutrophil count decreased			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis radiation			

subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fracture displacement			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot fracture			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	1 / 222 (0.45%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound secretion			

subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract traumatic			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest injury			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poisoning			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			

subjects affected / exposed	1 / 222 (0.45%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Forearm fracture			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Pyloric stenosis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve stenosis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute myocardial infarction			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiogenic shock			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac arrest			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiovascular insufficiency			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiopulmonary failure			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Angina pectoris			

subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure chronic			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 222 (0.45%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			

subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Syncope			
subjects affected / exposed	0 / 222 (0.00%)	3 / 444 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia			
subjects affected / exposed	1 / 222 (0.45%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiparesis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 222 (0.45%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 222 (0.45%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cauda equina syndrome			

subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic cerebral infarction			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bell's palsy			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 222 (0.45%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 222 (0.00%)	8 / 444 (1.80%)	
occurrences causally related to treatment / all	0 / 0	7 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 222 (0.00%)	5 / 444 (1.13%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 222 (0.45%)	3 / 444 (0.68%)	
occurrences causally related to treatment / all	0 / 1	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blindness			

subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic retinopathy			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lens dislocation			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myopia			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dry age-related macular degeneration			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			

subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 222 (0.00%)	3 / 444 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical ileus			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestinal obstruction			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			

subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	2 / 222 (0.90%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal stenosis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic gastritis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stenosis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Biliary colic			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	0 / 222 (0.00%)	5 / 444 (1.13%)	
occurrences causally related to treatment / all	0 / 0	3 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydronephrosis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal tubular necrosis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stag horn calculus			
subjects affected / exposed	1 / 222 (0.45%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract obstruction			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia of malignancy			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue			

disorders			
Bone pain			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pathological fracture			
subjects affected / exposed	0 / 222 (0.00%)	3 / 444 (0.68%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in jaw			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiolitis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	5 / 222 (2.25%)	4 / 444 (0.90%)	
occurrences causally related to treatment / all	0 / 6	2 / 5	
deaths causally related to treatment / all	0 / 1	1 / 1	
Pyelonephritis			
subjects affected / exposed	0 / 222 (0.00%)	3 / 444 (0.68%)	
occurrences causally related to treatment / all	0 / 0	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 222 (0.45%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 222 (0.00%)	3 / 444 (0.68%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tracheobronchitis			

subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 222 (0.00%)	6 / 444 (1.35%)	
occurrences causally related to treatment / all	0 / 0	4 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Aspergillus infection			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
COVID-19			
subjects affected / exposed	2 / 222 (0.90%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Endocarditis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal infection			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinitis			

subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spontaneous bacterial peritonitis			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Suspected COVID-19			
subjects affected / exposed	1 / 222 (0.45%)	0 / 444 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viraemia			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	1 / 222 (0.45%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 222 (0.00%)	2 / 444 (0.45%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			

subjects affected / exposed	0 / 222 (0.00%)	1 / 444 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo Plus Letrozole	Palbociclib Plus Letrozole	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	209 / 222 (94.14%)	435 / 444 (97.97%)	
Vascular disorders			
Hot flush			
subjects affected / exposed	69 / 222 (31.08%)	101 / 444 (22.75%)	
occurrences (all)	73	132	
Hypertension			
subjects affected / exposed	24 / 222 (10.81%)	45 / 444 (10.14%)	
occurrences (all)	34	142	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	20 / 222 (9.01%)	63 / 444 (14.19%)	
occurrences (all)	25	106	
Pain			
subjects affected / exposed	20 / 222 (9.01%)	44 / 444 (9.91%)	
occurrences (all)	22	54	
Oedema peripheral			
subjects affected / exposed	19 / 222 (8.56%)	65 / 444 (14.64%)	
occurrences (all)	20	83	
Mucosal inflammation			
subjects affected / exposed	9 / 222 (4.05%)	49 / 444 (11.04%)	
occurrences (all)	11	101	
Fatigue			
subjects affected / exposed	65 / 222 (29.28%)	183 / 444 (41.22%)	
occurrences (all)	107	356	
Asthenia			
subjects affected / exposed	27 / 222 (12.16%)	86 / 444 (19.37%)	
occurrences (all)	44	169	

