# 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 |

**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 |

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 |
| Objective Progression or Relapse | 286 | 172 |
| Adverse event, non-fatal | 32 | 9 |
| Participant Refused Continued Treatment | 27 | 15 |
| Site Terminated by Sponsor | 1 | - |
| Lost to follow-up | 3 | - |
| Global Deterioration of Health Status | 28 | 12 |
| Unspecified reasons | 52 | 8 |
| Protocol deviation | 5 | 3 |

## Baseline characteristics

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

| Reporting group values | Palbociclib Plus Letrozole | Placebo Plus Letrozole | Total |
|---|---|---|---|
| Number of subjects | 444 | 222 | 666 |
| Age categorical<br>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<br>Units: years | | | |
| arithmetic mean | 61.7 | 60.6 | |
| standard deviation | ± 10.6 | ± 11.2 | - |
| Sex: Female, Male<br>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 |

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: >=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 |

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 |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Palbociclib Plus Letrozole v Placebo Plus Letrozole |

| | |
|---|---|
| Number of subjects included in analysis | 509 |
| Analysis specification | Pre-specified |
| Analysis type | |
| 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) |

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 <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. SD: 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%) | 85.8 (82.2 to 88.9) | 71.2 (64.7 to 77.0) | | |

### Statistical analyses

| Statistical analysis title | Palbociclib + Letrozole vs Placebo + Letrozole |
|---|---|

Statistical analysis description:

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

| | |
|---|---|
| Comparison groups | Palbociclib Plus Letrozole v Placebo Plus Letrozole |

| | |
|---|---|
| Number of subjects included in analysis | 666 |
| Analysis specification | Pre-specified |
| Analysis type | |
| 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) |

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 |

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) |

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 |
|---|---|

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 <= 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:<br>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:<br>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:<br>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:<br>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:<br>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:

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.

| End point type | Secondary |
|---|---|

End point timeframe:

Time-matched triplicate ECGs were collected at 0 (predose), 2, 4, 6 and 8 hours on Day 0 and on Cycle1 Day 14

| 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) |
|---|---|

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 |
|---|---|

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) |
|---|---|

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 |
|---|---|

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] |
|---|---|

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 |
|---|---|

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:

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.

| 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 |
|---|---|

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 |
|---|---|

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 |
|---|---|

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, hypernatremia, 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 |
|---|---|

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.

| | |
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| Assessment type | Non-systematic |

### Dictionary used

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| Dictionary name | MedDRA |
| Dictionary version | 26.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Placebo Plus Letrozole |

Reporting group description:

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

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|---|---|
| Reporting group title | Palbociclib Plus Letrozole |

Reporting group description:

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

| Serious adverse events | Placebo Plus Letrozole | Palbociclib Plus Letrozole | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 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 | | | |

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|---|---|---|---|
| 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 | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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|---|---|---|---|
| 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 | | | |

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

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

| | | | |
|---|---|---|---|
| Dizziness | | | |
| subjects affected / exposed | 34 / 222 (15.32%) | 80 / 444 (18.02%) | |
| occurrences (all) | 43 | 122 | |
| Dysgeusia | | | |
| subjects affected / exposed | 7 / 222 (3.15%) | 37 / 444 (8.33%) | |
| occurrences (all) | 9 | 48 | |
| Headache | | | |
| subjects affected / exposed | 62 / 222 (27.93%) | 109 / 444 (24.55%) | |
| occurrences (all) | 103 | 197 | |
| Paraesthesia | | | |
| subjects affected / exposed | 9 / 222 (4.05%) | 26 / 444 (5.86%) | |
| occurrences (all) | 10 | 36 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 23 / 222 (10.36%) | 125 / 444 (28.15%) | |
| occurrences (all) | 62 | 471 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 222 (1.80%) | 64 / 444 (14.41%) | |
| occurrences (all) | 5 | 211 | |
| Neutropenia | | | |
| subjects affected / exposed | 8 / 222 (3.60%) | 308 / 444 (69.37%) | |
| occurrences (all) | 16 | 3898 | |
| Leukopenia | | | |
| subjects affected / exposed | 2 / 222 (0.90%) | 115 / 444 (25.90%) | |
| occurrences (all) | 2 | 798 | |
| Eye disorders | | | |
| Lacrimation increased | | | |
| subjects affected / exposed | 2 / 222 (0.90%) | 33 / 444 (7.43%) | |
| occurrences (all) | 5 | 46 | |
| Cataract | | | |
| subjects affected / exposed | 7 / 222 (3.15%) | 28 / 444 (6.31%) | |
| occurrences (all) | 8 | 37 | |
| Dry eye | | | |
| subjects affected / exposed | 10 / 222 (4.50%) | 28 / 444 (6.31%) | |
| occurrences (all) | 10 | 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 | 7 / 222 (3.15%) | 23 / 444 (5.18%) | |
| occurrences (all) | 8 | 29 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 36 / 222 (16.22%) | 150 / 444 (33.78%) | |
| occurrences (all) | 37 | 164 | |
| Dry skin | | | |
| subjects affected / exposed | 16 / 222 (7.21%) | 66 / 444 (14.86%) | |
| occurrences (all) | 16 | 99 | |
| Pruritus | | | |
| subjects affected / exposed | 11 / 222 (4.95%) | 49 / 444 (11.04%) | |
| occurrences (all) | 18 | 98 | |
| Rash | | | |
| subjects affected / exposed | 24 / 222 (10.81%) | 79 / 444 (17.79%) | |
| occurrences (all) | 32 | 137 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 89 / 222 (40.09%) | 187 / 444 (42.12%) | |
| occurrences (all) | 161 | 359 | |
| Back pain | | | |
| subjects affected / exposed | 52 / 222 (23.42%) | 117 / 444 (26.35%) | |
| occurrences (all) | 85 | 192 | |
| Bone pain | | | |
| subjects affected / exposed | 24 / 222 (10.81%) | 45 / 444 (10.14%) | |
| occurrences (all) | 33 | 75 | |
| Muscle spasms | | | |
| subjects affected / exposed | 13 / 222 (5.86%) | 46 / 444 (10.36%) | |
| occurrences (all) | 20 | 63 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 11 / 222 (4.95%) | 37 / 444 (8.33%) | |
| occurrences (all) | 15 | 57 | |
| Myalgia | | | |
| subjects affected / exposed | 20 / 222 (9.01%) | 65 / 444 (14.64%) | |
| occurrences (all) | 34 | 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<br>occurrences (all) | 8 / 222 (3.60%)<br>9 | 28 / 444 (6.31%)<br>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. |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported