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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Ibrance® or Palbociclib

PROTOCOL NO.: A5481023

PROTOCOL TITLE: Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial Of Fulvestrant (Faslodex®) With Or Without PD-0332991 (Palbociclib) ± Goserelin in Women with Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer Whose Disease Progressed After Prior Endocrine Therapy.

Study Center(s): As of the data cutoff date (05 Dec 2014), the study was conducted at 144 sites in 17 countries, that randomized subjects in Australia (11 sites), Belgium (11 sites), Canada (11 sites), Germany (2 sites), Ireland (1 site), Italy (9 sites), Japan (8 sites), Netherlands (6 sites), Portugal (2 sites), Romania (4 sites), Russian Federation (5 sites), Republic of South Korea (5 sites), Taiwan (2 sites), Turkey (1 site), Ukraine (6 sites), the United Kingdom (4 sites), and the United States (56 sites).

Study Initiation Date and Final Completion Dates

Study Initiation Date = 26 September 2013;
Date of cutoff = 05 December 2014.

Phase of Development: Phase 3

Study Objective(s):

Primary Objective:

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

Secondary Objectives:

- To compare measures of tumor control (including PFS, DR, CBR) between the treatment arms.
- To compare safety and tolerability between the treatment arms.
- To evaluate trough concentrations of palbociclib when given in combination with fulvestrant or fulvestrant plus goserelin compared to historical palbociclib data.

- To compare fulvestrant and goserelin trough concentrations when given in combination with palbociclib to those when given without palbociclib.
- To explore correlations between palbociclib exposures and efficacy/safety findings in this subject population.
- To compare Patient Reported Outcomes measures between treatment arms.
- To characterize alterations in genes, proteins, and RNAs relevant to the cell cycle, drug targets, tumor sensitivity and/or resistance.
- To conduct subgroup analysis for primary and secondary endpoints in stratified groups.

METHODS

Study Design: This study was an international, multicenter, 2:1 randomized, double-blind, placebo-controlled, parallel-group, Phase 3 clinical study with the primary objective of demonstrating the superiority in prolonging PFS of palbociclib in combination with fulvestrant (Faslodex®) over fulvestrant plus placebo in women with Hormone Receptor (HR)-positive, Human Epidermal Growth Factor Receptor (HER2)-negative metastatic breast cancer, regardless of their menopausal status, whose disease had progressed after prior endocrine therapy. Secondary endpoints [(progression free survival (PFS), overall response (OR), duration of response (DR), clinical benefit response (CBR), and overall survival (OS)], pharmacokinetic (PK), Patient-Reported Outcome (PRO) and safety of the 2 treatment arms were also compared. Pre- and perimenopausal women were to receive therapy with the luteinizing hormone-releasing hormone (LHRH) agonist goserelin (Zoladex® or generic).

Approximately 417 eligible women were planned to be randomized on a 2:1 basis to receive either palbociclib plus fulvestrant (approximately 278 women; investigational arm), or placebo plus fulvestrant (approximately 139 women; comparator arm).

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

Palbociclib/placebo was to be administered orally once a day for 21 days followed by 7 days off treatment of every 28-day cycle. In Cycle 1, fulvestrant was administered intramuscularly (IM) on Day 1 and Day 15, every 28 ±7 days thereafter starting on Cycle 1 Day 1. Pre- and perimenopausal women continued receiving concurrent ovarian function suppression with goserelin administered subcutaneously every 28 days during active treatment phase. These pre- or perimenopausal women should have started receiving goserelin or an alternative LHRH agonist at least 4 weeks before the start of study treatment. For each subject, the treatment phase lasted until study withdrawal criteria were met.

Subjects received their assigned study treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurred first.

Schedule of Activities provides an overview of the protocol visits and procedures (Table 1).

Table 1: Schedule of Activities

Protocol Activity	**Screening**	**Active Treatment Phase [a] - One Cycle = 28 days**			**End of Treatment/Withdrawal [c]**	**Post-Treatment Follow-Up [d]**
		Cycles 1 and 2		**Cycles ≥3**		
Study Day	**Within 28 days prior to randomization unless specified**	**Day 1 [b]**	**Day 15**	**Day 1**		
Visit Window		**±-2 days**	**±2 days**	**±7 days [a]**		**±7 days**
Informed Consent [e]	X					
Medical/Oncological History [f]	X					
Baseline Signs/Symptoms [g]		X [g]				
Physical Examination/Vital Signs [h]	X	X [b]		X	X	
Ophthalmic Examination [i]	X			X [i]	X	
ECOG Performance Status	X	X		X	X	
Laboratory Studies						
Hematology [j]	X	X [b]	X	X	X	
Blood Chemistry [j]	X	X [b]	X	X	X	
Pregnancy test, serum estradiol and FSH (if applicable) [j]	X					
12-Lead ECG (in triplicate)	X				X	
Disease Assessment						
CT/MRI Scans of Chest, Abdomen, Pelvis, any clinically indicated sites of disease, and of bone lesions; Clinical evaluation of superficial disease [k]	X	◄--► [k] Performed every 8 weeks (±7 days) for the first year, and then every 12 weeks (±7 days) from the date of randomization (See tumor assessment requirements flowchart)			X	X
Radionuclide Bone Scan, Whole Body [l]	X	As clinically indicated or to confirm complete response. (See tumor assessment requirements			X	X
Other Clinical Assessments						
Adverse Event Reporting [m]	X	X	X	X	X	X
Concomitant Medications/Treatments	◄--► Recorded from 28 days prior to the start of study treatment up to 28 days after the last dose of study					

Protocol Activity	**Screening**	**Active Treatment Phase [a] - One Cycle = 28 days**			**End of Treatment/Withdrawal [c]**	**Post-Treatment Follow-Up [d]**
		Cycles 1 and 2		**Cycles ≥3**		
Study Day	**Within 28 days prior to randomization unless specified**	**Day 1 [b]**	**Day 15**	**Day 1**		
Visit Window		**±-2 days**	**±2 days**	**±7 days [a]**		**±7 days**
Pharmacokinetics (PK) [n]		First 40 subjects: Sampling at pre-dose on Day 1 and Day 15 of Cycles 1 and 2, and Day 1 of Cycle 3; all other subjects: Pre-dose sampling on Day 15 of Cycles 1 and 2				
Banked Blood Biospecimens (Prep D1)		X				
Plasma banking (Prep B1) [p]		X	X		X	
Tumor Tissue for Biomarker Analysis [q]	X				X	
EuroQol-5D (EQ-5D) [r]		Pre-dose on Day 1 of Cycles 1, 2, 3, 4 and Day 1 of every other cycle thereafter starting with Cycle 6 (ie, Cycle 6,8, 10, etc)			X	
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire					X	
European Organisation for Research and Treatment of Cancer Breast Cancer Module (EORTC-QLQ-BR23)					X	
Survival Follow-up [s]						X
Study Treatment						
Randomization		X				
Fulvestrant (both treatment arms) [t]		◄--►[t] IM administration on Days 1 and 15 of Cycle 1, every 28 days (±7 days) thereafter starting from				
Palbociclib or placebo (Arm A only) [u]		◄--►[u] Orally once daily on Days 1 to 21of each Cycle followed by 7 days off treatment				
For pre-/peri-menopausal subjects only: Goserelin (both treatment arms, if applicable) [v]	SC administration at least 4 weeks before study treatment start [v]	◄--►[v] SC administration every 28 days				

a. **Active Treatment Phase:** Assessments should be performed prior to dosing on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. One cycle consists of 28 days. A cycle could be longer than 28 days if ersistent toxicity delays initiation of the subsequent cycle. **Day 1 of any cycle visit should coincide with the day the palbociclib/placebo treatment begins.** If there are delays due to toxicity, then the start of the next cycle visit will be delayed until the subject has recovered and can begin study treatment again. Fulvestrant injection will be given every 28 days (+/- 7 days) with the exception of Cycle 1 during which it will be administered on Days 1 and 15 (±2 days allowed according to the protocol visit time windows). Goserelin will be administered every 28 days (+/- number of days allowed according to the protocol visit time windows). The active treatment phase is ongoing as long as the subject is receiving both study drugs (ie, palbociclib/placebo and fulvestrant) or fulvestrant alone.

b. **Cycle 1/Day 1:** Blood chemistry, hematology, and physical examination not required if acceptable screening assessment is performed within 7 days prior to randomization.

c. **End of Treatment/Withdrawal:** Visit to be performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anticancer therapy. Obtain assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks or 12 weeks [as applicable] for disease assessments).

d. **Post Treatment Follow-up:** Subjects who discontinue study treatment should be contacted 28 calendar days (±7 days) after discontinuation of study treatment (palbociclib/placebo or fulvestrant) to assess if there have been any new adverse events and/or any change to any previously reported adverse events. Telephone contact is acceptable. Subjects who discontinue active study treatment for any reason other than objective disease progression or death will continue to have tumor assessments performed every 8 weeks (±7 days) for the first year, and then after 1 year every 12 weeks (±7 days) (calculated from the date of randomization) until documented progression or onset of new anticancer therapy. For subjects who discontinue study treatment due to objective disease progression, see table footnote s (Survival Follow-up) below.

e. **Informed Consent:** Informed consent must be obtained prior to any protocol required assessments being performed (with the exception of certain imaging assessments if meeting the criteria).

f. **Medical/Oncological History:** To include information on prior anticancer treatments.

g. **Baseline Signs/Symptoms:** Baseline tumor related signs and symptoms will be recorded at the Cycle 1 Day 1 visit prior to initiating treatment and then reported as adverse events during the trial if they worsen in severity or increase in frequency.

h. **Physical Examination/Vital signs:** A full physical examination including an examination of all major body systems and breasts, height (at screening only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider. Physical examinations will be carried out at Screening, Day 1 of every cycle and the End of Treatment/Withdrawal visit.

i. **Ophthalmology Examinations:** Upon approval of Amendment 1, newly enrolled lens grading evaluable subjects will undergo an ophthalmic examination by an ophthalmologist at screening, during study treatment on Cycle 4 Day 1, on Cycle 7 Day 1, on Cycle 13 Day 1 (ie, after 3, 6 and 12 months), every 12 months thereafter (ie, Days 1 of Cycles 25, 37, etc.) and at the End of Treatment/Withdrawal visit. Additional ophthalmic examinations may be performed as clinically indicated. It is expected that a minimum of 100 evaluable subjects will participate in these examinations. Sites will be informed once these examinations are no longer required for subjects newly enrolled in this study.

j. **Laboratory tests:** Hematology includes hemoglobin, WBC, absolute neutrophil count, platelet count. Blood chemistry includes AST/ALT, alkaline phosphatase, sodium, potassium, magnesium, total calcium, total bilirubin, blood urea nitrogen (BUN) (or urea), serum creatinine, and albumin. Additional hematology/chemistries panels may be performed as clinically indicated. Upon approval of Amendment 2, hemoglobin A1c will be measured in all subjects every 3 months from the date of randomization (ie, C4D1, C7D1, C10D1, etc), and at the End of Treatment/Withdrawal visit. Pregnancy test (serum) at screening only for women of childbearing potential. Test may be repeated as per request of IRB/IECs or if required by local regulations. Serum estradiol and Follicle stimulating hormone (FSH) levels are analysed at screening to confirm postmenopausal status of women <60 years old and who have been amenorrheic for at least 12 consecutive months.

k. **CT/MRI Scans of Chest, Abdomen, Pelvis:** Refer to the tumor assessment requirement flowchart for details and timing of procedures.

l. **Radionuclide Bone Scan, Whole Body:** Refer to the tumor assessment requirement flowchart for all details and timing of procedures.

m. **Adverse Events (AEs):** Serious Adverse events (SAEs) must be reported from the time the subject provides informed consent through and including 28 calendar days after the last administration of the study drug. SAEs occurring after the active reporting period has ended should be reported if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor. All AEs (serious and non serious) should be recorded on the CRF from the first dose of study treatment through last subject visit. It is expected that telephone contact with the subject will be made in order to assess SAEs and AEs 28 calendar days (+/- 7 days) after the last administration of the study drug.

n. **Pharmacokinetics (PK)**: In approximately the first 40 subjects randomized in the study, plasma PK samples will be drawn pre-dose on Day 1 and Day 15 of Cycles 1 and 2, and Day 1 of Cycle 3 for DDI assessment for palbociclib and fulvestrant (and goserelin if applicable). In all other subjects, plasma concentrations will be drawn on Day 15 of Cycle 1 and Cycle 2 for palbociclib only. Additional PK blood samples may be collected from subjects experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation.

o. **Banked Blood Biospecimens (Prep D1):** A single 4 mL blood sample will be collected pre-dose at the Cycle 1 Day 1 to be retained for potential pharmacogenomic/biomarker analyses related to drug response or adverse drug reactions. Samples will be collected from all subjects, unless prohibited by local regulations. .

p. **Plasma Banking (Prep B1):** Blood samples for plasma collection (2x 10 mL each) will be drawn for exploratory analyses from all subjects pre-dose on Cycle 1 Days 1 and 15 and at End of Treatment/Withdrawal, unless prohibited by local regulations.

q. **Tumor Tissue for Biomarker Assessments:** Tumor tissue is required for subject participation, and subjects must agree to provide tissue from the metastatic or recurrent site at the time of study entry. For the purpose of eligibility, documentation of ER-positive and/or PR-positive tumor and HER2-negative tumor will be based on local results utilizing an assay consistent with local standards. Archived formalin-fixed paraffin embedded (FFPE) specimen will be collected. If archived metastatic or recurrent tumor FFPE specimen is not available, a de novo biopsy will be required for subject participation, except for those with bone disease only who will need to provide the original diagnostic FFPE tumor specimen. Subjects who relapsed while receiving adjuvant therapy and had surgery within the last 3 years, may provide a tumor specimen from that surgery. Provision of new metastatic tissue from these subjects is strongly encouraged but not mandated. An optional de novo tumor biopsy will be collected from the site of progression at the End of Treatment visit. Details on sample preparation, processing, storage, and shipment will be provided in the Study Manual.

r. **Patient Reported Outcomes Assessments:** All self-assessment questionnaires must be completed by the subjects while in the clinic and cannot be taken home. Interviewer administration in clinic may be used under special circumstances.

s. **Survival Follow-Up:** For subjects who discontinue study treatment due to objective disease progression, survival data (ie, subject status along with start, stop and type of new anticancer therapy) will be collected every 3 months for the first 9 months (Month 3, 6, and 9, ±14 days), then every 6 months starting at Month 15 (±14 days), calculated from the last dose of study treatment. Telephone contact is acceptable.

t. **Fulvestrant:** To be administered on-site according to the local Summary of Product Characteristics for fulvestrant (Faslodex®). Fulvestrant injection will be given every 28 days (+/- 7 days) with the exception of Cycle 1 during which it will be administered on Days 1 and 15 (±2 days allowed according to the protocol visit time windows).

u. **Palbociclib or Placebo:** Subjects will be required to return all bottles of palbociclib/placebo as well as the completed subject diary on Day 1 of each cycle for drug accountability.

v. **Goserelin (if applicable):** Goserelin will be administered every 28 days (+/- number of days allowed according to the protocol visit time windows). Treatment with goserelin (Zoladex® or generic) as per local practice for all women who are pre- or peri-menopausal at study entry. Subjects must have commenced treatment with goserelin or an alternative luteinizing hormone-releasing hormone (LHRH) agonist at least 4 weeks prior to randomization. If subjects have not received goserelin as their LHRH agonist prior to study entry, they must switch to goserelin for the duration of the trial. It is recommended to administer goserelin (given every 28 days) on-site when monthly fulvestrant is given. If goserelin is administered at home by the subject, a subject diary will be implemented.

Number of Subjects (Planned and Analyzed)

Approximately 417 subjects were planned to be randomized, 521 subjects (Intent-to-Treat [ITT] population) were randomized and analyzed for efficacy, and 517 subjects (As-Treated [AT] population) were treated.

Diagnosis and Main Criteria for Inclusion

- Women 18 years or older with metastatic or locally advanced disease, not amenable to curative therapy
- Confirmed diagnosis of HR+/HER2- breast cancer
- Any menopausal status
- Progressed on or within 12 months from prior endocrine adjuvant therapy or progressed on or within 1 month from prior advanced/metastatic endocrine breast cancer therapy
- On an LHRH agonist for at least 28 days, if pre/perimenopausal, and willing to switch to goserelin (Zoladex ®) at time of randomization
- Measurable disease defined by response evaluation criteria in solid tumors (RECIST) version 1.1, or bone-only disease
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1
- Adequate organ and marrow function, resolution of all toxic effects of prior therapy or surgical procedures.
- Subject must agree to provide tumor tissue from metastatic tissue at baseline.

Study Treatment

Subjects were randomized to either palbociclib/fulvestrant or placebo/fulvestrant arms.

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

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

Efficacy, Pharmacokinetic, or Outcomes Research Endpoints

Primary Endpoint:

- Progression-Free Survival (PFS) as assessed by the Investigator.

Secondary Endpoints:

- Overall Survival (OS).
- 1-year, 2-year, and 3-year survival probabilities.
- Objective Response (OR): Complete Response (CR) or Partial Response (PR).
- Duration of Response (DR).
- Clinical Benefit Response (CBR): CR or PR or Stable Disease (SD) ≥24 weeks.
- Type, incidence, severity (as graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.0), seriousness and relationship to study medications of Adverse Events (AEs) and any laboratory abnormalities.
- Trough plasma concentration of palbociclib, fulvestrant and goserelin (if applicable) in the subgroup of approximately 40 subjects included in the initial safety review.
- PRO endpoints such as health related quality of life scores [EuroQol (EQ-5D) Score; European Organization for Research and Treatment of Cancer Quality of Life Instrument (EORTC QLQ-C30); European Organization for Research and Treatment of Cancer Breast Cancer Module (EORTC QLQ-BR23); minimally important difference (MID) cut-off, and time to deterioration (TTD) composite endpoint.
- Tumor tissue biomarkers, including genes (eg, copy numbers of CCND1 and CDKN2A, PIK3CA mutations), proteins (eg, Ki67, pRb, CCNE1), and RNA expression (eg, cdk4, cdk6).

Safety Evaluations

Safety assessment consisted of monitoring of all AEs, including SAEs, regular monitoring of hematology, serum chemistry, and routine monitoring of electrocardiograms (ECGs), physical examinations, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status, pregnancy tests and chest computed tomography (CT).

Statistical Methods

The following analysis population sets were used:

Intent-to-Treat Population (Full Analysis Set):

The intent-to-treat (ITT) population or full analysis set included all subjects who were randomized, with study drug assignment designated according to initial randomization, regardless of whether subjects received study drug or receive a different drug from that to

which they were randomized. The ITT population was the primary population for evaluating all efficacy endpoints and subject characteristics.

As-Treated (AT) Population (Safety Analysis Set):

The as-treated population or safety analysis set included subjects who received at least 1 dose of study medication, with treatment assignments designated according to actual study treatment received. The AT population was the primary population for evaluating treatment administration/compliance and safety. Efficacy and clinical benefits endpoints may be assessed in this population as well.

Other Analysis Sets:

Pharmacokinetic (PK) Analysis Sets: There were at least two PK analysis sets:

1. Early Safety Review Set: The 40 subjects participating in the early safety review, who are treated with palbociclib + fulvestrant ± goserelin or placebo + fulvestrant ± goserelin and have at least one measured plasma drug concentration.

2. Palbociclib PK Analysis Set: All subjects (including those in the Early Safety Review Set) who have PK blood samples collected for palbociclib and have at least one measured plasma drug concentration.

PK/Adverse Event Analysis Set (if applicable): subjects experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation who have PK blood samples collected for palbociclib or fulvestrant (or goserelin if applicable) and have at least one measured plasma drug concentration.

Patient Reported Outcome (PRO) Evaluable Population (PRO Analysis Set):

The PRO –evaluable population is defined as a subset of ITT subjects, who have completed a baseline and at least one post –baseline PRO assessment prior to end of study treatment.

Analysis of Primary Endpoint:

The primary endpoint was investigator-assessed PFS which was defined as the time from the date of randomization to the date of the first documentation of objective progression of disease (PD) or death due to any cause in the absence of documented PD, whichever occurred first. PFS data were censored on the date of the last tumor assessment on study for subjects who did not have objective tumor progression and who did not die while on study. Subjects lacking an evaluation of tumor response after randomization had their PFS time censored on the date of randomization with the duration of one day. Additionally, subjects who started a new anticancer therapy prior to documented PD were censored at the date of the last tumor assessment prior to the start of the new therapy. Subjects with documentation of PD or death after an unacceptably long interval (ie, 2 or more incomplete or non-evaluable assessments) since the last tumor assessment were censored at the time of last objective assessment that did not show PD. The primary analyses of PFS were performed in the ITT population. A log-rank test (1-sided) stratified by the presence of visceral metastases and

sensitivity to prior hormonal therapy was used to compare PFS time between the 2 treatment arms at the interim and/or final analyses with the overall significance level preserved at 0.025 (1 sided). PFS for the two treatment arms was assessed using Kaplan-Meier methods and displayed graphically. The median event times and 95% CIs were estimated. Cox regression models were used to estimate the HR and its 95% CI.

Sensitivity Analyses for the Primary Progression-Free Survival Endpoint:

The primary efficacy analysis on the primary PFS endpoint was based on well-documented and verifiable progression events and deaths due to any cause. Other data were censored at the time of the last tumor assessment documenting absence of PD and death. In addition, the sensitivity analyses (SA) on the primary PFS endpoint were performed in determining whether the results of the primary PFS analysis were robust.

Supportive Analyses for PFS

A sample-based blinded independent central review (BICR) approach was implemented as an auditing tool for PFS. A third-party core imaging laboratory performed BICR for a randomly selected subgroup of subjects independent of investigator assessment or investigator assessed determination of progression. The objective of this approach was to corroborate the analysis results of the primary endpoint (i.e., investigator-assessed PFS) and to assist in the evaluation of potential investigator bias. The BICR audit approach was not intended to provide an alternative means of definitive analysis.

Analysis of Secondary Endpoints:

Overall Survival (OS): OS was defined as the time from date of randomization to date of death due to any cause. In the absence of confirmation of death, survival time was censored to last date the subject was known to be alive. All subjects randomized were considered evaluable for OS. OS was hierarchically tested for significance at the time of PFS analysis, provided the primary PFS endpoint was statistically significant at the interim and/or final analyses. A stratified log-rank test (using the same stratification factors as for the PFS analysis) was used to compare OS between the treatment arms. OS for the two treatment arms was assessed using Kaplan-Meier methods and displayed graphically where appropriate. The median event times and 95% CIs were estimated. Cox regression models were used to estimate the HR and its 95% CI. The 1-year survival probability was estimated using the Kaplan-Meier method and a two sided 95% CI for the log [-log(1-year survival probability)] was calculated using a normal approximation using the Greenwood's formula, and then back-transformed to give a CI for the 1-year survival probability itself. The 2-year and 3-year survival probabilities were estimated similarly.

Objective Response (OR): OR was defined as a CR or PR according to RECIST v.1.1 recorded from randomization until disease progression or death due to any cause. A subject was considered to have achieved an OR if the subject had a sustained CR or PR according to RECIST v.1.1 definitions. Otherwise, the subject was considered as non-responders in the OR rate analysis. Additionally, subjects with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) were considered as non-responders in the

OR rate analysis. The OR rate in each randomized treatment arm was estimated by dividing the number of subjects with OR (CR or PR) by the number of subjects randomized to the respective treatment arm ("response rate"). A 95% CI for the response rates was provided. Response rate comparisons between the 2 treatment arms as randomized were assessed using the Cochran–Mantel–Haenszel (CMH) test with the same stratification factors as for the PFS analysis.

Analyses of OR rate were performed on the ITT population based on the investigator's assessment, on the investigator-assessed ITT population with measurable disease at baseline as well as on a randomly sampled audit subset of the ITT population based on the review of the blinded independent third-party core imaging laboratory.

Clinical Benefit Response (CBR): CBR was defined as CR or PR or SD ≥24 weeks according to the RECIST version 1.1 recorded in the time period between randomization and disease progression or death of any cause. The CBR rate in each randomized treatment arm was estimated by dividing the number of subjects with CR, PR, or SD ≥24 weeks by the number of subjects randomized to the treatment arm. A 95% CI for the CBR rate was provided. CBR rate comparison between the two treatment arms as randomized was assessed using the CMH test with the same stratification factors as for the PFS analysis. Analyses for CBR were performed on the ITT population based on the investigator's assessment and on a randomly sampled audit subset of the ITT population based on the review of the blinded independent third-party core imaging laboratory.

Duration of Response (DR): DR was defined as the time from the first documentation of objective tumor response (CR or PR) to the first documentation of objective tumor progression or to death due to any cause, whichever occurred first. DR data were censored on the date of the last tumor assessment on study for subjects who did not have objective tumor progression and who did not die due to any cause while on study. DR was only calculated for the subgroup of subjects with an OR. DR for the two treatment arms was summarized using Kaplan-Meier methods and displayed graphically, where appropriate. The median event time and 95% CI for the median were provided for each endpoint.

Patient-Reported Outcomes (PRO): Completion rates were summarized by cycle. Patient reported global QOL, functioning and symptom scores assessed using the EORTC QLQ-C30 and BR-23 and change from baseline scores were compared between the treatment arms using a longitudinal repeated measures mixed model approach adjusting for specified covariates. Statistical significance of within treatment arm change from baseline was interpreted using the 95% CIs of the average change from baseline score. In addition to the above analyses, the time to deterioration (TTD) in pain was carried out using survival analysis methods. Deterioration was defined as an increase in score of 10 points or greater from baseline. A log-rank test (1-sided) was used to compare time to deterioration between the 2 treatment arms. TTD associated with each treatment arm was summarized using the Kaplan-Meier method and displayed graphically. The Cox Proportional hazards model was used to compute the treatment HR and the corresponding 95% CI. EQ-5D general health status and EQ-5D Index scores between treatment arms were compared using longitudinal repeated measures models. No adjustments were made for multiple comparisons.

RESULTS

Subject Disposition

Between 26 Sep 2013 (first subject first visit [FSFV]) and 26 Aug 2014, a total of 521 subjects were randomized (Table 2) and reasons for discontinuation reported (Table 3).

Table 2: Subject Disposition

Number (%) of Subjects	Palbociclib plus Fulvestrant	Placebo plus Fulvestrant	Total
Randomized to study treatment	347	174	521
Randomized and not treated	2 (0.6)	2 (1.1)	4 (0.8)
Randomized and treated	345 (99.4)	172 (98.9)	517 (99.2)
Completed [1]	0	0	0
Discontinued [2]	107 (30.8)	97 (55.7)	204 (39.2)
Ongoing at data cutoff date	238 (68.6)	75 (43.1)	313 (60.1)

[1] Completion is from the Subject Summary End of Study (EOS) page.
[2] Includes subjects who discontinued palbociclib/placebo treatment for progression or any other reason.

Table 3: Subject Disposition at End of Treatment – Palbociclib plus Fulvestrant or Placebo and Fulvestrant – Intent-to-Treat Population

Number(%) of Subjects	Palbociclib plus Fulvestrant N=347 n (%)	Placebo plus Fulvestrant N=174 n (%)	Total N=521 n (%)
Reason for discontinuation [1]			
AE (reason for palbociclib/placebo discontinuation) [2]	9 (2.6)	3 (1.7)	12 (2.3)
AE (reason for fulvestrant discontinuation)	7 (2.0)	3 (1.7)	10 (1.9)
Global deterioration of health status	8 (2.3)	3 (1.7)	11 (2.1)
Lost to Follow-Up	0	0	0
Medication error without associated AE	0	0	0
Objective progression or relapse plus progressive disease	85 (24.5)	87 (50.0)	172 (33.0)
Protocol violation	0	0	0
Study terminated by the sponsor	0	0	0
Subject died	0	1 (0.6)	1 (0.2)
Subject refused to continue treatment for reason other than AE	1 (0.3)	1 (0.6)	2 (0.4)
Subject started new treatment for disease under study	0	0	0
Withdrew consent	4 (1.2)	2 (1.1)	6 (1.2)
Other	0	0	0

Abbreviation: AE: adverse event, CRF: Case Report Form, N: number of subjects, n: number of subjects affected
[1] Includes subjects who discontinued treatment for progression or any other reason. Discontinued is as per the Conclusion of Treatment page of the CRF.
[2] The subjects A and B completed the End of Treatment CRF page for palbociclib/placebo only.
Percentages are calculated using N as a denominator.
0 mg doses have not been excluded from the algorithm determining subject status.

Demography

Table 4 presents demographic and other baseline characteristics.

Table 4: Demographic Characteristics – Intent-to-Treat Population

Number(%) of Subjects	Palbociclib plus Fulvestrant N=347	Placebo plus Fulvestrant N=174	Total N=521
Age (years) n (%)			
<65	261 (75.2)	131 (75.3)	392 (75.2)
≥65	86 (24.8)	43 (24.7)	129 (24.8)
Mean (SD)	56.9 (11.7)	56.8 (10.4)	56.9 (11.3)
Median (range)	57.0 (30-88)	56.0 (29-80)	57.0 (29-88)
Race n (%)			
White	252 (72.6)	133 (76.4)	385 (73.9)
Black	12 (3.5)	8 (4.6)	20 (3.8)
Asian	74 (21.3)	31 (17.8)	105 (20.2)
Other	8 (2.3)	1 (0.6)	9 (1.7)
Unspecified	1 (0.3)	1 (0.6)	2 (0.4)
Ethnicity n (%)			
Hispanic/Latino	17 (4.9)	11 (6.3)	28 (5.4)
Not Hispanic/Latino	329 (94.8)	161 (92.5)	490 (94.0)
Unspecified	1 (0.3)	2 (1.1)	3 (0.6)
Weight (kg)			
n (%)	347 (100)	171 (98.3)	518 (99.4)
Mean (SD)	70.4 (17.5)	72.0 (17.6)	70.9 (17.6)
Median (range)	67.2 (35.6-142.0)	69.8 (35.1-126.8)	68.5 (35.1-142.0)
Height (cm)			
n (%)	347 (100)	174 (100)	521 (100)
Mean (SD)	161.1 (7.0)	(161.3 (7.6)	161.2 (7.2)
Median (range)	161.5 (139.8-182.9)	162.0 (121.9-180.3)	162.0 (121.9-182.9)

Abbreviations: N: number of subjects, n: number of subjects affected, SD: standard deviation,

Efficacy, Pharmacokinetic, or Outcomes Research Results

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

At the data cutoff date, the most common type of PFS event was disease progression, for 100 (28.8%) subjects in the palbociclib plus fulvestrant arm and 91 (52.3%) subjects in the placebo plus fulvestrant arm. Two deaths were reported in each treatment arm. (Table 5)

Table 5: Summary of Progression-Free Overall Survival by Treatment, Investigator Assessment – Intent-to-Treat Population

	Palbociclib plus Fulvestrant N=347	Placebo plus Fulvestrant N=174
	n (%)	n (%)
Number with event	102 (29.4)	93 (53.4)
Type of event		
Objective progression	100 (28.8)	91 (52.3)
Death without objective progression	2 (<1.0)	2 (1.1)
Number censored	245 (70.6)	81 (46.6)
Reason for censorship		
No adequate baseline assessments	1 (<1.0)	0
No on-study disease assessments	7 (2.0)	7 (4.0)
Given new anti-cancer treatment prior to disease progression and after last dose of study treatment	8 (2.3)	4 (2.3)
Discontinued study without disease progression or death	2 (<1.0)	0
Withdrew consent for follow-up	1 (<1.0)	0
Lost to follow-up	0	0
Other	1 (<1.0)	0
Unacceptable gap (>20 weeks) between PD or death to the most recent prior adequate assessment	0	0
In follow-up for progression	227 (65.4)	70 (40.2)
Probability of being event free at Month 12 [1] (95% CI [2])	-	-
Kaplan-Meier estimates of time to event (month)		
Quartiles (95% CI) [3]		
25%	3.9 [3.6, 5.5]	1.9 [1.8, 1.9]
50%	9.2 [7.5, NE]	3.8 [3.5, 5.5]
75%	NE [11.0, NE]	NE [5.7, NE]
Stratified analysis		
Hazard ratio [4]	0.422	
95% Hazard ratio	0.318-0.560	
p-value [5]	<0.000001	
Unstratified analysis [6]		
Hazard ratio [4]	0.417	
95% Hazard ratio	0.314-0.553	
p-value [5]	<0.000001	

Abbreviations: CI: confidence interval, N: number of subjects, n: number of subjects affected, NE: not estimable; PD: progressive disease

1. Estimated from the Kaplan-Meier curve.
2. Calculated with the product-limit method.
3. Based on the Brookmeyer and Crowley method.
4. Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of the palbociclib plus fulvestrant arm.
5. 1-sided p-value from the log-rank test stratified by the presence of visceral metastases and sensitivity to prior hormonal therapy per randomization.
6. Sensitivity analysis 2: used a 1-sided unstratified log-rank test and an unstratified Cox proportional hazards model.
7. Anti-cancer treatment included surgery containing a lesion removal or subsequent anti-cancer systemic therapies.

Secondary Endpoints:

Overall Survival (OS) and Survival Probabilities at Months 12, 24, and 36

The interim analysis of OS yielded inconclusive results due to immature OS data with a small number of deaths observed at the time of the PFS analysis; 19 (5.5%) subjects had died in the palbociclib plus fulvestrant arm and 9 (5.2%) subjects had died in the placebo plus fulvestrant arm (Table 6). The estimated survival probabilities at Month 12 were 89.3% for both treatment arms. The estimated survival probabilities at Month 24 and Month 36 could not be calculated. (Table 6)

Table 6: Summary of Overall Survival by Treatment – Intent-to-Treat Population

	Palbociclib plus Fulvestrant N=347	Placebo plus Fulvestrant N=174
	n (%)	n (%)
Number of deaths	19 (5.5)	9 (5.2)
Cause of death		
Disease Under Study	18 (5.2)	8 (4.6)
Study Treatment Toxicity	0	0
Unknown	1 (<1.0)	0
Other	0	1 (<1.0)
Number censored	328 (94.5)	165 (94.8)
Reason for censorship		
Subject Remains In Follow-up	324 (93.4)	157 (90.2)
Subject No Longer Being Followed For Survival	4 (1.2)	8 (4.6)
Survival Probability at Month 6 [1] (95% CI [2])	94.2 (90.7, 96.4)	95.9 (90.9, 98.2)
Survival Probability at Month 12 [1] (95% CI [2])	89.3 (78.1, 95.0)	89.3 (77.8, 95.0)
Survival Probability at Month 24 [1] (95% CI [2])	-	-
Survival Probability at Month 36 [1] (95% CI [2])	-	-

[1] Estimated from the Kaplan-Meier curve
[2] Calculated from the product-limit method.

Objective Response (OR) – percentage of participants with confirmed objective tumor response

The analysis of investigator-assessed OR demonstrated a numerically higher OR rate which did not reach statistical significance for palbociclib plus fulvestrant vs placebo plus fulvestrant (odds ratio of 1.725 [95% CI: 0.835, 3.896; stratified 1-sided p-value of 0.0791] (Table 7).

Table 7: Summary of Best Overall Tumor Response by Treatment, Investigator Assessment – Intent-to-Treat Population

	Palbociclib plus Fulvestrant N=347	Placebo plus Fulvestrant N=174
	n (%)	n (%)
Complete response	0	3 (1.7)

	Palbociclib plus Fulvestrant N=347	Placebo plus Fulvestrant N=174
	n (%)	**n (%)**
Partial response	36 (10.4)	8 (4.6)
Stable/no response	244 (70.3)	97 (55.7)
Objective progression	57 (16.4)	57 (32.8)
Indeterminate	10 (2.9)	9 (5.2)
Objective response and rate (complete response and partial response)	36 (10.4)	11 (6.3)
95% exact CI for OR rate [1]	[7.4, 14.1]	[3.2, 11.0]
Stratified analysis		
Odds ratio [2]	1.725	
95% exact CI	[0.835, 3.896]	
p-value [3]	0.0791	
Unstratified analysis		
Odds ratio [2]	1.715	
95% exact CI	[0.826, 3.834]	
p-value [4]	0.0843	

Abbreviations: CI: confidence interval, N: number of subjects, n: number of subjects affected, OR: objective response

1. CI was calculated using the exact (Clopper-Pearson) method.
2. An Odds Ratio >1 means better response in favor of the palbociclib plus fulvestrant arm.
3. 1-sided exact test stratified by the presence of visceral metastases and sensitivity to prior hormonal therapy per randomization.
4. 1-sided p-value is from exact test.

Duration of Response (DR)

The investigator-assessed median DR was longer in the palbociclib plus fulvestrant arm (9.3 months [95% CI: 4.0, not estimable] than in the placebo plus fulvestrant arm (5.7 months [95% CI: 3.7, 5.7]) (Table 8).

Table 8: Summary of Duration of Objective Response by Treatment, Investigator Assessments – Intent-to-Treat Population

	Palbociclib plus Fulvestrant	Placebo plus Fulvestrant
Investigator Assessment	**N=347 n (%)**	**N=174 n (%)**
Subjects with a response (CR/PR)	36 (10.4)	11 (6.3)
Number (%) of subjects with events	5 (13.9)	2 (18.2)
Number (%) of subjects censored	31 (86.1)	9 (81.8)
Kaplan-Meier estimate of duration of response (CR or PR) in months:		
Quartile (95% CI) [1]		
25%	4.0 [3.4, NE]	5.7 [3.7, 5.7]
50%	9.3 [4.0, NE]	5.7 [3.7, 5.7]
75%	NE [9.3, NE]	5.7 [NE, NE]

Abbreviations: CI: confidence interval, CR: complete response, N: number of subjects, n: number of subjects affected, NE: not estimable, PR: partial response
1) Based on the Brookmeyer Crowley method.
Transformation applied while calculating CI.
Percentages for subjects with a response were calculated in reference to N.
Percentages for subjects with events and subjects censored were calculated in reference to the number of subjects with a response.

Clinical Benefit Response (CBR)

The analysis of investigator-assessed CBR (CR, PR and SD≥24 weeks) in the ITT population demonstrated a statistically significant improvement in CBR for palbociclib plus fulvestrant compared with placebo plus fulvestrant (odds ratio of 2.189 [95% CI: 1.391, 3.523; stratified 1-sided p-value of 0.0002]) (Table 9).

Table 9: Summary of Clinical Benefit Response by Treatment, Investigator Assessment – Intent-to-Treat Population

	Palbociclib plus Fulvestrant N=347	Placebo plus Fulvestrant N=174
	n (%)	**n (%)**
Complete response	0	3 (1.7)
Partial response	36 (10.4)	8 (4.6)
Stable disease ≥24 weeks	82 (23.6)	22 (12.6)
Stable disease <24 weeks	162 (46.7)	75 (43.1)
Objective progression	57 (16.4)	57 (32.8)
Indeterminate	10 (2.9)	9 (5.2)
Clinical benefit response and rate (CR + PR + SD ≥24 weeks)	118 (34.0)	33 (19.0)
95% exact CI for CBR rate [1]	29.0, 39.3	13.4, 25.6
Stratified analysis		

	Palbociclib plus Fulvestrant N=347	Placebo plus Fulvestrant N=174
	n (%)	n (%)
Odds ratio [2]	2.189	
95% exact CI	1.391,3.523	
p-value [3]	0.0002	
Unstratified analysis		
Odds ratio [2]	2.202	
95% exact CI	1.396,3.530	
p-value [4]	0.0002	

Abbreviations: CBR: clinical benefit response, CI: confidence interval, CR: complete response, N: number of subjects, n: number of subjects affected, PR: partial response, SD: stable disease

1. CI was calculated using the exact (Clopper-Pearson) method.
2. An Odds Ratio > 1 means better response in favor of palbociclib plus fulvestrant arm.
3. 1-sided exact test stratified by the presence of visceral metastases and sensitivity to prior hormonal therapy per randomization.
4. 1-sided p-value is from exact test.

Minimum Observed Plasma Trough Concentration (Ctrough) for Palbociclib, Fulvestrant and Goserelin

The presence or absence of goserelin did not have a meaningful effect of palbociclib PK. Palbociclib geometric mean steady-state C_{trough} in the presence of concurrent fulvestrant administration (without regard for goserelin dosing) in Study 1023 was 76.62 ng/mL while the reported value from pooled historical studies where fulvestrant was not present was 58.77 ng/mL (Table 10).

Table 10: Summary of Plasma Palbociclib Steady-State Pharmacokinetic Parameters Following Daily 125 mg Oral Doses of Palbociclib by Unique Drug Combination

Unique Drug Combination	Parameter [Units]	Parameter Summary Statistics[1] by Treatment		
		Cycle 1/Day 15	Cycle 2/Day 15	Combined[2]
Palbociclib + Fulvestrant + Goserelin	N	35	33	43
	C_{trough} [ng/mL]	62.04 (51)	69.39 (50)	72.04 (48)
Palbociclib + Fulvestrant - Goserelin	N	130	127	175
	C_{trough} [ng/mL]	73.23 (42)	76.91 (42)	77.79 (40)
Palbociclib + Fulvestrant Total	N	165	160	218
	C_{trough} [ng/mL]	70.70 (44)	75.29 (44)	76.62 (41)
Palbociclib Historical Data[3]	N	--	--	98
	C_{trough} [ng/mL]	--	--	58.77 (45)

Abbreviation: CV: coefficient of variation, N: Number of subjects contributing to the geometric mean estimation

1. Geometric mean (% CV)
2. Within-subject mean of steady-state $C_{troughs}$.
3. From Studies 1001, 1002, and 1003.

The presence or absence of goserelin did not have an impact on fulvestrant PK, the "palbociclib plus fulvestrant Total" drug combination was the most appropriate selection for the test treatment group and the "placebo plus fulvestrant Total" drug combination was the

most appropriate selection for the reference group to assess the potential for palbociclib to fulvestrant plasma PK. (Table 11). Fulvestrant steady-state exposures, as measured by the geometric mean of the within-subject mean steady-state C_{trough} from Day 1 of Cycles 2 and 3, were 10.80 ng/mL and 8.85 ng/mL in the presence and absence of concurrent palbociclib administration respectively (Table 11).

Table 11: Summary of Plasma Fulvestrant Steady-State Pharmacokinetic Parameters by Unique Drug Combination

Unique Drug Combination	Parameter [Units]	Parameter Summary Statistics[1] by Treatment		
		Cycle 2/Day 1	Cycle 3/Day 1	Combined[2]
Palbociclib + Fulvestrant + Goserelin	N	8	7	9
	C_{trough} [ng/mL]	12.59 (42)	10.62 (57)	11.05 (49)
Palbociclib + Fulvestrant - Goserelin	N	27	22	28
	C_{trough} [ng/mL]	11.51 (41)	9.68 (35)	10.72 (36)
Palbociclib + Fulvestrant Total	N	35	29	37
	C_{trough} [ng/mL]	11.75 (41)	9.90 (42)	10.80 (39)
Placebo + Fulvestrant + Goserelin	N	5	3	5
	C_{trough} [ng/mL]	10.79 (36)	7.85 (21)	10.36 (40)
Placebo + Fulvestrant - Goserelin	N	14	11	14
	C_{trough} [ng/mL]	8.83 (59)	7.54 (79)	8.36 (64)
Placebo + Fulvestrant Total	N	19	14	19
	C_{trough} [ng/mL]	9.31 (52)	7.60 (72)	8.85 (57)

Abbreviation: CV: coefficient of variation, N: number of subjects contributing to the geometric mean estimation
1. Geometric mean (% CV)
2. Within-subject mean of steady-state C_{trough}

Goserelin steady-state exposures, as measured by the geometric mean of the within-subject mean steady-state C_{trough} from Day 1 of Cycles 2 and 3, were 302.9 pg/mL and 274.4 pg/mL in the presence and absence of concurrent palbociclib administration, respectively (Table 12).

Table 12: Summary of Plasma Goserelin Steady-State Pharmacokinetic Parameters by Unique Drug Combination

Unique Drug Combination	Parameter [Units]	Parameter Summary Statistics[1] by Treatment		
		Cycle 2/Day 1	Cycle 3/Day 1	Combined [2]
Palbociclib + Fulvestrant + Goserelin	N	9	7	9
	C_{trough} [pg/mL]	295.1 (153)	344.8 (64)	302.9 (115)
Placebo + Fulvestrant + Goserelin	N	5	3	5
	C_{trough} [pg/mL]	302.5 (74)	288.5 (40)	274.4 (49)

Abbreviation: CV: coefficient of variation, N=Number of subjects contributing to the geometric mean estimation, NC=not calculated
1. Geometric mean (% CV)
2. Within-subject mean of steady-state $C_{troughs}$

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

Descriptive statistics for change from baseline EORTC QLQ-C30 scores are presented in Table 13.

Table 13: QLQ-C30 Scale Scores Between Treatment Comparison (Mixed Effects Model) - PRO Analysis Set

Functional Scales	Palbociclib (PD-0332991) + Fulvestrant (N=335) Mean (95% CI)	Placebo + Fulvestrant (N= 166) Mean (95% CI)	Palbociclib (PD-0332991) + Fulvestrant – Placebo + Fulvestrant		
			Mean	95% CI	P-value
Global health status / QoL	-0.9 (-2.5 to 0.7)	-4.0 (-6.3 to -1.7)	3.1	0.3 , 6.0	0.0313
Physical functioning	-0.7 (-2.1 to 0.7)	-1.7 (-3.7 to 0.2)	1.0	-1.4, 3.5	0.4000
Role functioning	-1.8 (-3.7 to 0.1)	-3.7 (-6.5 to -0.9)	1.9	-1.5, 5.3	0.2615
Emotional functioning	2.7 (1.1 to 4.3)	-1.9 (-4.2 to 0.5)	4.6	1.7, 7.4	0.0016
Cognitive functioning	-1.7 (-3.1 to -0.2)	-2.9 (-5.0 to -0.7)	1.2	-1.4, 3.8	0.3650
Social functioning	-0.5 (-2.5 to 1.5)	-0.6 (-3.4 to 2.3)	0.1	-3.4, 3.5	0.9615

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.
QLQ-C30 questionnaire employs 4-point scales with responses from 'not at all' to 'very much' on 28 items and a 7-point scale with responses 'very poor' to 'excellent' on 2 items assessing global health and overall QOL. All scores are converted to a 0 to 100 scale. For functional and global QOL scales, higher scores represent a better level of functioning.
The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Change from Baseline in EORTC QLQ-C30 Symptom Scale Scores

Between-treatment comparisons of overall EORTC–QLQ-C30 scale scores from repeated measures analyses are presented in Table 14.

Table 14: QLQ-C30 Scale Scores Between Treatment Comparison (Mixed Effects Model) - PRO Analysis Set

Functional Scales	Palbociclib (PD-0332991) + Fulvestrant (N=335) Mean (95% CI)	Placebo + Fulvestrant (N= 166) Mean (95% CI)	Palbociclib (PD-0332991) + Fulvestrant – Placebo + Fulvestrant		
			Mean	95% CI	P-value
Fatigue	1.8 (0.1 to 3.5)	3.3 (0.9 to 5.8)	-1.5	-4.5, 1.5	0.3200
Nausea and vomiting	1.7 (0.4 to 3.0)	4.2 (2.3 to 6.1)	-2.5	-4.8, -0.2	0.0369
Pain	-3.3 (-5.1 to -1.5)	2.0 (-0.6 to 4.6)	-5.3	-8.5, -2.1	0.0011
Dyspnoea	2.8 (1.0 to 4.7)	3.3 (0.6 to 6.0)	-0.5	-3.7, 2.8	0.7699
Insomnia	-2.4 (-4.4 to -0.4)	-0.4 (-3.3 to 2.5)	-2.0	-5.5, 1.6	0.2721
Appetite loss	1.1 (-0.8 to 3.1)	1.7 (-1.1 to 4.6)	-0.6	-4.1, 2.9	0.7334
Constipation	3.5 (1.7 to 5.3)	2.8 (0.1 to 5.4)	0.7	-2.5, 3.9	0.6491
Diarrhoea	1.9 (0.6 to 3.1)	2.4 (0.5 to 4.3)	-0.6	-2.8, 1.7	0.6293
Financial difficulties	-3.7 (-5.6 to -1.9)	-4.0 (-6.7 to -1.3)	0.3	-3.1, 3.6	0.8812

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.
QLQ-C30 questionnaire employs 4-point scales with responses from 'not at all' to 'very much' on 28 items and a 7-point scale with responses 'very poor' to 'excellent' on 2 items assessing global health and overall QOL. All scores are converted to a 0 to 100 scale. For symptom-oriented scales, a higher score represents more severe symptoms.
The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

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

Between-treatment comparisons of overall EORTC -QLQ-BR23 functioning scale scores from the repeated measures analyses are presented in Table 15.

Table 15: QLQ-BR23 Scale Scores Between Treatment Comparison (Mixed Effects Model) - PRO Analysis Set

Functional Scales	Palbociclib (PD-0332991) + Fulvestrant (N=335) Mean (95% CI)	Placebo + Fulvestrant (N= 166) Mean (95% CI)	Palbociclib (PD-0332991) + Fulvestrant – Placebo + Fulvestrant		
			Mean	95% CI	P-value
Body image	1.9 (0.2 to 3.6)	-0.3 (-2.8 to 2.1)	2.3	-0.7, 5.2	0.1386
Sexual functioning	-1.1 (-2.5 to 0.2)	-0.4 (-2.3 to 1.5)	-0.8	-3.1, 1.6	0.5235
Sexual enjoyment	-5.2 (-8.3 to -2.1)	-6.6 (-11.6 to -1.7)	1.4	-4.4, 7.3	0.6271
Future perspective	8.1 (5.8 to 10.4)	4.5 (1.2 to 7.9)	3.6	-0.5, 7.6	0.0845

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.
QLQ-BR23 questionnaire employs 23 4 point scales with responses from 'not at all' to 'very much'. All scores are converted to a 0 to 100 scale. For functional scales, higher scores represent a better level of functioning.
The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Change from Baseline in EORTC QLQ BR23 Symptom Scale Scores

Between-treatment comparisons of overall EORTC –QLQ-BR23 symptom scale scores from the repeated measures analyses are presented in Table 16.

Table 16: QLQ-BR23 Scale Scores Between Treatment Comparison (Mixed Effects Model) - PRO Analysis Set

Functional Scales	Palbociclib (PD-0332991) + Fulvestrant (N=335) Mean (95% CI)	Placebo + Fulvestrant (N= 166) Mean (95% CI)	Palbociclib (PD-0332991) + Fulvestrant – Placebo + Fulvestrant		
			Mean	95% CI	P-value
Systemic therapy side effects	3.8 (2.6 to 4.9)	3.4 (1.8 to 5.0)	0.4	-1.6, 2.3	0.7273
Breast symptoms	-2.2 (-3.2 to -1.3)	-1.3 (-2.7 to 0.0)	-0.9	-2.6, 0.7	0.2671
Arm symptoms	-2.2 (-3.6 to -0.9)	-2.0 (-4.0 to -0.1)	-0.2	-2.6, 2.2	0.8750
Upset by hair loss	2.9 (-1.7 to 7.4)	-6.0 (-12.3 to 0.3)	8.9	1.1, 16.6	0.0255

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.
QLQ-BR23 questionnaire employs 23 4 point scales with responses from 'not at all' to 'very much'. All scores are converted to a 0 to 100 scale. For functional scales, higher scores represent a better level of functioning.
The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

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

The between-treatment comparisons of EQ-5D Index scores and comparison for change from baseline is presented in Table 17.

Table 17: EQ-5D Index Between Treatment Comparison (Mixed Effects Model) - PRO Analysis Set

	Palbociclib (PD-0332991) + Fulvestrant (N=335) Mean (95% CI)	Placebo + Fulvestrant (N= 166) Mean (95% CI)	Palbociclib (PD-0332991) + Fulvestrant – Placebo + Fulvestrant		
			Mean	95% CI	P-value
EuroQoL 5D – Health Index Scores	0.006 (-0.01 to 0.03)	-0.031 (-0.06 to 0.00)	0.037	0.00, 0.07	0.0308

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.
Based on subjects who completed all 5 items needed to calculate the index-based summary score at the respective cycle. Higher values indicate a better health state.
The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

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

The visual analog scale within the EQ-5D assesses general health status; the change from baseline scores is presented in Table 18.

Table 18: EQ-VAS Scale Change from Baseline - PRO Analysis Set

	Palbociclib (PD-0332991) + Fulvestrant (N=335) Mean (95% CI)	Placebo + Fulvestrant (N= 166) Mean (95% CI)	Palbociclib (PD-0332991) + Fulvestrant – Placebo + Fulvestrant		
			Mean	95% CI	P-value
EuroQoL 5D – Health Index Scores	-1.8 (-3.3 to -0.3)	-2.6 (-4.8 to -0.4)	0.8	-1.9, 3.5	0.5523

Analysis based on repeated measures mixed-effects model with an intercept term, treatment, time, treatment-by-time, and baseline as covariate.
EQ-VAS ranges from 0 (worst imaginable health state) to 100 (best imaginable health state). Change from baseline = Cycle X - Baseline. Negative changes from baseline indicate deterioration in health state.
The priori threshold for statistical significance is 2-sided alpha=0.05. The p-value was not adjusted for multiple comparisons.

Time to Deterioration (TTD)

An analysis of TTD in pain defined as time between baseline and first occurrence of increase of ≥10 points in pain was carried out based on survival analysis methods using cox proportional hazards model and log rank test. A summary of the TTD in pain is provided in Table 19.

Table 19: QLQ-C30 Time to Deterioration - Symptom Scale of Pain Increase of ≥10 Points - PRO Analysis Population

	Palbociclib plus Fulvestrant N=335	Placebo plus Fulvestrant N=166
	n (%)	n (%)
Subject had symptom scale of pain increase of ≥10 points while on study [n (%)]	131 (39.1)	83 (50.0)
Subject did not have symptom scale of pain increase of ≥10 points while on study [n (%)]	204 (60.9)	83 (50.0)
Kaplan-Meier estimates of time to event (month)		
Quartiles (95% CI) [1]		
25%	1.9 [1.2,2.2]	1.0 [1.0,1.9]
50%	8.0 [5.6, NE]	2.8 [2.3,5.4]
75%	NE	NE
Unstratified analysis [4]		
Hazard ratio [2]	0.642	
95% CI of Hazard ratio	0.487-0.846	
p-value [3]	<0.001	

Abbreviations: CI: confidence interval, EORTC-QLQ-C30: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, N: number of subjects, n: number of subjects affected, NE: not estimable, PRO: subject-reported outcome

1 Based on the Brookmeyer and Crowley Method.
2 Assuming proportional hazards, a hazard ratio less than 1 indicates a reduction in hazard rate in favor of the palbociclib plus fulvestrant arm.
3 Used a 1-sided unstratified log-rank test and an unstratified Cox proportional hazards model.

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

Overall, 490 (94.8%) of all subjects (AT population) experienced a total of 4096 TEAEs; 337 (97.7%) subjects in the palbociclib plus fulvestrant arm experienced 3045 TEAEs, and 153 (89.0%) subjects in the placebo plus fulvestrant arm experienced 1051 TEAEs (Table 20).

Table 20: Treatment-Emergent Adverse Events All Causalities – As-treated population

Number of subjects	Palbociclib plus Fulvestrant n (%)	Placebo plus Fulvestrant n (%)	Total n (%)
Number of subjects			
Subjects evaluable for AEs	345	172	517
Number of AEs	3045	1051	4096
Subjects with AEs	337 (97.7)	153 (89.0)	490 (94.8)
Subjects with SAEs	33 (9.6)	24 (14.0)	57 (11.0)
Subjects with Grade 3 or 4 AEs	242 (70.1)	31 (18.0)	273 (52.8)
Subjects with Grade 5 AEs [1]	3 (0.9)	2 (1.2)	5 (1.0)
Subjects discontinued study due to AEs	2 (0.6)	3 (1.7)	5 (1.0)
Subject discontinued palbociclib/placebo due to AEs	13 (3.8)	7 (4.1)	20 (3.9)
Subjects discontinued fulvestrant due to AEs	11 (3.2)	5 (2.9)	16 (3.1)
Subjects temporarily discontinued palbociclib/placebo due to AEs	223 (64.6)	14 (8.1)	237 (45.8)
Subjects temporarily discontinued fulvestrant due to AEs	83 (24.1)	6 (3.5)	89 (17.2)
Subjects with palbociclib/placebo dose reduction of due to AEs	107 (31.0)	3 (1.7)	110 (21.3)
Subjects with dose interruptions of fulvestrant due to AEs	3 (0.9)	0	3 (0.6)

Abbreviations: AE: adverse event, n: number of subjects affected, SAE: serious adverse event
Includes data up to 28 days after last dose of study drug.
Except for the Number of AEs subjects are counted only once per treatment in each row.
Percentages are calculated in the reference to number of subjects evaluable for AEs.
SAEs - according to the investigator's assessment.
Severity counts are based on the maximum severity or grade of events.
[1] Subject A died on study but no TEAE Grade 5 was recorded on CRF AE page.
MedDRA (v17.1) coding dictionary applied.

Safety Results

AEs

All causality and treatment-related non-serious AEs are presented in Table 21. Overall, 333 (96.5%) subjects in the Palbociclib + Fulvestrant arm and 147 (85.5%) subjects in the Placebo + Fulvestrant arm experienced all causality treatment-emergent, non-serious AEs. Overall, 311 (90.1%) subjects in the Palbociclib + Fulvestrant arm and 98 (57.0%) subjects in the Placebo + Fulvestrant arm experienced treatment-related non-serious AEs.

SAEs

All causality and treatment-related SAEs are presented in Table 22. Overall, only 33 (9.6%) subjects in the Palbociclib + Fulvestrant arm and 24 (14.0%) subjects in the Placebo + Fulvestrant arm experienced all causality treatment-emergent, SAEs. Overall, 12 (3.5%) subjects in the Palbociclib + Fulvestrant arm and 3 (1.7%) subjects in the Placebo + Fulvestrant arm experienced treatment-related serious AEs.

Table 21: Treatment-Emergent Non-Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-Related) – Safety Analysis Set.

System Organ Class Preferred Term	Palbociclib (PD-0332991) + Fulvestrant (N=345) n (%)		Placebo + Fulvestrant (N=172) n (%)	
	All Causalities	Treatment related	All Causalities	Treatment related
Number (%) of Subjects with Non-Serious Adverse Events by System Organ Class	**333 (96.5)**	**311 (90.1)**	**147 (85.5)**	**98 (57.0)**
Blood and lymphatic system disorders	**247 (71.6)**	**242 (70.1)**	**18 (10.5)**	**13 (7.6)**
Anaemia	88 (25.5)	80 (23.2)	17 (9.9)	12 (7.0)
Leukopenia	70 (20.3)	70 (20.3)	2 (1.2)	2 (1.2)
Neutropenia	212 (61.4)	209 (60.6)	3 (1.7)	2 (1.2)
Thrombocytopenia	40 (11.6)	39 (11.3)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	**203 (58.8)**	**139 (40.3)**	**89 (51.7)**	**59 (34.3)**
Abdominal pain	21 (6.1)	-	9 (5.2)	-
Abdominal pain upper	12 (3.5)	-	11 (6.4)	-
Constipation	58 (16.8)	28 (8.1)	24 (14.0)	13 (7.6)
Diarrhoea	66 (19.1)	37 (10.7)	30 (17.4)	20 (11.6)
Dry mouth	22 (6.4)	18 (5.2)	14 (8.1)	10 (5.8)
Dyspepsia	25 (7.2)	-	7 (4.1)	-
Nausea	100 (29.0)	77 (22.3)	44 (25.6)	34 (19.8)
Stomatitis	40 (11.6)	37 (10.7)	4 (2.3)	2 (1.2)
Vomiting	50 (14.5)	27 (7.8)	20 (11.6)	9 (5.2)
General disorders and administration site conditions	**181 (52.5)**	**109 (31.6)**	**81 (47.1)**	**43 (25.0)**
Asthenia	23 (6.7)	-	8 (4.7)	-
Chest pain	6 (1.7)	-	9 (5.2)	-
Fatigue	131 (38.0)	99 (28.7)	46 (26.7)	34 (19.8)
Injection site pain	19 (5.5)	17 (4.9)	16 (9.3)	13 (7.6)
Oedema peripheral	25 (7.2)	-	8 (4.7)	-
Pain	15 (4.3)	-	12 (7.0)	-
Pyrexia	27 (7.8)	-	6 (3.5)	-
Infections and infestations	**42 (12.2)**	**-**	**16 (9.3)**	**-**
Nasopharyngitis	25 (7.2)	-	9 (5.2)	-
Upper respiratory tract infection	20 (5.8)	-	7 (4.1)	-
Investigations	**128 (37.1)**	**117 (33.9)**	**12 (7.0)**	**5 (2.9)**
Aspartate aminotransferase increased	19 (5.5)	-	8 (4.7)	-
Neutrophil count decreased	73 (21.2)	72 (20.9)	3 (1.7)	2 (1.2)
Platelet count decreased	27 (7.8)	27 (7.8)	0 (0.0)	0 (0.0)
White blood cell count decreased	92 (26.7)	92 (26.7)	5 (2.9)	4 (2.3)
Metabolism and Nutrition Disorders	**44 (12.8)**	**26 (7.5)**	**13 (7.6)**	**10 (5.8)**
Decreased appetite	44 (12.8)	26 (7.5)	13 (7.6)	10 (5.8)
Musculoskeletal and Connective Tissue Disorders	**123 (35.7)**	**33 (9.6)**	**78 (45.3)**	**21 (12.2)**
Arthralgia	45 (13.0)	23 (6.7)	28 (16.3)	13 (7.6)
Back pain	38 (11.0)	-	25 (14.5)	-
Muscle spasms	21 (6.1)	-	11 (6.4)	-
Musculoskeletal chest pain	9 (2.6)	-	9 (5.2)	-
Musculoskeletal pain	20 (5.8)	-	11 (6.4)	-
Myalgia	23 (6.7)	16 (4.6)	12 (7.0)	9 (5.2)
Pain in extremity	33 (9.6)	-	19 (11.0)	-
Nervous System Disorders	**103 (29.9)**	**27 (7.8)**	**46 (26.7)**	**13 (7.6)**
Dizziness	37 (10.7)	-	16 (9.3)	-

Dysgeusia	22 (6.4)	-	3 (1.7)	-
Headache	73 (21.2)	27 (7.8)	30 (17.4)	13 (7.6)
Psychiatric Disorders	**48 (13.9)**	**-**	**27 (15.7)**	**-**
Anxiety	14 (4.1)	-	9 (5.2)	-
Depression	16 (4.6)	-	10 (5.8)	-
Insomnia	27 (7.8)	-	12 (7.0)	-
Respiratory, Thoracic and Mediastinal Disorders	**98 (28.4)**	**-**	**34 (19.8)**	**-**
Cough	45 (13.0)	-	18 (10.5)	-
Dyspnoea	37 (10.7)	-	10 (5.8)	-
Epistaxis	19 (5.5)	-	2 (1.2)	-
Oropharyngeal pain	32 (9.3)	-	9 (5.2)	-
Skin and Subcutaneous Tissue Disorders	**88 (25.5)**	**65 (18.8)**	**26 (15.1)**	**13 (7.6)**
Alopecia	51 (14.8)	45 (13.0)	10 (5.8)	9 (5.2)
Pruritus	19 (5.5)	-	10 (5.8)	-
Rash	31 (9.0)	24 (7.0)	7 (4.1)	4 (2.3)
Vascular Disorders	**51 (14.8)**	**39 (11.3)**	**28 (16.3)**	**21 (12.2)**
Hot flush	51 (14.8)	39 (11.3)	28 (16.3)	21 (12.2)

The symbol "-"represents the event was not captured in the source table.
Subjects are only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
MedDRA (v17.1) coding dictionary applied.

Table 22: Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities and Treatment-related) – Safety Analysis Set

System Organ Class Preferred Term	Palbociclib (PD-0332991) + Fulvestrant (N=345) n (%)		Placebo + Fulvestrant (N=172) n (%)	
	All Causalities	Treatment related	All Causalities	Treatment related
Number (%) of Subjects with Serious Adverse Events by System Organ Class	**33 (9.6)**	**12 (3.5)**	**24 (14.0)**	**3 (1.7)**
Blood and lymphatic system disorders	**3 (0.9)**	**2 (0.6)**	**1 (0.6)**	**0 (0.0)**
Disseminated intravascular coagulation	1 (0.3)	-	0 (0.0)	-
Febrile neutropenia	1 (0.3)	1 (0.3)	1 (0.6)	0 (0.0)
Neutropenia	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Cardiac Disorders	**2 (0.6)**	**1 (0.3)**	**0 (0.0)**	**0 (0.0)**
Atrial fibrillation	1 (0.3)	-	0 (0.0)	-
Pericarditis	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Endocrine Disorders	**1 (0.3)**	**-**	**0 (0.0)**	**-**
Hyperthyroidism	1 (0.3)	-	0 (0.0)	-
Gastrointestinal disorders	**4 (1.2)**	**1 (0.3)**	**2 (1.2)**	**0 (0.0)**
Abdominal pain	1 (0.3)	-	0 (0.0)	-
Ascites	0 (0.0)	-	2 (1.2)	-
Duodenogastric reflux	1 (0.3)	-	0 (0.0)	-
Intestinal obstruction	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Nausea	0 (0.0)	-	1 (0.6)	-
Pancreatitis	0 (0.0)	-	1 (0.6)	-
Vomiting	1 (0.3)	-	1 (0.6)	-
General disorders and administration site conditions	**8 (2.3)**	**0 (0.0)**	**4 (2.3)**	**1 (0.6)**
Chest pain	0 (0.0)	-	1 (0.6)	-
Device occlusion	1 (0.3)	-	0 (0.0)	-

Disease progression	2 (0.6)	-	0 (0.0)	-
General physical health deterioration	1 (0.3)	-	0 (0.0)	-
Non-cardiac chest pain	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
Oedema peripheral	1 (0.3)	-	1 (0.6)	-
Pain	1 (0.3)	-	0 (0.0)	-
Pyrexia	3 (0.9)	-	1 (0.6)	-
Hepatobiliary Disorders	**2 (0.6)**	**1 (0.3)**	**1 (0.6)**	**1 (0.6)**
Cholecystitis	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
Cholelithiasis	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Hepatic failure	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Infections and Infestations	**7 (2.0)**	**3 (0.9)**	**4 (2.3)**	**1 (0.6)**
Bacteraemia	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Cellulitis	1 (0.3)	-	0 (0.0)	-
Erysipelas	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Gastrointestinal infection	0 (0.0)	-	1 (0.6)	-
Otitis media acute	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Pharyngitis	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Pneumonia	1 (0.3)	-	2 (1.2)	-
Pyelonephritis	0 (0.0)	0 (0.0)	1 (0.6)	1 (0.6)
Upper respiratory tract infection	1 (0.3)	-	0 (0.0)	-
Urinary tract infection	1 (0.3)	-	0 (0.0)	-
Injury, Poisoning and Procedural Complications	**0 (0.0)**	**-**	**4 (2.3)**	**-**
Femur fracture	0 (0.0)	-	1 (0.6)	-
Fracture	0 (0.0)	-	1 (0.6)	-
Humerus fracture	0 (0.0)	-	1 (0.6)	-
Road traffic accident	0 (0.0)	-	1 (0.6)	-
Investigations	**4 (1.2)**	**3 (0.9)**	**0 (0.0)**	**0 (0.0)**
Alanine aminotransferase increased	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Electrocardiogram QT prolonged	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Neutrophil count	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Troponin increased	1 (0.3)	-	0 (0.0)	-
Metabolism and Nutrition Disorders	**1 (0.3)**	**-**	**0 (0.0)**	**-**
Dehydration	1 (0.3)	-	0 (0.0)	-
Musculoskeletal and Connective Tissue Disorders	**2 (0.6)**	**-**	**4 (2.3)**	**-**
Back pain	1 (0.3)	-	2 (1.2)	-
Osteonecrosis of jaw	0 (0.0)	-	1 (0.6)	-
Pain in extremity	1 (0.3)	-	0 (0.0)	-
Pathological fracture	0 (0.0)	-	1 (0.6)	-
Nervous System Disorders	**3 (0.9)**	**1 (0.3)**	**3 (1.7)**	**0 (0.0)**
Aphasia	0 (0.0)	-	1 (0.6)	-
Cerebral haemorrhage	0 (0.0)	-	1 (0.6)	-
Cerebrovascular accident	0 (0.0)	-	1 (0.6)	-
Dysarthria	0 (0.0)	-	1 (0.6)	-
Facial paresis	0 (0.0)	-	1 (0.6)	-
Migraine	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Sedation	1 (0.3)	-	0 (0.0)	-
Somnolence	1 (0.3)	-	0 (0.0)	-
Psychiatric Disorders	**2 (0.6)**	**-**	**0 (0.0)**	**-**
Depression	1 (0.3)	-	0 (0.0)	-
Psychotic disorder	1 (0.3)	-	0 (0.0)	-
Respiratory, Thoracic and Mediastinal Disorders	**6 (1.7)**	**-**	**7 (4.1)**	**-**
Acute respiratory distress syndrome	0 (0.0)	-	1 (0.6)	-
Chronic obstructive pulmonary syndrome	1 (0.3)	-	1 (0.6)	-
Dyspnoea	1 (0.3)	-	1 (0.6)	-
Pleural effusion	1 (0.3)	-	3 (1.7)	-
Pulmonary embolism	3 (0.9)	-	0 (0.0)	-

Pulmonary hypertension	0 (0.0)	-	1 (0.6)	-
Skin and Subcutaneous Tissue Disorders	**1 (0.3)**	**1 (0.3)**	**0 (0.0)**	0 (0.0)
Rach maculo-papular	1 (0.3)	1 (0.3)	0 (0.0)	0 (0.0)
Vascular Disorders	**1 (0.3)**	**-**	**0 (0.0)**	-
Deep vein thrombosis	1 (0.3)	-	0 (0.0)	-

The symbol "-"represents the event was not captured in the source table.
Subjects are only counted once per treatment for each row.
Includes data up to 28 days after last dose of study drug.
MedDRA (v17.1) coding dictionary applied.

Deaths

Table 23 presents the summary of deaths in this study.

Table 23: Summary of Deaths – As Treated

	Palbociclib plus Fulvestrant (N=345) n (%)	Placebo plus Fulvestrant (N=172) n (%)	Total (N= 517) n (%)
Number of deaths from start of treatment to last dose including 28 days after last dose	4 (1.2)	2 (1.2)	6 (1.2)
Cause of Death			
Disease under study	4 (1.2)	1 (0.6)	5 (1.0)
Study Treatment Toxicity	0	0	0
Other*	0	1 (0.6)	1 (0.2)
Unknown	0	0	0
Number of Deaths during Follow-Up period Occuring after 28 Days after Last Dose	15 (4.3)	7 (4.1)	22 (4.3)
Cause of Death			
Disease Under Study	14 (4.1)	7 (4.1)	21 (4.1)
Study Treatment Toxicity	0	0	0
Other	0	0	0
Unknown	1 (0.3)	0	1 (0.2)

*Other category for a subject is specified as 'Intracerebral Haemorrhage, likely caused by arterio-venous malformation'.

Permanent Discontinuations due to AEs

Overall, a similar percentage of subjects in the palbociclib plus fulvestrant arm and in the placebo plus fulvestrant arm experienced TEAEs associated with permanent discontinuation (3.8% vs 4.7%, respectively) of palbociclib/placebo or fulvestrant. In the palbociclib plus fulvestrant arm, no TEAEs that were associated with permanent discontinuation were reported in more than 2 (0.6%) subjects; only anemia, neutropenia and thrombocytopenia were reported in 2 subjects. All TEAEs associated with permanent discontinuation in the placebo plus fulvestrant arm were reported in 1 (0.6%) subject each, except for ascites and pleural effusion, which were reported in 2 (1.2%) subjects.

There were no notable differences between the treatment arms in the proportions of subjects who experienced TEAEs associated with permanent discontinuation of palbociclib/placebo (3.8% vs 4.1%) or who experienced TEAEs associated with permanent discontinuation of fulvestrant (3.2% vs 2.9%).

Conclusions:

- The addition of palbociclib to fulvestrant resulted in a statistically significant, and clinically meaningful improvement in PFS as compared with placebo plus fulvestrant in the treatment of pre/peri- and postmenopausal women with HR-positive, HER2-negative metastatic breast cancer whose disease had progressed after prior endocrine therapy (median PFS: 9.2 months vs 3.8 months; HR=0.422; 95% CI: 0.318 to 0.560, 1-sided $p<0.000001$).

- The results across response-based analyses, including supportive PFS analyses, OR, DR, and CBR, are consistent and support the robustness of the primary PFS analysis at the time of the data cutoff.

- The combination of palbociclib plus fulvestrant was well tolerated and the majority of TEAEs were non-serious and manageable, as evidenced by the low rates of permanent discontinuation due to treatment-related AEs. The majority of subjects experienced TEAEs that were mild to moderate in severity with the exception of the TEAEs under the system organ class (SOC) blood and lymphatic system disorders.

- There was a lack of a clinically relevant drug-drug interaction (DDI) between palbociclib and goserelin when the two drugs are coadministered.

- There was a lack of a clinically relevant DDI between palbociclib and fulvestrant when the two drugs are coadministered.

- The subject-reported outcomes support the positive impact of palbociclib plus fulvestrant, maintaining global QOL on treatment and resulting in a statistically significantly higher on-treatment global QOL compared to placebo plus fulvestrant. In addition, palbociclib plus fulvestrant had a statistically significantly greater improvement from baseline in emotional functioning and pain. A significantly greater delay in time to deterioration in pain was observed with palbociclib plus fulvestrant than with placebo plus fulvestrant.