Influenza like illness subjects affected / exposed occurrences (all)	11 / 222 (4.95%) 13	36 / 444 (8.11%) 76	
Chest pain subjects affected / exposed occurrences (all)	7 / 222 (3.15%) 11	31 / 444 (6.98%) 41	
Chills subjects affected / exposed occurrences (all)	7 / 222 (3.15%) 9	24 / 444 (5.41%) 35	
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all)	10 / 222 (4.50%) 11	24 / 444 (5.41%) 26	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	48 / 222 (21.62%) 63	127 / 444 (28.60%) 231	
Dyspnoea subjects affected / exposed occurrences (all)	35 / 222 (15.77%) 43	80 / 444 (18.02%) 109	
Epistaxis subjects affected / exposed occurrences (all)	16 / 222 (7.21%) 29	43 / 444 (9.68%) 59	
Oropharyngeal pain subjects affected / exposed occurrences (all)	9 / 222 (4.05%) 11	50 / 444 (11.26%) 74	
Nasal congestion subjects affected / exposed occurrences (all)	8 / 222 (3.60%) 8	23 / 444 (5.18%) 27	
Rhinorrhoea subjects affected / exposed occurrences (all)	4 / 222 (1.80%) 4	23 / 444 (5.18%) 27	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	27 / 222 (12.16%) 32	45 / 444 (10.14%) 53	

Depression subjects affected / exposed occurrences (all)	21 / 222 (9.46%) 25	39 / 444 (8.78%) 46	
Insomnia subjects affected / exposed occurrences (all)	30 / 222 (13.51%) 44	73 / 444 (16.44%) 89	
Investigations			
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	13 / 222 (5.86%) 16	65 / 444 (14.64%) 174	
Aspartate aminotransferase increased subjects affected / exposed occurrences (all)	14 / 222 (6.31%) 22	64 / 444 (14.41%) 189	
Neutrophil count decreased subjects affected / exposed occurrences (all)	7 / 222 (3.15%) 9	106 / 444 (23.87%) 1166	
Platelet count decreased subjects affected / exposed occurrences (all)	1 / 222 (0.45%) 2	38 / 444 (8.56%) 203	
Weight decreased subjects affected / exposed occurrences (all)	10 / 222 (4.50%) 18	30 / 444 (6.76%) 53	
White blood cell count decreased subjects affected / exposed occurrences (all)	4 / 222 (1.80%) 7	83 / 444 (18.69%) 625	
Blood creatinine increased subjects affected / exposed occurrences (all)	8 / 222 (3.60%) 11	33 / 444 (7.43%) 109	
Injury, poisoning and procedural complications			
Fall subjects affected / exposed occurrences (all)	18 / 222 (8.11%) 21	60 / 444 (13.51%) 86	
Contusion subjects affected / exposed occurrences (all)	6 / 222 (2.70%) 6	24 / 444 (5.41%) 28	
Nervous system disorders			

Dizziness subjects affected / exposed occurrences (all)	34 / 222 (15.32%) 43	80 / 444 (18.02%) 122	
Dysgeusia subjects affected / exposed occurrences (all)	7 / 222 (3.15%) 9	37 / 444 (8.33%) 48	
Headache subjects affected / exposed occurrences (all)	62 / 222 (27.93%) 103	109 / 444 (24.55%) 197	
Paraesthesia subjects affected / exposed occurrences (all)	9 / 222 (4.05%) 10	26 / 444 (5.86%) 36	
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	23 / 222 (10.36%) 62	125 / 444 (28.15%) 471	
Thrombocytopenia subjects affected / exposed occurrences (all)	4 / 222 (1.80%) 5	64 / 444 (14.41%) 211	
Neutropenia subjects affected / exposed occurrences (all)	8 / 222 (3.60%) 16	308 / 444 (69.37%) 3898	
Leukopenia subjects affected / exposed occurrences (all)	2 / 222 (0.90%) 2	115 / 444 (25.90%) 798	
Eye disorders			
Lacrimation increased subjects affected / exposed occurrences (all)	2 / 222 (0.90%) 5	33 / 444 (7.43%) 46	
Cataract subjects affected / exposed occurrences (all)	7 / 222 (3.15%) 8	28 / 444 (6.31%) 37	
Dry eye subjects affected / exposed occurrences (all)	10 / 222 (4.50%) 10	28 / 444 (6.31%) 32	
Vision blurred			

subjects affected / exposed	7 / 222 (3.15%)	23 / 444 (5.18%)	
occurrences (all)	7	27	
Gastrointestinal disorders			
Dry mouth			
subjects affected / exposed	12 / 222 (5.41%)	28 / 444 (6.31%)	
occurrences (all)	19	38	
Diarrhoea			
subjects affected / exposed	51 / 222 (22.97%)	136 / 444 (30.63%)	
occurrences (all)	95	372	
Constipation			
subjects affected / exposed	36 / 222 (16.22%)	105 / 444 (23.65%)	
occurrences (all)	46	149	
Abdominal pain upper			
subjects affected / exposed	20 / 222 (9.01%)	41 / 444 (9.23%)	
occurrences (all)	31	57	
Abdominal distension			
subjects affected / exposed	14 / 222 (6.31%)	21 / 444 (4.73%)	
occurrences (all)	16	32	
Dyspepsia			
subjects affected / exposed	29 / 222 (13.06%)	52 / 444 (11.71%)	
occurrences (all)	36	65	
Abdominal pain			
subjects affected / exposed	15 / 222 (6.76%)	67 / 444 (15.09%)	
occurrences (all)	23	96	
Vomiting			
subjects affected / exposed	37 / 222 (16.67%)	80 / 444 (18.02%)	
occurrences (all)	75	159	
Stomatitis			
subjects affected / exposed	15 / 222 (6.76%)	76 / 444 (17.12%)	
occurrences (all)	21	166	
Nausea			
subjects affected / exposed	59 / 222 (26.58%)	169 / 444 (38.06%)	
occurrences (all)	119	305	
Gastrooesophageal reflux disease			
subjects affected / exposed	8 / 222 (3.60%)	37 / 444 (8.33%)	
occurrences (all)	11	47	

Toothache subjects affected / exposed occurrences (all)	7 / 222 (3.15%) 8	23 / 444 (5.18%) 29	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	36 / 222 (16.22%) 37	150 / 444 (33.78%) 164	
Dry skin subjects affected / exposed occurrences (all)	16 / 222 (7.21%) 16	66 / 444 (14.86%) 99	
Pruritus subjects affected / exposed occurrences (all)	11 / 222 (4.95%) 18	49 / 444 (11.04%) 98	
Rash subjects affected / exposed occurrences (all)	24 / 222 (10.81%) 32	79 / 444 (17.79%) 137	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	89 / 222 (40.09%) 161	187 / 444 (42.12%) 359	
Back pain subjects affected / exposed occurrences (all)	52 / 222 (23.42%) 85	117 / 444 (26.35%) 192	
Bone pain subjects affected / exposed occurrences (all)	24 / 222 (10.81%) 33	45 / 444 (10.14%) 75	
Muscle spasms subjects affected / exposed occurrences (all)	13 / 222 (5.86%) 20	46 / 444 (10.36%) 63	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	11 / 222 (4.95%) 15	37 / 444 (8.33%) 57	
Myalgia subjects affected / exposed occurrences (all)	20 / 222 (9.01%) 34	65 / 444 (14.64%) 90	
Neck pain			

subjects affected / exposed	12 / 222 (5.41%)	27 / 444 (6.08%)	
occurrences (all)	16	39	
Pain in extremity			
subjects affected / exposed	41 / 222 (18.47%)	99 / 444 (22.30%)	
occurrences (all)	65	158	
Infections and infestations			
Oral herpes			
subjects affected / exposed	3 / 222 (1.35%)	31 / 444 (6.98%)	
occurrences (all)	8	69	
Sinusitis			
subjects affected / exposed	9 / 222 (4.05%)	30 / 444 (6.76%)	
occurrences (all)	19	61	
Upper respiratory tract infection			
subjects affected / exposed	26 / 222 (11.71%)	75 / 444 (16.89%)	
occurrences (all)	40	136	
Urinary tract infection			
subjects affected / exposed	20 / 222 (9.01%)	71 / 444 (15.99%)	
occurrences (all)	43	154	
Nasopharyngitis			
subjects affected / exposed	25 / 222 (11.26%)	95 / 444 (21.40%)	
occurrences (all)	39	174	
Influenza			
subjects affected / exposed	6 / 222 (2.70%)	24 / 444 (5.41%)	
occurrences (all)	7	29	
Rhinitis			
subjects affected / exposed	0 / 222 (0.00%)	24 / 444 (5.41%)	
occurrences (all)	0	27	
Bronchitis			
subjects affected / exposed	7 / 222 (3.15%)	27 / 444 (6.08%)	
occurrences (all)	11	35	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	21 / 222 (9.46%)	86 / 444 (19.37%)	
occurrences (all)	24	125	
Hypokalaemia			

subjects affected / exposed	8 / 222 (3.60%)	28 / 444 (6.31%)	
occurrences (all)	9	39	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

21 May 2018	Amendment 8: Added summary of the results from the primary analysis to support changes made in the body of the protocol. Clarified that the third-party core imaging laboratory will no longer perform blinded independent central review of tumor imaging scans and thus, the investigators will no longer be required to send the scans to the independent core imaging laboratory. Clarified that upon IRB/IEC approval of Amendment 8, new cycle Day 1 procedures (ie, physical examination, ECOG performance status, ECG, Quality of Life questionnaires, blood chemistry, hematology) that were performed prior to knowing the need to delay the start of the cycle do not need to be repeated unless required to determine whether study drug may be resumed. Chest CT scans will no longer be a required safety assessment to reflect that the choice of modality for tumor assessment is left at the investigator's discretion upon approval of Amendment 8.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported