



**A MULTICENTER, RANDOMIZED, DOUBLE-BLIND PHASE 3 STUDY OF  
PALBOCICLIB (ORAL CDK 4/6 INHIBITOR) PLUS LETROZOLE VERSUS  
PLACEBO PLUS LETROZOLE FOR THE TREATMENT OF PREVIOUSLY  
UNTREATED ASIAN POSTMENOPAUSAL WOMEN WITH ER (+), HER2 (-)  
ADVANCED BREAST CANCER**

<b>Compound:</b>	PD-0332991
<b>Compound Name:</b>	Palbociclib
<b>US IND Number:</b>	Not Applicable (N/A)
<b>European Clinical Trial Database (EudraCT) Number:</b>	N/A
<b>Protocol Number:</b>	A5481027
<b>Phase:</b>	3

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**Document History**

<b>Document</b>	<b>Version Date</b>	<b>Summary of Changes and Rationale (if applicable)</b>
Amendment 1	21 July 2014	<ol style="list-style-type: none"> <li>1. Study Title: Changed East Asian to Asian, and throughout as applicable.</li> <li>2. Background and Rationale: Updated A5481003 study final results.</li> <li>3. Secondary Objective: Included determination of trough Palbociclib plasma concentration in this patient population and exploration the correlations between exposure and response and/or safety findings;</li> <li>4. Secondary Endpoints: Added Trough plasma concentration of Palbociclib;</li> <li>5. Study design: Added region (China vs other) as a randomization stratification.</li> <li>6. Schedule of Activities / Section 6 Procedures: Added of ophthalmic procedures for all evaluable patients to assess the potential risk of palbociclib-associated crystalline lens changes.</li> <li>7. Schedule of Activities: Added heamatology assessment on Day 21 of Cycle 1, changed heamatology assessment on Day 14 of Cycle 2 to Day 21.</li> <li>8. Schedule of Activities: Added of 12-lead ECG assessments on Day 14 of Cycle 1 and Cycle 2, and on Day 1 from Cycle 3.</li> <li>9. Schedule of Activities / Section 6 Procedures: Added glucose levels and lipid levels to be assessed in all patients at various intervals.</li> <li>10. Schedule of Activities / Section 6 Procedures: Added of plasma PK samples collection for all patients.</li> <li>11. Section 1.2.5.2. – Added preliminary results from two clinical pharmacology studies</li> </ol>

		<p>supporting revisions of Sections 5.3.3, 5.5.1. and 5.5.2.</p> <p>12. Section 1.2.5.4. Ocular Preclinical Data: Included preliminary results from a preclinical ocular study with palbociclib in rats.</p> <p>13. Section 3 Study Design: Clarified that safety-related assessments must continue if patients continue study treatment beyond RECIST-defined disease progression.</p> <p>14. Clarified inclusion criterion #10 to emphasize the importance of collecting recurrent/metastatic tissue whenever possible.</p> <p>15. Clarified inclusion criterion #10 it is highly recommend to submit tissue block or 12 unstained slides, but if there would be technical difficulties or other issues refraining from obtaining tissue block or 12 unstained slides, however, it is still mandatory to collect a minimum 7 unstained slides.</p> <p>16. Modified inclusion criterion #4 to clarify that patients with FSH/estradiol blood levels within the post-menopausal range may be eligible.</p> <p>17. Clarified exclusion criterion #1 to highlight the need to confirm HER2 status on the most recent tumor sample whenever possible.</p> <p>18. Revised exclusion criterion #17 to only exclude patients participating in the active treatment phase of other interventional trials within the protocol-defined period.</p> <p>19. Section 5.3.3 - Added recommendation to take palbociclib with a meal instead of under minimal fasting conditions.</p> <p>20. Section 5.3.4 – Added Table 3.1 Palbociclib/Placebo Dose Modifications for Hematologic Toxicities (by CTCAE Grade and on Day of Treatment).</p> <p>21. Section 5.5.1 - Added prohibition to take</p>
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		<p>proton-pump inhibitors while receiving study drugs.</p> <p>22. Section 5.5.2 - Added recommendation to use local antacids as well as H<sub>2</sub>-receptor antagonist as alternative treatment for patients requiring gastroprotective treatment.</p> <p>23. Section 7.2.3. Ocular Safety Assessment: Section added to provide details on the ophthalmic procedures to be performed for all lens grading evaluable patients.</p> <p>24. Section 7.2.4. Added glucose levels and lipid levels to be monitored in all patients at various intervals as outlined in the Schedule of Activities.</p> <p>25. Section 7.3: Added pharmacokinetic assessment.</p> <p>26. Section 8 Adverse Event Reporting: Updated section to reflect current protocol template.</p> <p>27. Section 9.1 Sample Size Determination: Revised sample size to use the same assumption for the treatment effect as the corresponding global study (A5481008) originally proposed. The required number of PFS events increased from 137 to 213. This will allow the trial to have 90% power to detect statistically significant difference assuming a true hazard ratio of 0.64 in favor of palbociclib plus letrozole. Sample size justification for OS was also added.</p> <p>28. Section 9.1 Sample Size Determination / Section 9.6 Interim Analysis: Adjusted interim analysis to be performed after 65% target PFS events achieved (i.e., 139 PFS events). The interim analysis for OS was also added.</p> <p>29. Section 9.3.2 Analysis of Secondary Endpoints: Added pharmacokinetic analysis.</p> <p>30. Section 15.1 Communication of Results by Pfizer: Updated section to match updated</p>
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		<p>Pfizer protocol template.</p> <p>31. Appendix 6 FACT-B: updated</p> <p>32. Appendix 8 Wisconsin Age-Related Eye Disease Study (AREDS) 2008 Clinical Lens Opacity Grading Procedure added.</p> <p>33. Editorial changes made to adjust typos.</p>
Original Protocol	19 June 2013	N/A (Not Applicable)

This amendment incorporates all revisions to date, including amendments made at the request of country health authorities, institutional review boards/ethics committees (IRBs/ECs), etc.

## **PROTOCOL SUMMARY**

### **Indication:**

Estrogen receptor-positive (ER (+)), Human Epidermal Growth Factor Receptor 2-negative (HER2 (-)) Advanced Breast Cancer (ABC) in Asian patients who have not received any prior systemic anti-cancer therapy for their advanced disease.

### **Background and Rationale:**

Breast Cancer (BC) is the most common invasive cancer in women, with more than 1.3 million cases and over 450,000 deaths occurring worldwide annually. In Asia, the incidence of breast cancer is 26 per 100,000 individuals, the mortality rate is 9.5 per 100,000 individuals. In China, the incidence of breast cancer is 21.6 per 100,000 individuals, the mortality rate is 5.7 per 100,000 individuals. Although age-adjusted mortality from breast cancer has been decreasing since 1990, the median survival for patients with metastatic disease is still only approximately 18-24 months and the medical need for more active agents in this clinical setting remains very high.

The role of estrogens in breast cancer etiology and progression is well established. Modification of estrogen activity or synthesis represents the treatment of choice for postmenopausal women with hormonal receptor positive advanced breast cancer, particularly for those with slowly progressive disease and limited tumor-related symptoms. Letrozole is an oral nonsteroidal aromatase inhibitor approved worldwide for the first-line treatment of postmenopausal women with hormone receptor-positive advanced breast cancer (ABC).

Palbociclib is an oral cyclin-dependent kinase (CDK) 4/6 inhibitor that has been under investigation in Phase 1, 2 and 3 clinical trials in multiple indications. Palbociclib prevents cell cycle progression from G1 to S phase and has shown antitumor activity in multiple preclinical models, including in estrogen receptor-positive (ER+) luminal breast cancer cell lines.

Furthermore, pre-clinical exploration using a breast cancer cell line panel has demonstrated presence of retinoblastoma (Rb) protein and upregulation of cyclin D1 as well as decreased CDKN2A (p16) that were associated with sensitivity to Palbociclib as well as with its effects upon cell cycle and growth inhibition. These gene expression findings were also associated with the luminal subtype versus basal-like subtype of BC.

These results, together with published data on the interaction of estrogens and CDKs and the important role of cell cycle-related proteins in the genesis and maintenance of breast cancer, led to the initiation of a randomized Phase 2 clinical trial (A5481003) investigating the antitumor activity of Palbociclib in combination with letrozole and single-agent letrozole in the first-line treatment of ER(+)/HER2(-) ABC patients. The Phase 2 study was divided into 2 parts. In Part 1, patient selection was based only on ER/HER2 status while in Part 2, patients were additionally prospectively selected taking into account tumor Cyclin D1 (CCND1) amplification and/or CDKN2A (p16) loss.

Final results from Part 1 plus Part 2 of the Phase 2 portion included a total of 165 postmenopausal women with ER(+) / HER2(-) locally recurrent or metastatic breast cancer enrolled to either receive Palbociclib in combination with letrozole (n=84 patients) or letrozole monotherapy (n=81 patients).

The combination therapy was generally well tolerated when compared to letrozole alone with adverse events (AEs) similar to those seen with Palbociclib and letrozole when administered alone, with the exception of hematologic toxicity. Neutropenia(48%), leukopenia(19%) and anemia(5%)were the most frequent treatment-related Grade 3 adverse events in patients treated with the combination therapy. Grade 4 treatment-related events included neutropenia and anemia, reported in 6% and 1% , respectively, of patients treated with Palbociclib plus letrozole. However, the neutropenia observed with the combination in this study was non-cumulative and clinically manageable. Neutropenia is an on-target, anti-proliferative side effect of palbociclib and signifies inhibition of CDK4 and its effect on bone marrow.

Efficacy analyses were performed on the basis of radiologic assessment of disease status by investigators to determine preliminary antitumor activity according to Response Evaluation Criteria in Solid Tumors (RECIST) v.1.0. Median Progression Free Survival (PFS) was prolonged in patients who received combination therapy compared to letrozole alone (20.2 months vs. 10.2 months). Objective response and clinical benefit rates (43% vs. 33% and 81% vs. 58%, respectively) were also superior with the combination therapy.

Based on the encouraging results from this Phase 2 study in ABC, a global randomized Phase 3 study (A5481008) of Palbociclib in combination with letrozole is currently on-going in postmenopausal patients with ER(+), HER2(-) ABC.

A Phase 1 study (A5481010) is ongoing to evaluate Pharmacokinetic (PK), safety, tolerability and efficacy of Palbociclib in Japanese patients with advanced solid tumors and ER(+), HER2(-) ABC. To support the China Food and Drug Administration (CFDA) regulatory filing requirement of Palbociclib, a Phase 1 study (A5481019) has been designed to evaluate single-dose and multiple-dose PK, safety and efficacy of Palbociclib in combination with letrozole in postmenopausal Chinese women with ER(+), HER2(-) ABC.

This randomized Phase 3 Study (A5481027) provides the opportunity to confirm the clinical benefit of the combination of Palbociclib with letrozole observed in the randomized Phase 2 study in Asian patients. This study is designed to demonstrate that the combination of Palbociclib with letrozole provides superior clinical benefit compared to letrozole in combination with placebo in Asian postmenopausal women with ER(+)/HER2(-) ABC who have not received any prior systemic anti-cancer therapy for their advanced disease.

## **Objectives:**

### Primary Objective:

- To compare the combination of Palbociclib plus letrozole with placebo plus letrozole in term of progression-free survival (PFS) in Asian postmenopausal women with ER(+)/HER2(-) advanced breast cancer (ABC) who have not received any prior systemic anti-cancer therapy for advanced disease.

### Secondary Objectives:

- To compare Objective Response (OR), Duration of Response (DR), Disease Control Rate (DCR), and Overall Survival (OS) between the treatment arms;
- To evaluate the safeties and tolerability of the treatment arms;
- To determine trough Palbociclib plasma concentration in this patient population and explore the correlations between exposure and response and/or safety findings;
- To compare health-related quality of life between the treatment arms;
- To characterize alterations in genes, proteins, and ribonucleic acids (RNAs) expression relevant to the cell cycle, drug targets, and tumor sensitivity and/or resistance in tumor tissues;
- To explore the relationship between germline polymorphism in CDK6 gene and palbociclib treatment related neutropenia.

## **Study Design:**

This is a multicenter, randomized (1:1), double-blind, placebo-controlled, parallel-group phase 3 trial comparing the efficacy and safety of Palbociclib in combination with letrozole versus placebo plus letrozole in Asian postmenopausal women with ER(+)/HER2 (-) ABC. Eligible patients will have histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic disease and will be candidates to receive letrozole as first-line treatment for their advanced disease. In order to avoid inclusion of patients who are refractory or resistant to non-steroidal aromatase inhibitors, patients who received anastrozole or letrozole as a component of their (neo)adjuvant regimen may only enter the study if their disease did not progress while on or within 12 months from completion of their anastrozole/letrozole-containing (neo)adjuvant therapy. Patients will not have received any prior systemic anti-cancer therapy for their advanced disease and will not be candidates for curative therapies. Patients must have measurable disease as per RECIST v.1.1 or bone disease as their only site of disease. Tumor tissue availability is required for patient participation. At least approximately 330 patients will be randomized 1:1 between the investigational arm (Arm A: at least approximately 165 patients treated with Palbociclib plus letrozole) and the comparator arm (Arm B: at least approximately 165 patients treated with placebo plus letrozole). Among these approximately 330 patients, at least 264 patients will be from China and the rest of the patients will be from other Asia countries.



Patients will be stratified at randomization by region (China vs other), by site of disease (visceral vs non-visceral), by disease-free interval since completion of prior (neo)adjuvant therapy (de novo metastatic;  $\leq 12$  months;  $> 12$  months) and by the nature of prior (neo)adjuvant anticancer treatment received (prior hormonal therapy; no prior hormonal therapy).

Patients randomized to Arm A (investigational arm) will receive:

- Palbociclib, 125 mg, orally once daily on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment;

*in combination with*

- Letrozole, 2.5 mg, orally once daily (continuously).

Patients randomized to Arm B (comparator arm) will receive:

- Placebo orally once daily on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment;

*in combination with*

- Letrozole, 2.5 mg, orally once daily (continuously).

Patients will continue to receive their assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever would occur first. However, patients may continue treatment as assigned at randomization beyond the time of RECIST-defined disease progression at the discretion of the investigator if that is considered to be in the best interest of the patient and as long as no new anticancer treatment is initiated. In this case, the patient would continue with scheduled safety assessments as per the schedule of activities for the active treatment period.

The importance of timely and complete disease assessments in this study cannot be overstated. Disease assessments will be performed every 12 weeks ( $\pm 7$  days) from the date of randomization. Patients with bone lesions identified at baseline will also have repeat bone scans performed every 24 weeks ( $\pm 7$  days) from the date of randomization. Each assessment will be performed as scheduled according to the calendar regardless of any dosing delay to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point. Tumor assessments will be performed until radiographically and/or clinically (ie, for photographed or palpable lesions) documented Progressive Disease (PD) as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST-defined disease progression), initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever would occur first. A series of incomplete disease assessments will result in censoring of the primary endpoint of PFS back to the time of the last full assessment that did not show disease progression. Off schedule or incomplete disease assessments have the potential to weaken the conclusion of this clinical trial and must be avoided wherever possible.

Patients who discontinue study treatment for reasons other than radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1 will continue to have tumor assessment performed during the follow-up visits every 12 weeks ( $\pm$  7 days) and bone scans (as applicable) every 24 weeks ( $\pm$ 7 days) until RECIST-defined disease progression, initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first.

Patients discontinuing the active treatment phase will enter a follow-up period during which survival and new anti-cancer therapy information will be collected every 6 months from the last dose of investigational product. The follow-up period will conclude at the time of the final OS analysis. Crossover will not be allowed in the trial.

Efficacy analyses will be performed using the local radiologist's/investigator's tumor assessments as the primary data source. However, a blinded independent third-party core imaging laboratory will complete a retrospective review of radiographic images and clinical information collected on-study to verify the protocol-defined endpoints of disease response and progression determinations as assessed by the investigator.

An independent third party External Data Monitoring Committee (E-DMC) will monitor the safety data on a periodic basis. The E-DMC will make recommendation as to whether the trial should continue based on ongoing reviews of safety data. The E-DMC will also evaluate efficacy at the interim analysis and make a recommendation regarding study continuation based on observed results of the study. The E-DMC membership and governance is outlined in a separate charter.

## **Endpoints:**

### Primary Endpoint

- Progression-Free Survival (PFS) based on investigator's assessment.

### Secondary Endpoint(s)

- Progression-Free Survival (PFS) based on blinded independent central review (BICR).
- Objective Response (OR);
- Duration of Response (DR);
- Disease Control Rate (DCR);
- Overall Survival (OS);
- 1-year, 2-year, and 3-year Survival Probabilities;

- Trough plasma concentration of Palbociclib;
- Quality of life assessments: EuroQol (EQ-5D) Score and Functional Assessment of Cancer Therapy - Breast (FACT-B);
- Type, incidence, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events, NCI CTCAE v4.0), seriousness and relationship to study medications of adverse events (AE) and any laboratory abnormalities;
- Tumor tissue biomarkers, including genes, proteins, and RNA expression (eg, ER, Ki67).

### **Statistical Methods:**

The primary purpose of this study is to compare the combination of Palbociclib with letrozole versus placebo plus letrozole in prolonging PFS in Asian postmenopausal women with ER (+), HER2 (-) ABC who have not received any prior systemic anticancer treatment for advanced stage disease. All primary and secondary endpoints based on radiological (and photographic where applicable) assessments of tumor burden (ie PFS, OR, DR, DCR) will be derived using the local radiologist's/investigator's assessment. Tumor assessments will also be performed by a blinded independent third-party core imaging laboratory and the data will be used for secondary supportive analyses.

The sample size for this study is determined based on the assumptions that the median PFS for ABC patients receiving placebo plus letrozole in the first-line treatment setting is 9 months and it is desired to detect a risk reduction of 36% (hazard ratio 0.64), equivalent to an improvement in median PFS to 14 months in the Palbociclib plus letrozole treatment arm. A total of approximately 213 events are required in the 2 arms of the study based on a 1:1 randomization to have 90% power to detect a difference assuming a true hazard ratio of 0.64 in favor of the Palbociclib plus letrozole arm using a one-sided log-rank test at a significance level of 0.025. Assuming a 10% drop-out rate on either treatment arm, an accrual accomplished over a 19-month period and follow-up that will continue for about 12 months after the last patient is enrolled, a total sample size of approximately 330 patients (approximately 165 patients per arm) is required.

The sample size described above will also allow the assessment of differences in the secondary endpoint of OS. The OS outcomes of a Phase 3 clinical trial in a similar patient population demonstrated a median OS of 34 months for the arm receiving letrozole. Using this value as an assumption with a hypothesized 30% risk reduction (a hazard ratio of 0.7) or 43% improvement in median OS (from 34 months to 48.6 months) in patients randomized to receive palbociclib plus letrozole and a follow-up period of approximately 61 months, 330 patients will provide approximately 247 events for 80% power to detect such a difference using a 1-sided, log-rank test at a significance level of 0.025. Descriptive statistics will be used to summarize all patient characteristics, treatment administration, investigational drug compliance, efficacy endpoints, safety parameters, and biomarkers. Data will also be displayed graphically, where appropriate.

The primary efficacy analyses will be based on the *intent-to-treat* (ITT) population, defined as all patients randomized to the study. Some efficacy analyses will also be performed on the *as-treated* (AT) population, defined as patients who receive at least 1 dose of study treatment (ie, Palbociclib/placebo or letrozole), with treatment assignments designated according to actual study treatment received.

Time-to-event endpoints, including PFS, DR, and OS will be summarized using Kaplan Meier methods and displayed graphically. The median event time and 2 sided 95% confidence interval for the median will be provided for each endpoint. Stratified log rank tests will be used to compare PFS and OS between the treatment arms.

The 1-year, 2-year, and 3-year survival probabilities will be estimated using the Kaplan Meier method and a 2 sided 95% confidence interval for the log [-log(1-year, 2-year or 3-year survival probability)] will be calculated using a normal approximation and then back transformed to give a confidence interval for the 1-year, 2-year, and 3-year survival probability itself.

The objective response rate (ORR) will be summarized by treatment arm along with the corresponding exact 2 sided 95% confidence interval. Response rate comparisons between the 2 treatment arms as randomized will be assessed using Cochran-Mantel-Haenszel (CMH) test with the same stratification factors as for the PFS analysis.

The study is designed to have one interim analysis and the final analysis based on the primary endpoint of PFS. A formal efficacy stopping boundary for rejecting the null hypothesis is constructed by using the spending function methodology of power family design with  $\Delta = -0.5$ . The purposes for the interim analysis are to allow early stopping of the study for efficacy and to assess safety of the combination regimen. The analysis will be performed after approximately 139 patients have documented progressive disease or die (approximately 65% of the total events expected). If the results of the interim analysis indicate serious safety concerns, the sponsor will communicate with the Health Authorities regarding stopping the clinical trial.

An interim analysis of efficacy is also planned for the secondary endpoint OS. The analysis will be performed at the same time of the final analysis of PFS. Even if the improvement in PFS is significant at its interim and the study is stopped due to the overwhelming results, the interim OS analysis will still be performed at the approximately planned PFS final analysis time. The nominal significance levels for the interim analysis of OS will be determined by using the Lan-Demets procedure with an O'Brien-Flemming stopping rule. The overall significance level for the efficacy analysis of OS will be preserved at 0.025 (one-sided test).

All patients treated with at least one dose of study treatment (ie, Palbociclib/placebo or letrozole) will be included in all safety analyses. Summaries of AEs and other safety parameters will be provided as appropriate. Frequencies of patients experiencing at least one AE will be displayed by body system and preferred term according to MedDRA terminology. Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, severity, relationship to study drug, action taken, and clinical

outcome. Severity of the AEs will be graded according to the NCI CTCAE version 4.0. Summary tables of clinical laboratory results will be prepared to examine the worst toxicity grade on study and distribution of laboratory measures over time. Shift tables will be provided to examine the distribution of laboratory abnormalities.

Breast cancer-specific quality of life mean scores at each assessment time point and change from baseline scores will be compared between the treatment arms at various time points using a mixed model repeated measures (MMRM) approach adjusting for specified covariates. In addition, analyses will be performed to determine if the change from baseline scores achieve the appropriate minimally important difference (MID) cut-off for the scale being examined. Patients from the ITT population who completed a baseline assessment and at least one post-baseline assessment will be considered evaluable for the patient-reported outcome (PRO) analysis.

**SCHEDULE OF ACTIVITIES**

The Schedule of Activities table provides an overview of the protocol visits and procedures. Refer to [STUDY PROCEDURES](#) and [ASSESSMENTS](#) sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the wellbeing of the subject.

<b>A5481027 Schedule of Activities</b>								
Protocol Activity	Screening	Active Treatment Phase <sup>a</sup> - One Cycle = 28 days					End of Treatment / Withdrawal <sup>c</sup>	Post-Treatment Follow-Up <sup>d</sup>
		Cycles 1 and 2		Cycle 1	Cycle 2	Cycles ≥3		
Study Day	Within 28 days prior to randomization unless specified otherwise	Day 1 <sup>b,v</sup>	Day 14	Day 21	Day 21	Day 1 <sup>v</sup>		
Time Window		±2d	±2d	±2d	±2d	±2d		±7d
<b>Baseline Documentation</b>								
Informed Consent Process <sup>e</sup>	X							
Medical / Oncological History <sup>f</sup>	X							
Baseline Signs / Symptoms		X <sup>g</sup>						
Banked Biospecimen <sup>h</sup>		X						
Tumor Tissue for Biomarker <sup>i</sup>	X						X <sup>i</sup>	
Physical Examination/Vital signs <sup>j</sup>	X	X <sup>b</sup>				X	X	
Ophthalmic Examination <sup>k</sup>	X					X	X	
ECOG Performance Status	X	X				X	X	
<b>Laboratory Studies</b>								
Hematology <sup>l</sup>	X	X <sup>b</sup>	X (Only for Cycle 1)	X	X	X	X	
Blood Chemistry <sup>l</sup>	X	X <sup>b</sup>	X			X	X	

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Protocol Activity	Screening	Active Treatment Phase <sup>a</sup> - One Cycle = 28 days					End of Treatment / Withdrawal <sup>c</sup>	Post-Treatment Follow-Up <sup>d</sup>	
		Cycles 1 and 2		Cycle 1	Cycle 2	Cycles ≥3			
Study Day	Within 28 days prior to randomization unless specified otherwise	Day 1 <sup>b,v</sup>	Day 14	Day 21	Day 21	Day 1 <sup>v</sup>			
Time Window		±2d	±2d	±2d	±2d	±2d		±7d	
12-Lead ECG <sup>m</sup>	X	X <sup>b</sup>	X			X	X		
Fasting Glucose <sup>n</sup>		X (Cycle 1 Pre-dose)		X			X		
Fasting Insulin <sup>n</sup>		X (Cycle 1 Pre-dose)		X			X		
HgbA1C <sup>n</sup>		X (Cycle 1 Pre-dose)				C4D1 and every 3 months thereafter	X		
Fasting Lipid Panel (Total Cholesterol, HDL, LDL, triglycerides) <sup>n</sup>		X (Cycle 1 Pre-dose)					X		
<b>Disease Assessment</b>									
CT/MRI Scans of Chest, Abdomen, Pelvis, any clinically indicated sites of disease, and of bone lesions; Clinical evaluation of superficial disease <sup>o</sup>	X	◀--▶ <sup>p o</sup> Performed every 12 weeks (± 7 days) from the date of randomization						X	X <sup>o</sup>
Radionuclide Bone Scan, Whole Body <sup>p</sup>	X	◀--▶ <sup>q o</sup> Performed every 24 weeks (± 7 days) from the date of randomization						X	X <sup>o</sup>
<b>Other Clinical Assessments</b>									
Drug Compliance <sup>f</sup>		◀--▶							
Averse Event Reporting <sup>s</sup>	X	X	X			X	X	X	
Review Concomitant Medications/Treatments <sup>t</sup>	X	X	X			X	X	X	
EuroQol; EQ-5D <sup>u</sup>		X				X	X		
FACT - Breast Questionnaire <sup>u</sup>		X <sup>u</sup>				X	X		

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Protocol Activity	Screening	Active Treatment Phase <sup>a</sup> - One Cycle = 28 days					End of Treatment / Withdrawal <sup>c</sup>	Post-Treatment Follow-Up <sup>d</sup>
		Cycles 1 and 2		Cycle 1	Cycle 2	Cycles ≥3		
Study Day	Within 28 days prior to randomization unless specified otherwise	Day 1 <sup>b, v</sup>	Day 14	Day 21	Day 21	Day 1 <sup>v</sup>		
Time Window		±2d	±2d	±2d	±2d	±2d		±7d
Survival Follow-up <sup>w</sup>								X
<b>Study Treatment</b>								
Randomization	X							
Letrozole (both treatment arms)		Once Daily ◀--▶ <sup>x</sup>						
Palbociclib or Placebo		◀--▶ <sup>y</sup> Once Daily on Day 1 to Day 21 of each cycle followed by 7 days off						
<b>Special Laboratory Studies</b>								
Pharmacokinetics <sup>z</sup>			X(Pre-dose)					

- Active Treatment Phase:** All assessments should be performed prior to dosing with study medications on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers.
- Cycle 1/Day 1:** Blood chemistry, hematology, 12-lead ECG and physical examination not required if acceptable screening assessment is performed within 7 days prior to randomization.
- End of Treatment/Withdrawal:** Obtain these assessments if not completed during the previous 4 weeks on study (or within the previous 8 weeks for disease assessments).
- Post Treatment Follow-up:** After discontinuation of study treatment, post-treatment follow-up (including survival status and post-study anticancer therapy evaluation) will be collected every 6 months (±7 days) from the last dose of study treatment. Telephone contact is acceptable.
- Informed Consent:** Informed consent may be obtained greater than 28 days from randomization; however, must be obtained prior to any protocol required assessments being performed.
- Medical/Oncological History:** To include information on prior anticancer treatments.
- 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.
- Banked Biospecimen:** A single 4 mL blood sample (Prep D1; K2 EDTA whole blood collection optimized for DNA analysis) will be collected pre-dose at the Cycle 1 Day 1 visit from all patients, unless prohibited by local regulations, to be retained for potential pharmacogenomic analyses related to drug response or adverse drug reactions.



- i. **Mandatory Tumor Tissue For Confirmatory Testing and for Biomarker Assessments:** Tumor tissue is required for patient participation. Submission of formalin-fixed paraffin embedded (FFPE) tumor samples (blocks) of adequate size to allow for three 0.6 mm diameter x 5 mm deep cores that will be used to generate a tissue microarray are needed. If FFPE tissue block cannot be provided, then 12 glass slides each containing an unstained 5-micron FFPE tissue section, will be required for patient participation (highly recommend to submit tissue block or 12 unstained slides, but if there would be technical difficulties or other issues refraining from obtaining tissue block or 12 unstained slides, however, it is still mandatory to collect a minimum 7 unstained slides). Archived FFPE specimen from the original diagnostic tumor tissue will be collected and sent to the sponsor-designated central laboratories for assessment of biomarkers associated with sensitivity and/or resistance to Palbociclib (eg, Ki67, ER). Tissue sample from a metastatic or recurrent tumor lesion, if available, will also be collected for retrospective confirmation of ER status by the central laboratory. If a tissue sample from a recurrent tumor or distant metastasis is unavailable, then a de novo fresh biopsy is recommended when, in the investigator's judgment, such biopsy is feasible and can be safely performed. Original diagnostic tumor tissue will be used for confirmation of ER status in the event that a recurrent/metastatic tissue sample is not available and a fresh biopsy of the recurrent/metastatic lesion is not feasible. An optional fresh tumor biopsy will be collected at the end of treatment visit, only for patients who discontinue treatment due to disease progression. The tumor tissue will be used to determine possible mechanisms of resistance. Tissue samples from all patients will be used for additional biomarker analyses. Detailed information about biomarker sample collection, preparation, storage, labeling, and shipment is indicated in the Study Reference Manual.
- j. **Physical Examination/Vital signs:** A full physical examination including an examination of all major body systems, 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, will be required at screening and, Day 1 of Cycles 1 and 2. Symptom-directed physical examinations, blood pressure and pulse rate will be performed at subsequent visits.
- k. **Ophthalmic Examinations:** All enrolled patients will undergo an ophthalmic examination at screening, and on study treatment after 3 months (Cycle 4 Day 1), 6 months (Cycle 7 Day 1), 12 months (Cycle 13 Day 1), every 12 months (Day 1 of Cycles 25, 37 etc.) thereafter, and at the End of Treatment visit. Additional ophthalmic examinations may be performed during the study as clinically indicated (including for patients randomized prior to Amendment 3 approval). The ophthalmic examinations will include: best corrected distant visual acuity (Snellen), refractive error associated with best corrected distant visual acuity, intraocular pressure (IOP – one reading), slit lamp biomicroscopy of the anterior segment including cell count and flare grading, crystalline lens grading using the Wisconsin Age-Related Eye Disease Study (AREDS) 2008 Clinical Lens Opacity Grading procedure, and funduscopy. All ophthalmic examinations will be performed by an ophthalmologist. Refer to [Section 7.2.3](#). Ocular Safety Assessments for further details on these procedures.
- l. **Hematology, and Blood Chemistry Panel:** Hematology includes hemoglobin, WBC, absolute neutrophils, platelet count. Blood chemistry includes AST/ALT, alkaline phosphatase, sodium, potassium, magnesium, total calcium, total bilirubin, BUN (or urea), serum creatinine, and albumin. Additional hematology/chemistries panels may be performed as clinically indicated.
- m. **12-Lead ECG:** At each time-point, three consecutive 12-lead ECGs will be performed approximately 2 minutes apart to determine the mean QTc interval. If the mean QTc interval is prolonged (>500 msec), then the ECGs should be re-read by a cardiologist or other qualified person at the site for confirmation. Additional triplicate ECGs may be performed as clinically indicated.
- n. **Fasting Glucose, Fasting Insulin, HgbA1c and Fasting Lipid Panel (Total Cholesterol, HDL, LDL, triglycerides):** On Day 1, all the baseline assessments should be performed prior to dosing (pre-dose). Fasting glucose and fasting insulin will be assessed on Cycle 1 Day 21 and at the End of Treatment visit; HgbA1C will be assessed on Cycle 4 Day 1, every 3 months (Day 1 of Cycles 7, 10 etc.) thereafter, and at the End of Treatment visit; fasting lipid panel will be assessed at the End of Treatment visit.
- o. **Disease Assessments:** Please refer to the tumor assessment requirement flowchart for details and timing of procedures. A blinded independent third-party core imaging laboratory will complete a retrospective review of radiographic images and clinical information collected on-study to verify the protocol-defined endpoints of disease response and progression determinations as assessed by the investigator.

- p. **CT/MRI Scans of Chest, Abdomen, Pelvis, any clinically indicated sites of disease, and of bone lesions; clinical evaluation of superficial disease:** Please refer to the tumor assessment requirement flowchart for details and timing of procedures.
- q. **Radionuclide Bone Scan, Whole Body:** Please refer to the tumor assessment requirement flowchart for details and timing of procedures.
- r. **Drug Compliance:** Palbociclib, placebo and letrozole bottles including any unused capsules/tablets will be returned to the clinic for drug accountability. Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle.
- s. **Adverse Events:** For SAEs, the active reporting period begins from the time that the patient provides informed consent through and including 28 calendar days after the last administration of the investigational product. AEs (serious and non serious) should be recorded on the CRF from the time the patient has taken at least one dose of study treatment through last patient visit.
- t. **Concomitant Medications/Treatments:** Concomitant medications and treatments will be recorded from 28 days prior to the start of study treatment and up to 28 days after the last dose of study treatment.
- u. **EQ-5D, FACT-B Assessments:** Patients will complete questionnaires prior to any study or medical procedure on Day 1 of Cycles 1, 2 and 3 and then Day 1 of every other cycle thereafter starting with Cycle 5 (ie, Cycle 5, 7, 9, etc), and at the end of treatment visit. All self-assessment questionnaires must be completed by the patients while in the clinic and cannot be taken home. Interviewer administration in clinic may be used under special circumstances.
- v. **Cycle X, Day 1:** In the event that the start of a new cycle is delayed due to treatment related toxicity, procedures required on Day 1 of the given cycle will be performed when Palbociclib/placebo is resumed. 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 (1) if not required to determine whether study drug may be resumed and (2) if performed within 7 days prior to study drug resumption.
- w. **Survival Follow-Up:** After discontinuation of study treatment, post-study survival status (including post-study anticancer therapies) will be collected every 6 months ( $\pm 7$  days) from the last dose of study treatment. Telephone contact is acceptable.
- x. **Letrozole (both treatment arms):** To be taken orally once daily continuously.
- y. **Palbociclib or Placebo:** To be taken orally once daily from Day 1 to Day 21 (21 days) of every 28-day cycle followed by 7 days off treatment.
- z. **Pharmacokinetics:** For all patients, plasma PK samples for Palbociclib determination will be collected prior to dosing (pre-dose) on Day 14 of Cycle 1 and Cycle 2.  
Additional blood samples may be requested from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation.

### TUMOR ASSESSMENT REQUIREMENTS FLOWCHART

	Screening <sup>a</sup>	Treatment Period <sup>b</sup>	End of Treatment Visit <sup>c</sup>
CT <sup>d</sup> or MRI of chest, abdomen, and pelvis (CAP)	Required <sup>e</sup>	Required	Required
CT <sup>d</sup> or MRI of any other site of disease, as clinically indicated	Required <sup>e,f</sup>	Required for sites of disease identified at screening	Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere
Radionuclide bone scan (whole body) and correlative bone imaging	Required <sup>g,h</sup>	Required for sites of disease identified at screening or if clinically indicated <sup>i</sup>	Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere
Photographs of all superficial lesions as applicable <sup>j</sup>	Required	Required for sites of disease identified at screening	Required for sites of disease identified at screening, unless disease progression has been confirmed elsewhere

- a. Screening scans must occur within 4 weeks (ie, 28 days) prior to randomization unless otherwise specified.
- b. Tumor assessment must be done during the treatment period, every 12 weeks ( $\pm 7$  days) and bone scans (as applicable) every 24 weeks ( $\pm 7$  days) from randomization until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST-defined disease progression), initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow up), whichever occurs first. The schedule of assessments should be fixed according to the calendar, regardless of treatment delays/interruptions. Imaging assessments are to be scheduled using the randomization date as the reference date for all time-points and are NOT to be scheduled based on the date of the previous imaging time-point. Imaging assessment delay to conform to treatment delay is not permitted. The same tumor assessment technique MUST be used throughout the study for a given lesion/patient.
- c. Patients who have already demonstrated objective disease progression as per RECIST v.1.1 do not need to have scans repeated at the end of treatment visit or during the post-treatment follow-up. For patients who do not have documented objective disease progression at time of study treatment discontinuation, tumor assessment will continue to be performed every 12 weeks ( $\pm 7$  days) and bone scans (as applicable) every 24 weeks ( $\pm 7$  days) until radiographically and/or clinically confirmed objective disease progression, initiation of new anticancer therapy, or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up).
- d. The CT scans, including brain CT scan if applicable, should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. MRI of the abdomen

and pelvis can be substituted for CT if MRI adequately depicts the disease. However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such case CT will be performed without contrast. If MRI is used to follow-up bone lesion(s) it must be performed before any treatment that may affect bone-marrow cellularity (eg, G-CSF).

- e. Radiographic assessments obtained per the patient's standard of care prior to randomization into the study do not need to be repeated and are acceptable to use as baseline evaluations, if (1) obtained within 28 days before randomization, (2) they were performed using the method requirements outlined in RECIST v.1.1 (3) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient, and (4) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.
- f. Baseline brain scans are only required if signs and symptoms suggest presence of metastatic brain disease. Brain scans performed before the signing of informed consent as routine procedures (but within 6 weeks before randomization) do not need to be repeated and may be used as baseline assessments as long as (1) tests were performed using the method requirements outlined in RECIST v.1.1 (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes. Post-baseline repeat brain scans will only be required only if metastases are suspected.
- g. Bone scans will be carried out at baseline for all patients within 12 weeks prior to randomization in order to detect bony sites of disease. Bone scans performed before the signing of informed consent as routine procedures (but within 12 weeks before randomization) do not need to be repeated and may be used as baseline assessments as long as (1) tests were performed using the method requirements outlined in RECIST v.1.1 (2) the same technique/modality can be used to follow identified lesions throughout the trial for a given patient (3) appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.
- h. Any suspicious abnormalities (ie, hotspots) identified on the bone scans at baseline and on subsequent bone scans MUST be confirmed by X-ray, CT scan with bone windows or MRI. The same modality must be used throughout the trial for confirmation for a given lesion/patient. Bone lesions identified at baseline will be followed up according to the same assessment schedule (ie, every 12 weeks  $\pm$ 7 days from randomization) as for all other lesions. Areas that have received palliative radiotherapy cannot be used to assess response to study treatment.
- i. If bone lesions were identified at baseline bone scans will be repeated during the active treatment phase every 24 week ( $\pm$ 7 days) from the date of randomization and at the time of confirmation of CR. If no bone lesions were identified at baseline, bone scans will only be repeated during the active treatment phase when clinically indicated (ie, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases) but are required at the time of confirmation of CR. New Abnormalities found on subsequent bone scans must also be confirmed by X-ray, CT scan with bone windows or MRI.
- j. Clinical assessment of superficial disease must be carried out on the same date as the imaging studies and will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the case report form (CRF).

**Notes:**

- Radiographic tumor assessments may be done at any time if there is clinical suspicion of disease progression at the discretion of the investigator. If progressive disease is confirmed per RECIST v.1.1, patients are expected to discontinue study therapy and begin the follow-up phase of the trial. However, patients may continue treatment as assigned at randomization beyond the time of RECIST-defined PD at the discretion of the investigator if that is considered to be in the best interest of the patient and as long as no new anticancer treatment is initiated.

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## 1. INTRODUCTION

Breast Cancer (BC) is the most common invasive cancer in women, with more than 1.3 million cases and over 450,000 deaths occurring worldwide annually. In Asia, the incidence of breast cancer is 26 per 100,000 individuals, the mortality rate is 9.5 per 100,000 individuals. In China, the incidence of breast cancer is 21.6 per 100,000 individuals, the mortality rate is 5.7 per 100,000 individuals.<sup>1</sup> Although age-adjusted mortality from breast cancer has been decreasing since 1990, the median survival for patients with metastatic disease is still only approximately 18 to 24 months<sup>2</sup> and the medical need for more active agents in this clinical setting remains very high.

The role of estrogens in breast cancer etiology and progression is well established. Modification of estrogen activity or synthesis represents the treatment of choice for postmenopausal women with hormonal receptor positive advanced breast cancer, particularly for those with slowly progressive disease and limited tumor-related symptoms. Letrozole is an oral nonsteroidal aromatase inhibitor and it is approved worldwide for the first-line treatment of postmenopausal women with hormone receptor-positive advanced breast cancer (ABC).

### 1.1. Indication

Estrogen receptor-positive (ER (+)), HER2-negative (HER2 (-)) Advanced Breast Cancer (ABC) in Asian patients who have not received any prior systemic anti-cancer therapy for advanced stage disease.

### 1.2. Background and Rationale

#### 1.2.1. Role of Letrozole in the Treatment of Estrogen Receptor Positive Breast Cancer

Approximately two-thirds of breast cancers express estrogen receptor (ER)<sup>3</sup> and a role for estrogens in breast cancer etiology and progression is well established. Modification of estrogen activity or synthesis represents the treatment of choice for postmenopausal women with hormone receptor-positive ABC, particularly for those with slowly progressive disease and limited tumor-related symptoms.<sup>2</sup>

Conversion of androgens to estrogens via aromatase enzyme action represents the main source of estrogens in postmenopausal women. Letrozole is an oral nonsteroidal aromatase inhibitor that is approved worldwide for the first-line treatment of postmenopausal women with hormone receptor-positive ABC. In a multicenter Phase 3 trial,<sup>4</sup> 916 patients with

hormone receptor-positive or hormone receptor-unknown ABC were randomized to receive either letrozole or tamoxifen until disease progression. Most of the patients (91%) had received no prior treatment for their advanced disease. Letrozole was superior to tamoxifen for time to tumor progression (median, 9.4 vs 6.0 months,  $P < 0.0001$ ), time to treatment failure (median, 9 vs 5.7 months,  $P < 0.0001$ ), overall objective response rate (32% vs 21%,  $P = 0.0002$ ), and overall clinical benefit (50% vs 38%,  $P = 0.0004$ ). Median overall survival (OS) was slightly prolonged for the letrozole arm (34 vs 30 months); however, approximately 50% of the patients in the tamoxifen arm crossed over to letrozole at disease progression.

Letrozole is administered orally on a continuous 2.5 mg daily dosing regimen. Multiple clinical studies have shown that letrozole is well tolerated.

### **1.2.2. Interaction of Estrogens and Cyclin-Dependent Kinases in Breast Cancer Cells**

Studies of ER-positive breast cancer cell lines indicate that estrogens<sup>5</sup> and antiestrogens<sup>6</sup> act on sensitive populations of cells in early to mid-G1 phase. G1/S transition is under the control of CDKs activated by specific complex formation with regulatory cyclins. CDK4 and CDK6 are activated by binding to D-type cyclins and act early in G1 phase.<sup>7, 8, 9, 10</sup> A primary target of CDK action in G1 phase is the retinoblastoma susceptibility gene product (pRb), which mediates G1 arrest through sequestration of transcriptional factors of the E2F-DP family. Phosphorylation of pRb and other members of the pocket protein family (p107 and p130) by active cyclin-CDK complexes leads to release of E2F and DP transcription factors and transcription of requisite genes for S-phase entry.<sup>10</sup>

D-type cyclins play an essential role in recognition of extracellular growth stimuli and initiation of G1 transit,<sup>11, 12</sup> and several lines of evidence have linked estrogen regulation of cellular proliferation to cyclin D1 expression. Estrogen-induced proliferation of normal uterine and breast epithelium *in vivo* is associated with increased expression of cyclin D1 mRNA and protein.<sup>13, 14, 15, 16</sup> Expression of cyclin D1 in breast tumor isolates correlates with ER-positive status.<sup>17, 18, 19</sup> MCF-7 breast cancer cells treated with estrogen exhibit increased expression of cyclin D1 mRNA and protein, formation of active cyclin D1-CDK4 complexes, and phosphorylation of pRb leading to G1 /S transition.<sup>20, 21, 22, 23</sup> Estrogen-induced S-phase entry in these cells is inhibited by microinjection of antibodies to cyclin D1.<sup>24</sup> Antiestrogen-induced growth arrest of ER-positive breast cancer cells is associated with decreased cyclin D1 expression.<sup>25</sup> Collectively, these studies are consistent with a model of estrogen action in which receptor activation induces increased cyclin D1 expression, CDK4 activation, and cell cycle progression. An upstream role for

cyclin D1 has been suggested by recent reports describing direct physical interactions between cyclin D1 and the ER, leading to recruitment of steroid receptor coactivators and activation of ER-dependent transcription. This occurs in the absence of hormone and is independent of D-type cyclin association with CDK4.<sup>26, 27, 28, 29</sup>

Constraint upon CDK activity and G1 progression is provided by the universal CDK inhibitors of the Cip-Kip family, including gp21Cip1 and p27Kip1, and the specific CDK4 and CDK6 inhibitors of the INK4 family, typified by p16<sup>INK4a</sup>.<sup>12, 30, 31, 32, 33</sup> The CDKN2A gene product inhibits formation of active D-type cyclin-CDK complexes through specific binding interactions with CDK4 or CDK6 that prevent D-type cyclin-CDK association.<sup>34, 35, 36</sup> Over expression of p16<sup>INK4a</sup> in cells with functional pRb results in inhibition of both CDK4- and CDK6-associated kinase activity and pRb phosphorylation, with subsequent cell cycle arrest.<sup>34, 35</sup> In addition, inhibition of D-type cyclin-CDK4 complex formation by p16<sup>INK4a</sup> prevents sequestration of p21<sup>Cip1</sup> and p27<sup>Kip1</sup> by these complexes in early G1, leading to suppression of cyclin E-CDK2 activity.<sup>37, 38, 39</sup>

Overexpression of p16<sup>INK4a</sup> through adenoviral transduction of CDKN2A into MCF-7 cells leads to G1 arrest associated with inhibited CDK activity.<sup>40, 41</sup> Cell cycle progression induced by estradiol requires action of the steroid through mid-G1, well beyond the point of cyclin D1-CDK4 activation.<sup>21</sup> Functional association of cyclin D1-CDK4 is required for estrogen-induced CDK2 activation and G1/S transition and estrogen regulates expression of p21<sup>Cip1</sup>, p27<sup>Kip1</sup>, and Cdc25A independent of D-type cyclin-CDK4 function.<sup>42</sup>

### **1.2.3. Deregulation of Cell Cycle Related Genes and Proteins in Breast Cancer**

Cell cycle related genes and proteins are frequently deregulated in breast cancer. Approximately 15%–20% of human breast cancers exhibit amplification of the cyclin D1 (CCND1) gene,<sup>43, 44, 45</sup> while the majority of human mammary carcinomas over express cyclin D1 protein.<sup>46, 47, 48</sup> Over expression of cyclin D1 is seen early in breast cancer, and it is maintained at all stages of breast cancer progression, including metastatic lesions.<sup>46, 49</sup> Amplification of the CDK4 gene, located at 12q13-q14, has been shown as an alternative genetic alteration to CDKN2A inactivation in various human tumor including breast cancer.<sup>50, 51</sup> The continued presence of CDK4-associated kinase activity is actually required to maintain breast tumorigenesis.<sup>52</sup> Direct analyses of primary tumors have revealed loss of pRb expression in 20–35% of tumors, and loss of heterozygosity or other alterations of the Rb locus in 7–37% of tumors.<sup>53, 54, 55, 56</sup> In preclinical models, Rb depletion appears to be associated with resistance to antiestrogen therapy.<sup>57</sup> Finally, virtually all ER-positive cell

lines harbor loss of p16<sup>INK4a</sup> 58, 59 expression, and low expression of CDK inhibitors p21 and p27 and high expression level of cyclin E and D1 have all been associated with resistance to anti-estrogen therapy.

#### **1.2.4. ER and HER2 Status in Breast Cancer**

The ER and HER2 status of breast metastatic disease are usually assumed to be the same as that of the primary tumor. However, mounting evidences from both prospective and retrospective studies have shown a discordant rate of approximately 25% in either ER or HER2 status between primary breast tumor and its metastatic lesions.<sup>60, 61</sup> The change can be from ER- positive primary tumor to ER-negative metastatic disease or vice versa. The analytical variables of immunohistochemistry (IHC) testing such as antigen retrieval and subjectivity in observer analysis also contribute to the observed discordance.<sup>62</sup> Another dilemma in ER testing accuracy has been primary institutional site testing versus high volume central laboratory testing. It has been stated in the recently published American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines for ER testing that the concordance rate between local and central laboratory testing for ER is about 80 to 90%.<sup>63</sup> This variation may be due to the lack of rigorous assay optimization and/or reproducibility of IHC testing procedures at some of local testing laboratories including methods of antigen retrieval and subjectivity in observer analysis. This highlights the importance of confirmative testing of ER status using Food and Drug Administration (FDA)-cleared and/or approved kits and platform at a central Clinical Laboratory Improvement Amendments (CLIA)/CAP certified laboratory to minimize, if not eliminate, these differences/variables for patients participating in clinical trials.

#### **1.2.5. Overview of Palbociclib**

Palbociclib (Molecular Weight: 573.67) is an orally active potent and highly selective reversible inhibitor of CDK4 and CDK6 that has been under investigation in Phase 1, 2 and 3 clinical trials in multiple indications. The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase and has shown antitumor activity in multiple preclinical models and phase I or phase II study, including in estrogen receptor-positive (ER+) luminal breast cancer cell lines.

### 1.2.5.1. Preclinical Data

Treatment of cultured tumor cells with Palbociclib causes growth arrest that is accompanied by the inhibition of specific pRb phosphorylation by CDK4 or CDK6 on residues serine -780 and -795 of pRb. The IC<sub>50</sub> values for reduction of pRb phosphorylation at serine -780 and -795 in MDA-MB-435 breast carcinoma cells were 0.066 and 0.063 μM, respectively. The IC<sub>50</sub> values for reduction of pRb phosphorylation are similar to the IC<sub>50</sub> values of inhibition of thymidine incorporation across a range of cultured tumor and normal cells.

Palbociclib was tested in vitro on molecularly characterized human breast cancer cell lines. Results from these experiments indicate that those cell lines that are more sensitive to Palbociclib (IC<sub>50</sub> < 150 nM) have low levels of CDKN2A (p16) and high levels of Rb1, while resistant cell lines show the opposite characteristics. Sensitive cell lines in this panel represent mostly the luminal ER+ subtype.<sup>64</sup> The combination of Palbociclib and aromatase inhibitors has not been tested in preclinical models. However, the combination of Palbociclib with tamoxifen has recently been tested in vitro in ER+ human breast cancer cell lines indicating a synergistic interaction<sup>64</sup> and provides a biologic rationale for evaluating the combination of Palbociclib with anti-hormonal therapy in the clinic.

### 1.2.5.2. Human Pharmacokinetic (PK) Data

To date, pharmacokinetic data have been collected in 4 clinical studies in cancer patients (A5481001, A5481002, A5481003 and A5481004). Pharmacokinetic parameters are available from all 74 patients enrolled in Study A5481001 following a single dose (Day 1 of Cycle 1), and from 51 patients following multiple-dose administration (Day 8 of Cycle 1) at daily doses ranging from 25 to 225 mg of Palbociclib. In addition, PK parameters are also available for nine patients on Day 14 of Cycle 1 (from patients on Schedule 2/1, ie, 2 weeks on treatment followed by 1 week off treatment) and 4 patients on Day 21 of Cycle 1 (from patients on Schedule 3/1, ie, 3 weeks on treatment followed by 1 week off treatment). The exposure (AUC(0-10) and C<sub>max</sub>) increased in a dose proportional manner over the dose range of 25 to 225 mg once daily (QD) following Palbociclib administration on Days 1 and 8 of Cycle 1, although some variability (low to moderate) around these doses was observed particularly at the 150 mg QD dose level. Following repeated daily dosing to Day 14 and Day 21 (assumed to be steady state), Palbociclib was absorbed with a median T<sub>max</sub> of ~4 hours. The mean Palbociclib V<sub>z</sub>/F was 3103 L, which is significantly greater than total body water (42 L), indicating that Palbociclib extensively penetrates into peripheral tissues.



Palbociclib was eliminated slowly; the mean  $t_{1/2}$  was 26.5 hours (ranged 15.8 to 36.2 hours) and the mean CL/F was 86.1 L/hour. Palbociclib accumulated following repeated dosing with a median  $R_{ac}$  of 2.4, which is consistent with a half life of ~27 hours.

A pilot food effect assessment was built into Protocol A5481001 and conducted in 12 patients following administration of either 125 mg or 200 mg doses (the Maximum Tolerated Dose/ Recommended Phase 2 Dose (MTD/RP2D) for the 3/1 and 2/1 schedules, respectively). In general, no change in the rate of absorption was observed between the fed and fasted state (median  $T_{max}$  = 7 hours for both; range 3.5-23 hours). However, higher exposures and peak concentrations were observed in the fed state compared to the fasted state (mean AUC(0-10): 370.5 vs 290.5 ng•hr/mL, respectively; mean  $C_{max}$ : 59.7 vs 42.8 ng/mL, respectively). Based on these data, it can be concluded that since administration of Palbociclib with a high fat meal may increase Palbociclib exposure, patients should be fasted from 1 hour before to 2 hours after dosing (water is allowed), unless otherwise indicated in clinical protocols. The effect of a non-fat meal on the pharmacokinetics of Palbociclib has not been evaluated.

Preliminary results from the recently performed food effect study, *A5481021, a Phase 1, open-label 4 sequence 4 period crossover study of palbociclib (PD-0332991) in healthy volunteers to estimate the effect of food on the bioavailability of palbociclib*, suggest that the administration of palbociclib with food results in more consistent drug absorption and exposure than administration of palbociclib in a fasted state. As a result of these findings, patients should be instructed to take palbociclib with food.

Preliminary results from the recently performed antacid effect study, *A5481018, a Phase 1, open-label fixed-sequence 2-period crossover study of palbociclib in healthy subjects to investigate the potential effect of antacid treatment on the pharmacokinetics of a single oral dose administered under fasted conditions*, suggest that the administration of proton-pump inhibitors concomitantly with palbociclib treatment leads to a significant decrease in palbociclib exposure. Since proton-pump inhibitors affect the pH of the upper GI tract for an extended period the concomitant use of proton-pump inhibitors with Palbociclib should be avoided. Further recommendations about the use of antacid are provided under [Section 5.5.2](#).

Pharmacokinetic data from Study A5481002 indicate that Palbociclib exposure at steady state in mantle cell lymphoma patients, is similar to that observed in solid tumors (Protocol A5481001).

Pharmacokinetic analysis of preliminary data from the Phase 1 portion of Study A5481003 (breast cancer, combination with letrozole) was conducted to evaluate the potential for drug-drug interaction between Palbociclib and letrozole. The results indicate lack of a potential for drug-drug interaction between Palbociclib and letrozole when administered in combination.

Palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, Palbociclib is primarily metabolized by CYP3A4 enzymes. CCI [REDACTED]

[REDACTED] PF-05089326 was also observed in the circulation of rats following repeated daily oral administration of Palbociclib at the dose levels of 50 and 100 mg/kg/day. Plasma protein binding of Palbociclib and PF-05089326 is ~85% and 95%, respectively.

### 1.2.5.3. QTc Evaluation Data

In vitro (Human Ether-à-Go-Go, hERG) and in vivo (dog telemetry) studies revealed a potential for QT prolongation at unbound concentrations  $\geq 14$ -fold the unbound steady-state  $C_{\max}$  associated with the clinical dose of 125 mg QD (refer to the Palbociclib investigator's brochure for additional details).

A preliminary pharmacokinetic/pharmacodynamic analysis has been conducted to explore the QT/QTc and plasma Palbociclib concentration relationship for Study A5481001 (First in Human, FIH study) by using graphical methods and mixed effects linear modeling (NONMEM). Data from 73 patients were used for the analysis, and an analysis of the QTcF and QTcB data demonstrated that QTcF was the more appropriate correction method based on plots of the QTc versus RR interval. No patient had a maximum on treatment QTcF value of  $\geq 500$  msec. The QTcF changes from the baseline at the mean  $C_{\max}$  calculated for 200 mg dose were simulated for 10000 patients. The mean and upper 95% confidence interval of QTcF change from the baseline were 5.8 and 9.4 msec, respectively.

#### 1.2.5.4. Preclinical Ocular Data

Preliminary results from an ongoing 27-week repeat-dose oral toxicity study with Palbociclib in Sprague-Dawley rats identified a potential nonclinical safety finding related to the eye. Palbociclib was administered by oral gavage at doses of 0, 10, 30, and 100 mg/kg/day in males and 0, 50, 100, and 300 mg/kg/day in females (20/sex/group; 15/sex/group in main and 5/sex/group in recovery) on an intermittent dosing schedule (7 cycles of treatment where each cycle consisted of 3 weeks of continuous daily dosing followed by a 1-week non-dosing period) for 27 weeks. Animals were evaluated by indirect ophthalmoscopy and by slit lamp biomicroscopy predose and prior to termination (within 7 days prior to scheduled necropsy). Indirect ophthalmoscopy results revealed a degraded view of the fundus and the presence of cataracts in males treated at high dose (100 mg/kg/day) that had normal fundus examinations prior to the start of the study. Cataracts (anterior cortical, incomplete, and complete) were identified by slit lamp biomicroscopy in male rats at  $\geq 30$  mg/kg/day with dose-related severity (Table 1), but not in females at any dose tested (up to 300 mg/kg/day).

Lens degeneration was observed microscopically with dose-related incidence and with minimal to moderate severity in males at  $\geq 30$  mg/kg/day and minimal severity in males at 10 mg/kg/day and females at  $\leq 100$  mg/kg/day (not identified in females at 300 mg/kg/day). Lens degeneration was identified in all animals that were noted with cataracts by slit lamp ophthalmoscopy.

The available data suggests that the cataracts (lens degeneration) observed at the lowest doses in both male and female rats are palbociclib-related. Exposures in this non clinical study are comparable to clinical exposures at the recommended human dose of 125 mg QD (unbound AUC 301 ng•h/mL).

The mechanism for cataract formation in palbociclib-treated rats is unknown; however, its pathogenesis may be related to primary pharmacology. CDK4 expression (mRNA and protein) has been identified in the lens epithelial layer and in lens fibers of rats, suggesting its importance to lens fiber differentiation.<sup>65</sup> Altered cell growth of the lens epithelium is also recognized as a potential mechanism for cataract formation.<sup>66</sup> As CDK 4 and 6 expressions have also been identified in the human lens epithelial cell<sup>67</sup> a potential risk for cataract formation in palbociclib-treated patients cannot be completely excluded.

To date, approximately 700 patients have enrolled in palbociclib trials. A review of the Pfizer safety database for cases received through 14 January 2014 identified no serious cases from clinical studies or other solicited sources including palbociclib or blinded therapy that included adverse events which code to the MedDRA (Version 16.1) High Level Group Term “Anterior eye structural change, deposit and degeneration”. In addition, no cases coding to the aforementioned MedDRA term were reported to the safety database from any other sources during this period for patients who received palbociclib. Cataract has been reported as an adverse event in 2 patients (1 Grade 2 and 1 Grade 3) out of approximately 400 patients who have been treated with palbociclib in Pfizer-sponsored studies. Neither event was considered serious nor related to palbociclib and both patients had other identifiable risk factors for cataracts, such as age and long term corticosteroid use. Both patients continued on treatment for 16-18 months beyond the diagnosis of cataract.

Literature report suggests that the incidence of cataract in women aged 35 and older with risk of breast cancer is approximately 2.3%.<sup>69</sup> Cataract has also been reported in patients treated with tamoxifen or letrozole.<sup>68,69</sup>

#### **1.2.5.5. Palbociclib Dose Rationale**

Palbociclib has been tested in a Phase 1 dose escalation Study (A5481001) in 74 patients with advanced cancer. Two dosing schedules were evaluated: Schedule 3/1 (3 weeks on treatment/1 week off treatment) and Schedule 2/1 (2 weeks on treatment/1 week off treatment).

All Dose Limiting Toxicity (DLTs) observed in this study were related to myelosuppression and mainly consisted of Grade 3 neutropenia lasting more than 7 days after the end of the treatment cycle. However, neutropenia was reversible and non-cumulative. The most common non-hematological adverse events included fatigue, diarrhea, constipation, vomiting and dyspnea, all with mild to moderate severity. A greater proportion of patients on the 2/1 schedule had treatment-related Treatment Emergent Adverse Events (TEAEs) during and after Cycle 1 than patients on the 3/1 schedule although the proportion of patients with treatment-related neutropenia was similar with respect to the 2 dosing schedules, both during and after Cycle 1. One partial response was reported in a patient with testicular cancer. A total of 13/37 patients treated with Schedule 3/1 evaluable for efficacy experienced stable disease (SD), including 6 patients with SD lasting 40 weeks or longer. One of these patients was a woman with ER+ breast cancer who had previously received 7 lines of treatment for her disease. This patient remained on treatment for 80 weeks (7 cycles at 50 mg/d and

13 cycles at 75 mg/d) and eventually discontinued treatment due to disease progression. Based on the relatively improved safety profile of Schedule 3/1, and the efficacy results from this study, the Schedule 3/1 has been selected for further clinical development and the RP2D for this schedule was determined to be 125 mg/d. This schedule and associated RP2D was further explored in combination with letrozole in the Phase I/II study in patients with ABC described below.

#### **1.2.5.6. Phase I/II Data in Combination with Letrozole in Advanced Breast Cancer**

Based on the preclinical evidence that Palbociclib is highly active in ER(+) cell lines and the encouraging safety and PK profiles observed in the initial clinical studies, a randomized, multicenter active-controlled Phase 1/2 Study (A5481003) was designed to assess the efficacy, safety and pharmacokinetics of letrozole 2.5 mg QD (continuously) in combination with Palbociclib 125 mg QD (schedule 3/1) versus single agent letrozole 2.5 mg QD (continuously) for the first-line treatment of ER(+), HER2 (-) ABC in postmenopausal women. Letrozole was selected as the active control based on its worldwide approval and use as standard of care for the first-line hormonal treatment of postmenopausal women with ER(+) ABC.

Study A5481003 was comprised of a limited Phase 1 portion, aimed at confirming the safety and tolerability of the combination and excluding a PK interaction with the combination, and a randomized Phase 2 portion aimed at evaluating the efficacy and safety of letrozole in combination with Palbociclib when compared to letrozole alone in the first-line treatment of postmenopausal patients with ER(+), HER2(-) ABC. The Phase 2 portion consisted of 2 parts. In Part 1, patient selection was based only on ER/HER2 status. In Part 2, patients were prospectively selected also taking into account tumor CCND1 amplification and/or p16 loss. As of 18 May 2012, 177 patients have been enrolled in this study and enrollment is closed. Twelve (12) were enrolled in the Phase 1 portion and 165 (66 and 99 in Part 1 and 2, respectively) were enrolled in the Phase 2 portion.

Results from the Phase 1 portion,<sup>70</sup> indicated no PK interaction between Palbociclib and letrozole with mean AUC(0-24) of 2002 and 2043 ng•hr/mL (n=11) for Palbociclib in the absence and presence of letrozole, respectively, and 1990 and 1730 ng•hr/mL (n=10) for letrozole in the absence and presence of Palbociclib, respectively. The RP2D was determined to be 125 mg QD on Schedule 3/1 (3 weeks continuous treatment followed by 1 week off treatment) in combination with letrozole 2.5 mg QD continuously. Partial responses were reported for 3 (33%) out of 9 patients with measurable disease (3 had

bone-only disease). Another 5 patients (42%) had stable disease for  $\geq 6$  months and the clinical benefit rate (PR + SD  $\geq 6$  months) was 67%. Eight (8) patients discontinued from the study due to disease progression, including 2 patients with clinical progression, and 4 patients are still ongoing.

Final results from Part 1 plus Part 2 of the Phase 2 portion were presented at the 2014 American Association for Cancer Research (AACR) annual meeting<sup>71</sup> and included a total of 165 postmenopausal women with ER(+) / HER2(-) locally recurrent or metastatic breast cancer enrolled to either receive Palbociclib in combination with letrozole (n=84 patients) or letrozole monotherapy (n=81 patients).

The combination therapy was generally well tolerated when compared to letrozole alone with adverse events (AEs) similar to those seen with Palbociclib and letrozole when administered alone, with the exception of hematologic toxicity. Neutropenia(48%), leukopenia(19%) and anemia(5%) were the most frequent treatment-related Grade 3 adverse events in patients treated with the combination therapy. Grade 4 treatment-related events included neutropenia and anemia, reported in 6% and 1% , respectively, of patients treated with Palbociclib plus letrozole. However, the neutropenia observed with the combination in this study was non-cumulative and clinically manageable. Neutropenia is an on-target, anti-proliferative side effect of palbociclib and signifies inhibition of CDK4 and its effect on bone marrow.

Efficacy analyses were performed on the basis of radiologic assessment of disease status by investigators to determine preliminary antitumor activity according to Response Evaluation Criteria in Solid Tumors (RECIST) v.1.0. Median Progression Free Survival (PFS) was prolonged in patients who received combination therapy compared to letrozole alone (20.2 months vs. 10.2 months). Objective response and clinical benefit rates (43% vs. 33% and 81% vs. 58%, respectively) were also superior with the combination therapy.

These results indicate that the combination of Palbociclib with letrozole is well tolerated with AEs similar to those seen with either Palbociclib or letrozole when administered alone. Additionally, the combination demonstrated antitumor activity which was consistent with the sensitivity of ER(+) breast cancer observed in the preclinical models.

### 1.2.6. Study Rationale

In the first-line treatment setting, letrozole is among the preferred anti-hormonal therapies for postmenopausal women with ER(+)/HER2(-) ABC.<sup>72</sup> It is approved and commercially available globally with a well known and manageable safety profile. However, median progression-free survival in this patient population remains less than 1 year and median overall survival is approximately 3 years.<sup>4</sup> Furthermore, aromatase inhibitor failure has been linked to increased proliferative index and cell cycle dysregulation, providing a strong rationale for combining letrozole with Palbociclib. Preliminary data from Phase 1/2 Study A5481003 suggest that the combination of Palbociclib inhibition of CDK 4/6 (blocking DNA synthesis by prohibiting progression of the cell cycle from G1 to S phase) with the antiproliferative effects of letrozole provides greater antitumor activity and prolongs PFS (ie median 26.1 months vs 7.5 months) when compared to single agent letrozole. Additionally, the study shows that the combination is generally well tolerated with uncomplicated neutropenia as the most frequent adverse event.<sup>71</sup>

This randomized Phase 3 Study (A5481027) provides the opportunity to confirm the clinical benefit of the combination of Palbociclib with letrozole observed in the randomized Phase 2 study in Asian patients. The study is designed to demonstrate that Palbociclib in combination with letrozole provides superior clinical benefit compared to letrozole in combination with placebo in Asian postmenopausal women with ER(+)/HER2(-) locoregionally recurrent or metastatic advanced breast cancer who have not received any prior systemic anti-cancer therapies for advanced stage disease.

Complete information for Palbociclib may be found in the Single Reference Safety Document for the compound, which for this study is the Investigator's Brochure. The Single Reference Safety Document for the active comparator agent, letrozole, is the local package insert.

## **2. STUDY OBJECTIVES AND ENDPOINTS**

### **2.1. Objectives**

#### Primary Objective:

- To compare the combination of Palbociclib plus letrozole with placebo plus letrozole in term of progression-free survival (PFS) in Asian postmenopausal women with ER(+)/HER2(-) advanced breast cancer (ABC) who have not received any prior systemic anti-cancer therapy for advanced disease.

#### Secondary Objectives:

- To compare Objective Response (OR), Duration of Response (DR), Disease Control Rate (DCR), and Overall Survival (OS) between the treatment arms;
- To evaluate the safeties and tolerability of the treatment arms;
- To determine trough Palbociclib plasma concentration in this patient population and explore the correlations between exposure and response and/or safety findings; To compare health-related quality of life between the treatment arms;
- To characterize alterations in genes, proteins, and RNAs relevant to the cell cycle, drug targets, and tumor sensitivity and/or resistance in tumor tissues;
- To explore the relationship between germline polymorphism in CDK6 gene and palbociclib treatment related neutropenia.

### **2.2. Endpoints**

#### Primary Endpoint

- Progression-Free Survival (PFS) based on investigator's assessment.

#### Secondary Endpoint(s)

- Progression-Free Survival (PFS) based on blinded independent central review (BICR);
- Objective Response (OR);



- Duration of Response (DR);
- Disease Control Rate (DCR);
- Overall Survival (OS);
- 1-year, 2-year, and 3-year Survival Probabilities;
- Trough plasma concentration of Palbociclib;
- Quality of life assessments: EuroQol (EQ-5D) Score (see [Appendix 5](#)) and Functional Assessment of Cancer Therapy - Breast (FACT-B) (See [Appendix 6](#));
- Type, incidence, severity (as graded by NCI CTCAE v4.0), seriousness and relationship to study medications of adverse events (AE) and any laboratory abnormalities;
- Tumor tissue biomarkers, including genes, proteins, and RNA expression (eg, ER, Ki67).

### 3. STUDY DESIGN

This is an international, multicenter, randomized(1:1), double-blind, placebo-controlled, parallel-group, Phase 3 clinical trial comparing the efficacy and safety of Palbociclib in combination with letrozole versus placebo in combination with letrozole in postmenopausal Asian women with ER(+)/HER2 (-) advanced breast cancer. Eligible patients will have histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic disease and will be candidates to receive letrozole as first-line treatment for their advanced disease. In order to avoid inclusion of patients who are refractory or resistant to non-steroidal aromatase inhibitors, patients who received anastrozole or letrozole as a component of their (neo)adjuvant regimen may only enter the study if their disease did not progress while on or within 12 months from completion of their anastrozole/letrozole-containing (neo)adjuvant therapy. Patients will not have received any prior systemic anti-cancer therapy for their advanced disease and will not be candidates for curative therapies. Patients must have measurable disease as per RECIST v.1.1 or bone disease as their only site of disease. Tumor tissue availability is required for patient participation.

At least approximately 330 eligible patients will be randomized 1:1 to receive either Palbociclib plus letrozole (Arm A: at least approximately 165 patients) or placebo plus letrozole (Arm B: at least approximately 165 patients). Among these approximately 330 patients, at least 264 patients will be from China and the rest of the patients will be from other Asia countries. Patients will be stratified at randomization by region (China vs other), by site of disease (visceral\* vs non-visceral\*\*), by disease-free interval since completion of prior (neo)adjuvant therapy (de novo metastatic;  $\leq 12$  months;  $> 12$  months), and by the nature of prior (neo)adjuvant anticancer treatment received (prior hormonal therapy; no prior hormonal therapy).

\*"Visceral" refers to any lung and/or liver involvement.

\*\*"Non-visceral" refers to absence of lung and/or liver involvement.

Patients randomized to Arm A (investigational arm) will receive:

- Palbociclib, 125 mg, orally once daily on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment;

*in combination with*

- Letrozole, 2.5 mg, orally once daily (continuously).

Patients randomized to Arm B (comparator arm) will receive:

- Placebo orally once daily on Day 1 to Day 21 of every 28-day cycle followed by 7 days off treatment;

*in combination with*

- Letrozole, 2.5 mg, orally once daily (continuously).

Patients will continue to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first. However, patients may continue treatment as assigned at randomization beyond the time of RECIST-defined disease progression at the discretion of the investigator if that is considered to be in the best interest of the patient and as long as no new anticancer treatment is initiated. In this case, the patient would continue with routine safety relevant assessments as per the Schedule of Activities for the active treatment period.

The importance of timely and complete disease assessments in this study cannot be overstated. Disease assessments will be performed every 12 weeks ( $\pm 7$  days) from the date of randomization. Patients with bone lesions identified at baseline will also have repeat bone scans performed every 24 weeks ( $\pm 7$  days) from the date of randomization. Each assessment will be performed as scheduled according to the calendar regardless of any dosing delay to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point. Tumor assessments will be performed until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST-defined disease progression), initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. A series of incomplete disease assessments will result in censoring of the primary endpoint of PFS back to the time of the last full assessment that did not show progression.

Patients who discontinue study treatment for reasons other than radiographically and/or clinically (ie for photographed or palpable lesions) documented PD as per RECIST v.1.1 will continue to have tumor assessments performed during the follow-up visits every 12 weeks ( $\pm 7$  days) and bone scans (if applicable) every 24 weeks ( $\pm 7$  days) until RECIST-defined disease progression, initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first.

Efficacy analyses will be performed using the local radiologist's/investigator's tumor assessments as primary data source. However, a blinded independent third-party core imaging laboratory will complete a retrospective review of radiographic images and clinical information collected on-study to verify the protocol-defined endpoints of disease response and progression as assessed by the investigator.

Patients discontinuing the active treatment phase will enter a follow-up period during which survival and new anti-cancer therapy information will be collected every 6 months from the last dose of investigational product. The follow-up period will conclude at the time of the final OS analysis. Crossover will not be allowed in the trial.

Patients will undergo study-related safety and efficacy assessments as outlined in the relevant Schedule of Activities located in the summary section.

The study also includes molecular profiling components aimed at characterizing alterations in genes, proteins, and RNAs relevant to the cell cycle, drug targets, and tumor sensitivity and/or resistance in tumor tissues, and assessing the relationship between germline polymorphism in CDK6 gene and palbociclib treatment related neutropenia.

#### **4. PATIENT SELECTION**

This study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom the protocol treatment is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

##### **4.1. Inclusion Criteria**

Patient eligibility should be reviewed and documented by an appropriate member of the investigator's study team before patients are included in the study.

Patients must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Adult Asian women (ages 18-70 years, inclusive) with proven diagnosis of adenocarcinoma of the breast with evidence of locoregionally recurrent or metastatic disease not amenable to resection or radiation therapy with curative intent and for whom chemotherapy is not clinically indicated.
2. Documentation of histologically or cytologically confirmed diagnosis of estrogen-receptor positive (ER+) breast cancer based on local laboratory results.
3. Previously untreated with any systemic anti-cancer therapy for their locoregionally recurrent or metastatic ER+ disease.
4. Postmenopausal status defined as :
  - Prior bilateral surgical oophorectomy, or
  - Medically confirmed post-menopausal status defined as spontaneous cessation of regular menses for at least 12 consecutive months or follicle-stimulating hormone (FSH) and estradiol blood levels in their respective postmenopausal ranges with no alternative pathological or physiological cause.

5. Measurable disease as defined per RECIST v.1.1 (see [Appendix 7](#)) or bone-only disease. Tumor lesions previously irradiated or subjected to other locoregional therapy will only be deemed measurable if disease progression at the treated site after completion of therapy is clearly documented.
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1 (see [Appendix 1](#)).
7. Adequate organ and bone marrow function defined as follows:
  - Absolute Neutrophil Count (ANC)  $\geq 1,500/\text{mm}^3$  ( $1.5 \times 10^9 /\text{L}$ );
  - Platelets  $\geq 100,000/\text{mm}^3$  ( $100 \times 10^9 /\text{L}$ );
  - Hemoglobin  $\geq 9$  g/dL (90 g/L);
  - Serum creatinine  $\leq 1.5$  x Upper Limit of Normal (ULN) or estimated creatinine clearance  $\geq 60$  mL/min as calculated using the method standard for the institution;
  - Total serum bilirubin  $\leq 1.5$  x ULN ( $\leq 3.0$  x ULN if Gilbert's disease);
  - AST and/or ALT  $\leq 3$  x ULN ( $\leq 5.0$  x ULN if liver metastases present);
  - Alkaline phosphatase  $\leq 2.5$  x ULN ( $\leq 5.0$  x ULN if bone or liver metastases present).
8. Resolution of all acute toxic effects of prior anti-cancer therapy or surgical procedures to NCI CTCAE version 4.0 Grade  $\leq 1$  (except alopecia or other toxicities not considered a safety risk for the patient at investigator's discretion).
9. Willingness and ability to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
10. All patients must agree to provide tumor tissues for centralized retrospective confirmation of ER status and to evaluate correlation between genes, proteins, and RNAs relevant to the cell cycle pathways and sensitivity/resistance to the investigational agents. Freshly biopsied, recurrent/metastatic tumor samples must be provided whenever possible. If such a biopsy is not feasible or cannot be safely performed, then an archived tumor sample may be accepted. In either case a formalin fixed, paraffin embedded (FFPE) block or 12 unstained FFPE slides (highly recommend to submit tissue block or

12 unstained slides, but if there would be technical difficulties or other issues refraining from obtaining tissue block or 12 unstained slides, however, it is still mandatory to collect a minimum 7 unstained slides) are required for patient participation.

11. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

#### **4.2. Exclusion Criteria**

Patients presenting with any of the following will not be included in the study:

1. HER2-positive tumor as defined by documentation of erbB-2 gene amplification by FISH (as defined by a HER2/CEP17 ratio  $\geq 2$ ) or chromogenic in situ hybridization (CISH, as defined by the manufacturer's kit instruction) or documentation of HER2-overexpression by IHC (defined as IHC3+, or IHC2+ with FISH or CISH confirmation) based on local laboratory results utilizing one of the sponsor-approved assays (see [Appendix 2](#)). If HER2 status is unavailable or was determined using a test other than a sponsor-approved assay, then testing must be performed/repeated using one of these assays prior to randomization. If tissue sample from both primary and recurrent/metastatic tumors are available, HER2 assessment from the most recent sample (ie, recurrent/metastatic sample) should be used to define eligibility whenever feasible.
2. Patients with advanced, symptomatic, visceral spread, that are at risk of life-threatening complications in the short term (including patients with massive uncontrolled effusions [pleural, pericardial, peritoneal], pulmonary lymphangitis, and over 50% liver involvement).
3. Known active uncontrolled or symptomatic CNS metastases, carcinomatous meningitis, or leptomeningeal disease as indicated by clinical symptoms, cerebral edema, and/or progressive growth. Patients with a history of CNS metastases or cord compression are eligible if they have been definitively treated with local therapy (eg, radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before randomization.
4. Prior neoadjuvant or adjuvant treatment with a non-steroidal aromatase inhibitor (ie, anastrozole or letrozole) with disease recurrence while on or within 12 months of completing treatment.

5. Prior treatment with any CDK4/6 inhibitor.
6. Patients treated within the last 7 days prior to randomization with:
  - Food or drugs that are known to be CYP3A4 inhibitors (ie, amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit or grapefruit juice);
  - Drugs that are known to be CYP3A4 inducers (ie, carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort);
  - Drugs that are known to prolong the QT interval (see [Appendix 3](#)).
7. Major surgery, chemotherapy, radiotherapy, any investigational agents, or other anti-cancer therapy within 2 weeks before randomization. Patients who received prior radiotherapy to  $\geq 25\%$  of bone marrow are not eligible independent of when it was received (see [Appendix 4](#)).
8. Diagnosis of any other malignancy within 3 years prior to randomization, except for adequately treated basal cell or squamous cell skin cancer, or carcinoma in situ of the cervix.
9. Machine-read QTc  $> 480$  msec (based on the mean value of the triplicate Electrocardiogram, ECGs), family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation, or Torsade de Pointes (TdP).
10. Uncontrolled electrolyte disorders that can compound the effects of a QTc-prolonging drug (eg, hypocalcemia, hypokalemia, hypomagnesemia).
11. Any of the following within 6 months of randomization: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE version 4.0 Grade  $\geq 2$ , atrial fibrillation of any grade, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident including transient ischemic attack, or symptomatic pulmonary embolism.

12. Active inflammatory bowel disease or chronic diarrhea, short bowel syndrome, or any upper gastrointestinal surgery including gastric resection.
13. Known hypersensitivity to letrozole, or any of its excipients, or to any Palbociclib/placebo excipients.
14. Known human immunodeficiency virus infection.
15. Other severe acute or chronic medical or psychiatric condition (including recent or active suicidal ideation or behavior) or laboratory abnormality that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study.
16. Patients who are investigational site staff members directly involved in the conduct of the trial and their family members, site staff members otherwise supervised by the Investigator, or subjects who are Pfizer employees directly involved in the conduct of the trial.
17. Participation in other studies involving investigational drug(s) (Phase 1-4) within 4 weeks before the current study begins and/or during study participation in the active treatment phase of the trial.

#### **4.3. Randomization Criteria**

- Patients will be randomized into the study provided they have satisfied all patient selection criteria.
- The investigators or their pre-specified designee will randomize eligible patients by interactive randomization technology (IRT) as described in the Study Reference Manual.
- At the time of randomization, information about patient demographics and stratification factors [ie, region (China vs other), site of disease (visceral vs non-visceral), disease-free interval since the end of the (neo)adjuvant treatment to disease recurrence (de novo metastatic vs  $\leq 12$  months vs  $> 12$  months), nature of prior (neo)adjuvant anticancer therapies (prior hormonal therapy vs no prior hormonal therapy)] will be requested.
- The central computerized system will provide the randomization number and treatment assignment.



#### **4.4. Sponsor Qualified Medical Personnel**

The contact information for the sponsor's appropriately qualified medical personnel for the trial is documented in the study contact list located in the team sharepoint site.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, patient study number, contact information for the investigational site and contact details for a help desk in the event that the investigational site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subjects participation in the study. The help desk number can also be used by investigational staff if they are seeking advice on medical questions or problems, however it should only be used in the event that the established communication pathways between the investigational site and the study team are not available. It is therefore intended to augment, but not replace the established communication pathways between the investigational site and study team for advice on medical questions or problems that may arise during the study. The help desk number is not intended for use by the subject directly and if a subject calls that number they will be directed back to the investigational site.

### **5. STUDY TREATMENTS**

#### **5.1. Allocation to Treatment**

If the patient is found to be eligible for the study, she should be randomized using a centralized internet/telephone registration system no more than 4 business days before administration of the first dose of investigational product.

After a patient has provided written informed consent, has completed the necessary baseline assessments, and is found to be eligible for the study, the clinical site must complete a Patient Pre-Randomization Form which includes key eligibility criteria (eg, breast cancer diagnosis, stage of disease at initial diagnosis and at screening, hormonal receptor and HER2 status as per local results, prior systemic therapy, disease free interval (DFI) from prior (neo)adjuvant letrozole or anastrozole (if applicable)) and send it to the sponsor for approval of randomization. Upon receipt of the sponsor's approval the site must contact a centralized internet/telephone registration system as described in the Study Reference Manual, to enroll the patient on study (see [Section 4.3](#)).

Eligible patients will be randomly assigned in a 1:1 ratio to either Arm A (investigational arm: Palbociclib plus letrozole) or Arm B (comparator arm: placebo plus letrozole) stratified according to region, site of disease, disease-free interval since completion of prior (neo)adjuvant therapy, and nature of prior (neo)adjuvant anticancer treatment received (see [Section 4.3](#)).

Clinical sites must complete the screening case report forms (CRFs) for all registered and randomized patients, even if the patient is not subsequently treated in this study.

At the time of registration, the clinical site staff must provide site and patient identifiers and demographic information. The IRT will assign a unique patient identification number. The IRT system will also be used to assign study medication.

If a patient does not receive the correct study treatment for their allocated treatment arm, the reason must be clearly documented in CRF. The patient will remain on study, baseline data will be collected and follow up will continue as described in the relevant Schedule of Activities table.

## **5.2. Breaking the Blind**

This study will be patient and investigator blinded. At the initiation of the trial, the trial site will be instructed on the method for breaking the blind. The method will be by contacting the interactive response technology (IRT) provider. Blinding codes should only be broken in emergency situations for reason of patient safety. Blinding codes may also be broken after a patient discontinues treatment due to disease progression, as determined by the treating investigator using RECIST v.1.1 criteria, but only if deemed essential to allow the investigator to select the patient's next treatment regimen and after discussion and agreement with the sponsor. Code should not be broken in the absence of emergency situations or progressive disease as per RECIST v.1.1 (eg, in case of clinical deterioration, increase in tumor markers or any other evidence suggestive of disease progression but in the absence of RECIST-defined disease progression). When the blinding code is broken, the date and reason for unblinding must be fully documented in source documents and entered on the case report form. However, every effort should be made by the site staff to ensure that the treatment arm in which the unblinded patient is assigned is not communicated to any sponsor personnel or designee involved in the conduct of the trial.

### 5.3. Drug Supplies

The investigational drug used in the course of this trial is Palbociclib/placebo. In addition, all patients will receive letrozole. All three medications will be supplied by the sponsor.

#### 5.3.1. Formulation and Packaging

##### 5.3.1.1. Palbociclib

Palbociclib will be supplied as capsules containing 75 mg, 100 mg, or 125 mg equivalents of Palbociclib free base. The sponsor will supply the oral drug formulation to sites in High Density Polyethylene (HDPE) bottles containing 75 mg, 100 mg, or 125 mg capsules. The capsules can be differentiated by their size and color (see below).

**Table 1. Palbociclib/Placebo Capsule Characteristics**

Dosage	Capsule color	Capsule size
75 mg	Sunset Yellow/Sunset Yellow	2
100 mg	Caramel/Sunset Yellow	1
125 mg	Caramel/Caramel	0

##### 5.3.1.2. Placebo

Placebo will be indistinguishable from the Palbociclib capsules and will be supplied as capsules matching in size and color the various Palbociclib formulations (see Table 1). The sponsor will supply placebo to sites in HDPE bottles.

##### 5.3.1.3. Letrozole

Commercially available letrozole 2.5 mg film-coated tablets will be supplied to sites by the sponsor. Complete information about letrozole formulation can be found in the local package insert.

#### 5.3.2. Preparation and Dispensing

##### 5.3.2.1. Palbociclib/Placebo

Palbociclib will be provided in non-patient-specific bottles containing either 75 mg, 100 mg or 125 mg capsules. Matching placebo capsules will be provided in non-patient-specific bottles as to be indistinguishable from Palbociclib.

The patient number should be recorded on the bottle label in the spaces provided by site personnel at the time of assignment to patient. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit. Returned unused medication **MUST NOT** be re-dispensed to patient.

Palbociclib/placebo is an agent that must be handled and administered with care. Patients should be instructed to keep their medication in the bottles provided and not transfer it to any other container. Due to possible unknown hazards associated with topical and environmental exposure to experimental agents, capsules must not be opened and/or emptied into any vehicle for oral ingestion; capsules must be swallowed intact.

Only one capsule strength will be dispensed to the patient at each dispensing visit. In the event of dose modification, request should be made of the patient to return all previously dispensed medication to the clinic and new capsules will be dispensed.

### **5.3.2.2. Letrozole**

Letrozole should be prepared and dispensed according to the package insert or standard practice at the study site.

The patient number should be recorded on the bottle label in the spaces provided by site personnel at time of assignment to patient. Site personnel must ensure that patients clearly understand the directions for self-medication. Patients should be given a sufficient supply to last until their next study visit. Unused drug and/or empty bottles should be returned to the site at the next study visit.

### **5.3.3. Administration**

#### **5.3.3.1. Palbociclib/Placebo**

Patients should be instructed to swallow Palbociclib/placebo capsules whole and not to chew them prior to swallowing. No capsule should be ingested if it is broken, cracked, or otherwise not intact. Patients should be encouraged to take their dose at approximately the same time each day. Patients should be instructed to record daily administration of the study drugs in a patient diary.

Palbociclib/placebo will be administered together with letrozole. Patients should take Palbociclib /placebo with food. Palbociclib/placebo will be administered orally once a day for 21 days of every 28-day cycle followed by 7 days off treatment.

Patients experiencing investigational product related toxicity may have their dose modified according to [Section 5.3.4](#).

### **5.3.3.2. Letrozole**

Letrozole will be administered orally once daily continuously together with Palbociclib/placebo.

Refer to the local package insert for Letrozole for additional administration instructions.

### **5.3.3.3. General Rules**

For both Palbociclib/placebo and letrozole:

- Patients who miss a day's dose entirely must be instructed NOT to "make it up" the next day.
- Patients who vomit anytime after taking a dose must be instructed NOT to "make it up," and to resume treatment the next day as prescribed.
- Patients who inadvertently take 1 extra dose during a day must be instructed to skip the next day's dose. Also refer to [Section 5.3.5](#) for further details on medication errors and overdose.

### **5.3.4. Dose Modification**

Every effort should be made to administer study treatment on the planned dose and schedule. However, in the event of significant treatment-related toxicity, administration of study drugs (Palbociclib/placebo or letrozole) may need to be adjusted as described in the following sections. Depending on the nature of the toxicity observed, dosing adjustment may be required for just one or both study drugs in the combination. In the event treatment interruption is deemed necessary for just one of the study drugs in the combination, treatment with the other study drug will continue as planned.

#### **5.3.4.1. Letrozole**

No dose adjustment for letrozole is permitted but dosing interruptions are allowed. Treatment interruption for letrozole-related toxicities will be performed as per the investigator's best medical judgment.

Patients discontinuing letrozole treatment due to treatment-related toxicity will be discontinued from the active treatment phase of the study and enter the follow-up phase.

#### **5.3.4.2. Palbociclib/Placebo**

In the event of significant treatment-related toxicity, Palbociclib/placebo dosing may be interrupted or delayed and/or reduced as described below. In the event of multiple toxicities, dose modification should be based on the worst toxicity observed. Patients are to be instructed to notify Investigators at the first occurrence of any adverse sign or symptom.

Dose modifications may occur in three ways:

- Within a cycle: dosing interruption until adequate recovery and dose reduction, if required, during a given treatment cycle;
- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start;
- In the next cycle: dose reduction may be required in a subsequent cycle based on toxicity experienced in the previous cycle.

Patients discontinuing Palbociclib/placebo treatment due to treatment-related toxicity may continue on the active treatment phase of the study receiving letrozole monotherapy as per the investigator's discretion.

##### **5.3.4.2.1. Dosing Interruptions**

Patients experiencing the following adverse events should have their treatment interrupted/delayed:

- Uncomplicated Grade 3 neutropenia ( $ANC < 1000/mm^3$ );
- Grade 3 neutropenia ( $ANC < 1000/mm^3$ ) associated with a documented infection or fever  $\geq 38.5^\circ C$ ;

- Grade 4 neutropenia ( $ANC < 500/mm^3$ );
- Grade 4 thrombocytopenia (Platelet count  $< 25,000/mm^3$ );
- Grade  $\geq 3$  non-hematologic toxicity (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment);
- Grade 3 QTc prolongation ( $QTc \geq 501$  msec on at least two separate ECGs).

Appropriate follow up assessments should be done until adequate recovery occurs as assessed by the Investigator. Criteria required before treatment can resume are described in [Section 5.3.4.2.2](#).

Doses may be held as needed until toxicity resolution. Depending on when the adverse event resolved, a treatment interruption may lead to the patient missing all subsequent planned doses within that same cycle or even to delay the initiation of the subsequent cycle.

If the adverse event that led to the treatment interruption recovers within the same cycle, then re-dosing in that cycle is allowed. Doses omitted for toxicity are not replaced within the same cycle. The need for a dose reduction at the time of treatment resumption should be based on the criteria defined in [Section 5.3.4.2.3 Dose Reductions](#) unless expressly agreed otherwise following discussion between the investigator and the sponsor. If a dose reduction is applied in the same cycle, the patient will need to return to the clinic to receive new drug supply.

In the event of a treatment interruption for reasons other than treatment-related toxicity (eg, non-cancer related surgery) lasting  $> 2$  weeks, treatment resumption will be decided in consultation with the sponsor.

#### **5.3.4.2.2. Dose Delay**

Retreatment following treatment interruption for treatment related toxicity or at the start of any new cycle may not occur until all of the following parameters have been met:

- Platelet count  $\geq 50,000/mm^3$ ;
- $ANC \geq 1000/mm^3$  and no fever;

- Grade 3 or higher treatment-related non-hematologic AEs (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment), with the exception of alopecia, have recovered to Grade  $\leq 1$  or baseline (or, at the investigator's discretion, Grade  $\leq 2$  if not considered a safety risk for the patient).
- QTc  $< 501$  msec and potential reversible causes (eg, electrolyte imbalance, concomitant medications known to prolong QTc) corrected. If QTc remains above 480 msec, ECG should be monitored more frequently as per the investigator's best medical judgement until QTc  $\leq 480$  msec.

If a treatment delay results from decline in hematologic parameters, the frequency of blood count assessments should be increased as clinically indicated.

If these parameters are met within 2 weeks of treatment interruption or cycle delay, Palbociclib/placebo may be resumed. Please refer to [Section 5.3.4.2.3 Dose Reductions](#) for adverse events requiring dose reduction at the time of treatment resumption.

If these parameters have not been met after 2 weeks of dose interruption (including the scheduled 1 week off treatment) or 2 weeks of cycle delay, permanent discontinuation of Palbociclib/placebo treatment should be considered. Treatment resumption for patients recovering from treatment-related toxicity after  $> 2$  weeks of treatment interruption or cycle delay but deemed to be deriving obvious clinical benefit per the investigator's best medical judgment is left at the investigator's discretion.

#### **5.3.4.2.3. Dose Reductions**

Following dose interruption or cycle delay the Palbociclib/placebo dose may need to be reduced when treatment is resumed.

No specific dose adjustments are recommended for Grade 1/2 treatment-related toxicity. However, investigators should always manage their patients according to their medical judgment based on the particular clinical circumstances.

Dose reduction of Palbociclib /placebo by 1 and, if needed, 2 dose levels ([Table 2](#)) will be allowed depending on the type and severity of toxicity encountered. Patients requiring more than 2 dose reductions will be discontinued from the study and entered into the follow-up phase. All dose modifications/adjustments must be clearly documented in the patient's source notes and Investigational product administration CRF.



Once a dose has been reduced for a given patient, all subsequent cycles should be administered at that dose level, unless further dose reduction is required. Dose re-escalation is not allowed.

**Table 2. Available Dose Levels**

Dose Level	Palbociclib/Placebo for 3 out of 4 weeks (3/1 schedule)	Letrozole on a continuous daily dosing regimen
Starting dose	125 mg/d	2.5 mg/d
-1	100 mg/d	2.5 mg/d
-2	75 mg/d*	2.5 mg/d
Discontinue Study Treatment		

\* Palbociclib/placebo dose de-escalation below 75 mg/d is not allowed.

Palbociclib/placebo recommended dose modifications for treatment related toxicities requiring treatment interruption/delay or persisting despite optimal medical treatment are described in Table 3 and [Table 4](#).

<b>Table 3. Palbociclib/Placebo Dose Modifications for Treatment Related Toxicities Requiring Treatment Interruption/Delay or Persisting Despite Optimal Medical Treatment.</b>	
Type and Grade of Toxicity:	Restart Palbociclib/Placebo Treatment at:
<b>Uncomplicated Grade 3 neutropenia</b> ( $ANC < 1000/mm^3$ )	Same dose level
<b>Grade 3 neutropenia</b> ( $ANC < 1000/mm^3$ ) <b>associated with a documented infection or fever <math>\geq 38.5^\circ C</math></b>	↓ 1 Dose Level
<b>Grade 4 neutropenia</b> ( $ANC < 500/mm^3$ )	↓ 1 Dose Level
<b>Grade 4 thrombocytopenia</b> ( $Platelet\ count < 25,000/mm^3$ )	↓ 1 Dose Level
<b>Grade <math>\geq 3</math> non-hematologic toxicity</b> (including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment)	↓ 1 Dose Level

<b>Table 4. Palbociclib/Placebo Dose Modifications for Hematologic Toxicities (by CTCAE Grade and on Day of Treatment)<sup>a</sup></b>		
Day of treatment	CTCAE Grade	Dose modifications
Cycle 1 Day 14	Grade 1, 2, and 3 <sup>b</sup>	No dose adjustment is required
	Grade 3 <sup>c</sup> with documented infection or fever $\geq 38.5^{\circ}\text{C}$ Grade 4 <sup>d</sup>	Withhold until recovery to Grade $\leq 2$ , then resume at next lower dose at start of next cycle
Cycle 1 Day 21	Grade 1, 2, and 3 <sup>b</sup>	No dose adjustment is required
	Grade 3 <sup>c</sup> with documented infection or fever $\geq 38.5^{\circ}\text{C}$ Grade 4 <sup>d</sup>	Withhold until recovery to Grade $\leq 2$ , then resume at next lower dose at start of next cycle
Cycle 2 Day 1	Grade 1 and 2	No dose adjustment is required
	Grade 3 <sup>b</sup>	Withhold until recovery to Grade $\leq 2$ , then resume at current dose
	Grade 3 <sup>c</sup> with documented infection or fever $\geq 38.5^{\circ}\text{C}$ Grade 4 <sup>d</sup>	Withhold until recovery to Grade $\leq 2$ , then resume at next lower dose
Cycle 2 Day 21	Grade 1, 2, and 3 <sup>b</sup>	No dose adjustment is required
	Grade 3 <sup>c</sup> with documented infection or fever $\geq 38.5^{\circ}\text{C}$ Grade 4 <sup>d</sup>	Withhold until recovery to Grade $\leq 2$ , then resume at next lower dose at start of next cycle
Day 1 of subsequent cycles	Grade 1 and 2	No dose adjustment is required
	Grade 3 <sup>b</sup>	Withhold until recovery to Grade $\leq 2$ , then resume at current dose
	Grade 3 <sup>c</sup> with documented infection or fever $\geq 38.5^{\circ}\text{C}$ Grade 4 <sup>d</sup>	Withhold until recovery to Grade $\leq 2$ , then resume at next lower dose
<p>Grading according to CTCAE Version 4.0.  ANC=absolute neutrophil count; CTCAE=Common Terminology Criteria for Adverse Events.</p> <p><sup>a</sup> Monitor complete blood count prior to starting Palbociclib and on Day 14 and 21 of the first cycle. Obtain complete blood count at the start of, and on Day 21 of the second cycle. Continue monthly monitoring of complete blood count at the beginning of each cycle for at least 4 subsequent cycles. Once complete blood count has stabilized, monitor as clinically indicated.</p> <p><sup>b</sup> Patients experiencing uncomplicated Grade 3 neutropenia (<math>\text{ANC} &lt; 1000/\text{mm}^3</math>) should still have their treatment interrupted/delayed until recovery to Grade <math>\leq 2</math>, then resume at the same current dose.</p> <p><sup>c</sup> Patients with Grade 3 neutropenia (<math>\text{ANC} &lt; 1000/\text{mm}^3</math>) associated with a documented infection or fever <math>\geq 38.5^{\circ}\text{C}</math> should have their treatment interrupted/delayed until recovery to Grade <math>\leq 2</math> and fever is no longer present, then resume at next lower dose.</p> <p><sup>d</sup> Except lymphopenia (unless associated with clinical events, eg, opportunistic infections).</p>		

## QTc prolongation management

In the event of QTc prolongation of, possible alternative reversible causes such as serum electrolytes abnormalities, or usage of concomitant medications with the potential to prolong the QTc interval should be evaluated.

If such reversible causes are identified, then they should be corrected accordingly (ie, correction of electrolyte abnormalities with supplements to within normal limits and/or discontinuation (if possible) of concomitant medications known to prolong the QT interval).

Recommended dose modifications in the event of QTc prolongation are provided in Table 5.

**Table 5. Palbociclib/Placebo Dose Modifications in the Event of QTc Prolongation**

	Toxicity (NCI CTC Grade, Version 4.0)		
	Grade 2 QTc prolongation	Grade 3 QTc prolongation	Grade 4 QTc prolongation
Reversible cause identified	Treat reversible cause Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc≤480 msec Continue at the <u>same dose level</u> <sup>(1)</sup>	Treat reversible cause Withhold treatment until QTc<501 msec Resume treatment at the <u>same dose level</u> . Monitor ECG more frequently as per investigator's best medical judgment until QTc≤480 msec.	Permanently discontinue
No reversible cause identified	Initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc≤480 msec Continue at the <u>same dose level</u> <sup>(1)</sup>	Withhold treatment until QTc<501 msec Resume treatment at the <u>next lower dose level</u> <sup>(2)</sup> Monitor ECG more frequently as per investigator's best medical judgment until QTc≤480 msec.	Permanently discontinue

1. If the QTc remains above 480 msec more than 2 cycles or if Grade 2 QTc prolongation recurs in the absence of other alternative causes or despite correction of alternative causes, dose adjustment and/or discontinuation should be considered in consultation with a cardiologist and the study medical monitor, taking into account the emerging safety data from Palbociclib trials and the investigator's best medical judgment.
2. If the Grade 3 QTc prolongation occurs again after one dose reduction, further dose adjustment and/or discontinuation should be discussed with study medical monitor in consultation with a cardiologist, taking into consideration the emerging safety data from Palbociclib trials and the investigator's best medical judgment.

### 5.3.5. Medication Errors and Overdose

Medication errors may result in this study from the administration or consumption of the wrong drug, by the wrong patient, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the medication error case report form (CRF) which is a specific version of the adverse event (AE) page and on the serious adverse event (SAE) form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating patient.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error should be captured on the medication error version of the adverse event (AE) page and, if applicable, any associated adverse event(s) are captured on an adverse event (AE) CRF page.

### 5.3.6. Compliance

Patients will be required to return all bottles of Palbociclib/placebo and all bottles of letrozole as well as the completed patient diary at the beginning of each cycle for drug accountability. Drug accountability will be performed on Day 1 of every cycle prior to dispensing drug supply for the next cycle. The number of remaining capsules/tablets will be documented and recorded.

To be considered compliant, each study patient must have received at least 80% of the planned number of doses of primary therapy based on the number of days of actual dose administration. Dose adjustments must follow instructions provided in the [dose adjustment guidelines](#) section.

### 5.4. Drug Storage and Drug Accountability

Storage conditions stated in the Study Reference Safety Document (ie, Investigator's Brochure (IB) or Local Product Document (LPD)) may be superseded by the label storage.

Investigators and site staff are reminded to *check temperatures daily (ie, manually or by using alarm systems to alert of any excursions)* and ensure that thermometers are working

correctly as required for proper storage of investigational products (See [Sections 5.4.1 & 5.4.2](#)). These include thermometers for both the room storage and refrigerator storage. Any temperature excursions should be reported to the sponsor. The investigational product(s) must be stored as indicated. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once a deviation is identified, the investigational products (Palbociclib/placebo or letrozole) **MUST** be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

At the end of the trial, the sponsor will provide instructions as to disposition of any unused investigational product. If the sponsor authorizes destruction at the trial site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by the sponsor. Destruction must be adequately documented.

#### **5.4.1. Palbociclib/Placebo**

Palbociclib/placebo capsules should be stored at controlled room temperature (15-30°C, 59-86°F) in their original container.

Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Returned medication should be stored separately from medication that needs to be dispensed.

To ensure adequate records, Palbociclib/placebo capsules will be accounted for as instructed by the sponsor. Patients are requested to return previously dispensed containers as well as their completed patient diary to the clinic at each visit for accountability purposes even if they will not be issued with new medication at that visit.

#### **5.4.2. Letrozole**

Letrozole tablets must be stored according to the instructions detailed in the local package insert.

Medication should be kept in a secured locked area at the study site in accordance with applicable regulatory requirements. Returned medication should be stored separately from medication that needs to be dispensed.

To ensure adequate records, letrozole tablets will be accounted for as instructed by the sponsor. Patients are requested to return previously dispensed containers as well as their completed patient diary to the clinic at each visit for accountability purposes even if they will not be issued with new medication at that visit.

## 5.5. Concomitant Medications

Patients must be instructed not to take any additional medications (over-the-counter or other products) during the study without prior consultation with the investigator. Any medications including herbal supplements, vitamins, or treatment taken by the patient from 28 days prior to the start of study treatment and up to 28 days following the last dose of investigational product and the reason for their administration must be recorded on the CRF.

Routine postoperative care, such as dressing changes, suture removal, drain removal, or venous access (central or peripheral), does not need to be recorded. Anesthetics used for any surgical procedures performed during the patient's participation in the study can be recorded as "unspecified anesthesia" on the concomitant treatment records; it is not necessary to list the specific anesthetics. Palliative and supportive care for cancer-related symptoms will be offered to all patients in this study.

### 5.5.1. Prohibited Medications

The following treatments are prohibited throughout the duration of the active treatment phase:

- **Anticancer agents:** No additional investigational or commercial anticancer agents such as chemotherapy, immunotherapy, targeted therapy, biological response modifiers, or endocrine therapy other than letrozole will be permitted during the active treatment phase. In general, any drugs containing "for the treatment of breast cancer" on the product insert are not permitted on study. No Chinese anti-cancer herbal medicines will be permitted, any usage of Chinese herbal medicine should be recorded.
- **Strong CYP3A inhibitors/inducers:** Palbociclib is metabolized to multiple metabolites in a qualitatively similar manner in rat, dog and human liver microsomes. In vitro, Palbociclib is primarily metabolized by CYP3A4 enzymes. Co-administration with drugs that are CYP3A inhibitors and inducers may change the plasma concentrations of Palbociclib in humans. The concurrent use of CYP3A

inhibitors, including amprenavir, atazanavir, boceprevir, clarithromycin, conivaptan, delavirdine, diltiazem, erythromycin, fosamprenavir, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, verapamil, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit, are not allowed in the study. The concurrent use of CYP3A inducers, including carbamazepine, felbamate, nevirapine, phenobarbital, phenytoin, primidone, rifabutin, rifampin, rifapentin, and St. John's wort, are not allowed in the study.

- **Drugs known to cause QT interval prolongation** are prohibited during the active treatment phase. Refers to [Appendix 3](#) for a list of drugs known to predispose to Torsade de Pointes.
- **Hormone replacement therapy**, topical estrogens (including any intra-vaginal preparations), **megestrol acetate** and **selective estrogen-receptor modulators** (eg, raloxifene) are prohibited during the active treatment phase.
- **Proton-pump inhibitors:** the concomitant use of proton-pump inhibitors (including, but not limited to, dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) with Palbociclib/placebo is prohibited. Further recommendations about the use of antacids are provided under [Section 5.5.2](#).

### 5.5.2. Medications Not Recommended

The following treatments are not recommended throughout the duration of the active treatment phase. Alternative therapies should be considered whenever possible. If usage of the following treatments is deemed necessary, consultation and agreement with the sponsor is required prior to treatment initiation.

- **Moderate CYP3A Inducers:** The concurrent use of moderate CYP3A inducers such as dexamethasone or omeprazole is not recommended.
- **CYP3A Substrates:** Palbociclib and its oxidative metabolite, PF-05089326, demonstrated little or no inhibition of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2D6 enzyme activities and thus, showed low potential for CYP-mediated pharmacokinetic drug interactions. However, Palbociclib and PF-05089326 caused time-dependent inhibition of CYP3A midazolam 1'-hydroxylase and testosterone 6 $\beta$  hydroxylase activities with  $K_i$  and

kinact values for Palbociclib of 10  $\mu\text{M}$ , 0.036  $\text{min}^{-1}$  and 19  $\mu\text{M}$ , 0.087  $\text{min}^{-1}$  and for PF 05089326 of 7.0  $\mu\text{M}$ , 0.094  $\text{min}^{-1}$  and 6.4  $\mu\text{M}$ , 0.15  $\text{min}^{-1}$ , respectively.

Therefore, Palbociclib and its metabolite may have the potential for pharmacokinetic drug interactions with compounds for which CYP3A-mediated metabolism constitutes the primary mechanism of clearance. While the clinical significance of this inhibitory effect is yet to be investigated, caution must be exercised in patients receiving Palbociclib in combination with drugs that are predominantly metabolized by CYP3A. In particular, co-administration of Palbociclib with CYP3A4 substrates with narrow therapeutic index including, but not limited to alfentanil, aripiprazole, cyclosporine, ergotamine, fentanyl, halofantrine, pimozone, quinidine, sirolimus, tacrolimus, triazolam, astemizole\*, cisapride\*, and terfenadine\* are not recommended during the active treatment phase of the trial. Alternative therapies should be used when available.

- **Chronic immunosuppressive therapies** should be avoided, including systemic corticosteroids. Steroids given for physiological replacement, as anti-emetics or inhaled as well as short course of oral/topical steroids given for allergic reactions or asthma flares are allowed.
- **The use of herbal medicine** is not recommended during the active treatment phase (anticancer herbal medicine is prohibited).
- **Local antacids** may decrease Palbociclib absorption and exposure; however, if needed, local antacid should be given at least 2 hours before or after Palbociclib /placebo administration.
- **H<sub>2</sub>-receptor antagonists**: no data on the potential effect of these agents (including, but not limited to, cimetidine, famotidine, nizatidine, ranitidine) on Palbociclib exposure has been collected. As acid lowering agents, they could potentially affect Palbociclib exposure. If needed, administer these agents with a staggered dosing regimen (twice daily). The dosing of Palbociclib/placebo should occur at least 10 hours after H<sub>2</sub>-receptor antagonist evening dose and 2 hours before the H<sub>2</sub>-receptor antagonist morning dose.



### 5.5.3. Permitted Medications

The following treatments are permitted throughout the duration of the active treatment phase:

- **Standard therapies** for pre-existing medical conditions, medical and/or surgical complications, and palliation. Any medication intended solely for supportive care (eg, analgesics, antidiarrheals, antidepressants) may also be used at the investigator's discretion. All medications should be recorded.
- **Bisphosphonates and receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors** for the treatment of osteoporosis or management of existing bone metastases may be continued for patients who have been receiving them at a stable dose for at least 2 weeks prior to randomization. However the need to initiate or increase the dose of these therapies during the study will be considered as indicative of disease progression leading to the discontinuation of patient from the active treatment phase unless disease progression can be completely ruled out and the exact reason for the use of these therapies clearly documented in the subject's source documentation.
- **Hematopoietic growth factors** (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage colony stimulating factor [GM-CSF]): Primary prophylactic use of granulocyte-colony stimulating factors is not permitted but they may be used to treat treatment-emergent neutropenia as indicated by the current American Society of Clinical Oncology (ASCO) guideline.<sup>73</sup> If neutropenic complications are observed in a cycle in which primary prophylaxis with CSFs was not received, secondary prophylaxis may be given at the discretion of the investigator, but only if dose reduction or delay are not considered to be a reasonable alternative.
- **Erythropoietin** may be used at the investigator's discretion for the supportive treatment of anemia.

### 5.6. Concomitant Radiotherapy or Surgery

Any concurrent radiotherapy (except palliative radiotherapy as specified below) or cancer-related surgery are prohibited throughout the duration of the active treatment phase of the study. Patients requiring any of these procedures will be discontinued from the active treatment phase and will enter the follow-up phase.

Palliative radiotherapy is permitted for the treatment of painful bony lesions provided that the lesions were known to be present at the time of study entry and the investigator clearly documents that the need for palliative radiotherapy is not indicative of disease progression. In view of the current lack of data about the interaction of Palbociclib with radiotherapy, Palbociclib/placebo treatment should be interrupted during palliative radiotherapy, stopping 1 day before and resuming treatment 1 week after. For patients with bone involvement, it is suggested to institute palliative radiotherapy before study initiation if possible and clinically appropriate (eg, lesions at risk for spontaneous micro-fractures or painful lesions). Palliative radiotherapy during the active treatment phase will be considered alternative cancer therapy and will result in censoring of the PFS endpoint. The dates on which palliative radiotherapy is administered should be recorded on the appropriate CRFs.

Caution is advised on theoretical grounds for any surgical procedures during the study. The appropriate interval of time between surgery and Palbociclib required to minimize the risk of impaired wound healing and bleeding has not been determined. Based on the available pharmacokinetic data, stopping Palbociclib/placebo is recommended at least 7 days prior to elective surgery. Postoperatively, the decision to reinitiate Palbociclib/placebo treatment should be based on a clinical assessment of satisfactory wound healing and recovery from surgery.

## **6. STUDY PROCEDURES**

Prior to undergoing any study specific procedures (with the exception of certain imaging assessments if meeting the criteria defined in [Section 6.1](#)), patients must read and sign the consent form. All study procedures and the timing when they must be performed are detailed in the Schedule of Activities tables. All data obtained for these assessments must be supported in the patients' source documentation.

For the purpose of this trial one cycle = 28 days.

### **6.1. Screening**

Voluntary, written, dated, and signed informed consent must be obtained before any study specific procedures are performed (with the exception of certain imaging assessments if meeting the criteria defined in this section); however, it may be obtained more than 28 days before randomization.

Radiographic tumor assessments (as documented on the [Tumor Assessment Requirement Flowchart](#)) that were performed before the signing of the informed consent form as routine procedures (but within 28 days prior to randomization) do not need to be repeated and may be used as baseline assessments, as long as:

- The tests were performed per the method requirements outlined in the [Tumor Assessment Requirement Flowchart](#), the [Efficacy Assessments](#) sections.
- Appropriate documentation indicating that these radiographic tumor assessments were performed as standard of care is available in the patient's source notes.

Bone scans performed as routine procedures within 12 weeks prior to randomization may also be accepted as baseline assessment if they meet the same requirements listed above.

Brain scans performed as routine procedures within 6 weeks prior to randomization may also be accepted as baseline assessment if they meet the same requirements listed above.

All lens grading evaluable patients will undergo the following ophthalmic procedures at screening:

- Best corrected distant visual acuity (Snellen);
- Refractive error associated with best corrected distant visual acuity;
- Intraocular pressure (IOP - one reading);
- Slit lamp biomicroscopy of the anterior segment including cell count and flare grading;
- Lens grading with the Wisconsin Age-Related Eye Disease Study (AREDS) 2008 Clinical Lens Opacity Grading Procedures using a laminated reference pocket card (See [Appendix 8](#)) - (pupil dilated examination);
- Funduscopy (Ophthalmoscopy – pupils must be dilated).

Patients with ophthalmic conditions (eg, anophthalmus, phthisis, aphakia, pseudophakia) that would prevent grading of the lens in both eyes will not be considered evaluable for this ophthalmic assessment and do not need to undergo these ophthalmic procedures. Reasons for not being evaluable must be clearly documented in the patient source notes.

All ophthalmic examinations will be performed by an ophthalmologist. Refer to [Section 7.2.3](#). Ocular Safety Assessments for further details on these procedures.

For details on baseline procedures, see the Schedule of Activities tables.

### **6.1.1. Screen Failure**

Patients who completed the informed consent process but do **NOT** meet all eligibility criteria and therefore are **NOT** randomized to either treatment arm will be considered as screen failures.

Clinical sites must provide for all screen failures the following information using the appropriate case report forms (CRFs): screening number, demographic data as well as the final subject summary including the reason for screening failure.

### **6.2. Active Treatment Phase**

For details on procedures during the active treatment phase, see the Schedule of Activities tables.

In the event that the start of a new cycle is delayed due to treatment-related toxicity, procedures required on Day 1 of the given cycle will be performed when Palbociclib/placebo is resumed. 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 (1) if not required to determine whether study drug may be resumed and (2) if performed within 7 days prior to study drug resumption.

All lens grading evaluable patients randomized will repeat screening ophthalmic procedures also during the active treatment phase after 3 months (Cycle 4 Day 1), 6 months (Cycle 7 Day 1), 12 months (Cycle 13 Day 1) then every 12 months (Day 1 of Cycles 25, 37, etc.) thereafter. Additional ophthalmic examinations may be repeated during the study as clinically indicated.

### **6.3. End of Treatment Visit**

The end of treatment visit will be performed as soon as possible but no later than 4 weeks (ie, 28 days)  $\pm$  7 days from last dose of investigational product and prior to the initiation of any new anticancer therapy.

All lens grading evaluable patients randomized will repeat screening ophthalmic procedures also at the End of Treatment visit.

For details on procedures to be performed at the End of Treatment visit, see the Schedule of Activities tables.

#### **6.4. Follow-up Visit**

After discontinuation of study treatment, post-study survival status (including post study anticancer therapies) will be collected approximately every 6 months ( $\pm 7$  days) from the last dose of study treatment. Telephone contact is acceptable.

Patients who discontinue study treatment for reasons other than radiographically and/or clinically (ie, for photographed or palpable lesions) documented disease progression as per RECIST definitions will continue to have tumor assessment performed during the follow-up visits every 12 weeks ( $\pm 7$  days) and bone scans (as applicable) every 24 weeks ( $\pm 7$  days) from the date of randomization until disease progression, initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first.

For details on follow-up visit procedures, see the Schedule of Activities tables.

#### **6.5. Patient Withdrawal**

##### **6.5.1. Active Treatment Phase Discontinuation**

The term "interruption" refers to a patient stopping the investigational product during the course of the study, but then re-starting it at a later time in the study. The reason for dosing interruption will be collected on the appropriate CRF.

The term "discontinuation" refers to a patient's withdrawal from the active treatment phase. The reason for discontinuation from treatment will be collected on the appropriate CRF.

Patients may be withdrawn from the active treatment phase in case of:

- Disease progression as per RECIST v.1.1;
- Symptomatic deterioration (ie, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression as per RECIST v.1.1);

- Need for additional anticancer therapy not specified in the protocol;
- Unacceptable toxicities;
- Investigator conclusion that it is in the patient's best interest to discontinue therapy (eg, poor compliance with either protocol monitoring or with taking the study medications, etc);
- Lost to follow-up\* ;
- Patient choice to withdraw from treatment (follow-up permitted by patient);
- Withdrawal of patient consent (cessation of follow-up);
- Death.

\*If a patient does not return for a scheduled visit, every effort should be made to contact the patient. If after 3 unsuccessful attempts to contact the patient, one of which is by registered letter, the patient should be considered "lost to follow-up". Steps taken to contact the patient (eg, dates of telephone calls, registered letters, etc) must be clearly documented in the source documents.

Patient who discontinue from the active treatment phase must have end of treatment/withdrawal evaluations performed as soon as possible but no later than 4 weeks from the last dose of investigational product and prior to initiation of any new anticancer therapy. Data to be collected for the end of study treatment/withdrawal are described in the Schedule of Activities tables.

If a patient opts to discontinue from the active treatment phase as a result of an unacceptable adverse drug reaction, "withdrawal of consent" should not be the reason for discontinuation. Instead, the reason for discontinuation of active treatment phase, must be recorded as "Unacceptable toxicity" and an appropriate action taken must be assigned on the AE CRF to the adverse event leading to the patient's withdrawal of consent.

### **6.5.2. Study Discontinuation**

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the patient to comply with the protocol required schedule of study visits or procedures at a given study site.

Patients will be withdrawn from study in the case of:

- Withdrawal of consent (ie, refuses tumor assessments or survival status after end of treatment);
- Lost to follow-up\*;
- Death.
- \*If a patient does not return for a scheduled visit, every effort should be made to contact the patient. If after three unsuccessful attempts to contact the patient, one of which is by registered letter, the patient should be considered “lost to follow-up”. Steps taken to contact the patient (eg, dates of telephone calls, registered letters, etc) must be clearly documented in the source documents. In any circumstance, every effort should be made to document patient outcome, if possible. The investigator should inquire about the reason for withdrawal, request the patient to return all unused investigational product(s), request the patient to return for a final visit, if applicable, and follow-up with the patient regarding any unresolved adverse events (AEs).

Data to be collected for the end of study treatment/withdrawal are described in the Schedule of Activities tables.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

## **7. ASSESSMENTS**

All study procedures are described in the Schedule of Activities tables footnotes.

Every effort should be made to ensure that the protocol required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, that may make it unfeasible to perform the test. In these cases, the investigator will take all steps necessary to ensure the safety and well being of the patient. When a protocol-required test cannot be performed the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

## **7.1. Efficacy Assessments**

### **7.1.1. Independent Review of Disease Assessments**

A blinded independent third-party core imaging laboratory will perform a retrospective review of radiographic images and clinical information collected on-study to verify the protocol defined endpoints of disease response and progression as assessed by the investigator.

It is important to the integrity of the study that all imaging studies and clinical information (including photographs) are forwarded to the independent core imaging laboratory as each patient enrolls and progresses through the study.

Materials to be forwarded for independent review are the following:

- All imaging studies performed on study, preferably in digital format on compact disc or optical disc. All digital media must be in Digital Imaging and Communications in Medicine (DICOM) format. Films may be forwarded for review if necessary; all films must be originals (second original films acceptable) rather than copies of films.
- Photographs of sites of disease assessed using clinical methods. Details concerning clinically assessed lesions will be collected on the CRFs and made available to the core imaging laboratory.

Further information on materials to be forwarded for independent review, correct procedures for the coding/blinding of the patient's name/identity and the return of the source data/documents to the site is provided in the core imaging laboratory Study Coordinator Manual.



### 7.1.2. Tumor Assessments

The importance of timely and complete disease assessments in this study cannot be understated. Disease assessments must be performed as scheduled according to the calendar, regardless of treatment delays resulting from toxicity, to prevent the introduction of bias into the assessment of efficacy. Failure to perform any of the required disease assessments will result in the inability to determine disease status for that time point. A series of incomplete disease assessments will result in censoring of the primary endpoint of PFS back to the time of the last full assessment that did not show progression. Frequent off schedule or incomplete disease assessments have the potential to weaken the conclusion of this clinical trial.

Radiographic tumor assessments may be done at any time if there is clinical suspicion of disease progression at the discretion of the investigator. If progressive disease is confirmed per RECIST v.1.1, patients are expected to discontinue study therapy and begin the follow-up phase of the trial. However, patients may continue treatment as assigned at enrollment beyond the time of RECIST-defined PD at the discretion of the investigator if that is considered to be in the best interest of the patient and as long as no new anticancer treatment is initiated.

**Screening/baseline tumor assessment** will be carried out within 28 days of randomization (unless otherwise specified below).

Disease assessment for all patients at baseline will include:

- Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) scan of the chest, abdomen, and pelvis (CAP).
- CT or MRI scan of any other sites of disease as clinically indicated.
- Clinical assessment of superficial disease which will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the CRF.
- Bone scans in order to detect bony sites of disease. Any suspicious abnormalities (ie, hotspots) identified on the bone scans at baseline must be confirmed by X-ray, CT scan with bone windows or MRI. Bone lesions identified at baseline will follow the same assessment schedule as for measurable lesions. Baseline brain CT or MRI are only required in case signs and symptoms suggest the presence of metastatic brain disease. Refer to [Section 6.1](#) for further details on timing allowance for baseline brain and bone scans.

**Post-baseline tumor assessments** will be performed every 12 weeks ( $\pm 7$  days) and bone scans (as applicable) every 24 weeks ( $\pm 7$  days) from randomization until radiographically and/or clinically (ie, for photographed or palpable lesions) documented PD as per RECIST v.1.1, study treatment discontinuation (for patients continuing treatment beyond RECIST-defined disease progression), initiation of new anticancer therapy, or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up). Imaging assessments are to be scheduled using the randomization date as the reference date for all time-points and are NOT to be scheduled based on the date of the previous imaging time-point. Imaging assessment delay to conform to treatment delay is not permitted.

Patients who discontinue study treatment for reasons other than radiographically and/or clinically (ie, for photographed or palpable lesions) documented disease progression as per RECIST definitions will continue to have tumor assessment performed during the follow-up visits every 12 weeks ( $\pm 7$  days) and bone scans (as applicable) every 24 weeks ( $\pm 7$  days) until documented disease progression, initiation of new anticancer therapy or discontinuation of patient from overall study participation (eg, death, patient's request, lost to follow-up), whichever occurs first. Every effort should be made to perform a last tumor assessment before starting a new anticancer therapy. Additional unscheduled tumor assessments may be performed as clinically indicated at any time.

Post-baseline tumor assessments will include:

- CT or MRI scan of the chest, abdomen, and pelvis (CAP).
- CT or MRI scan of any other sites of disease identified at baseline.
- Clinical assessment of sites of superficial disease identified at baseline. Clinical assessment of superficial disease must coincide with the imaging studies and will include photographs of all superficial metastatic lesions. All lesion measurements must be recorded in the CRF.

- Bone lesions imaging:
  - If bone lesions were identified at baseline the following assessment must be performed:
    - X-ray/CT scan/MRI every 12 weeks ( $\pm$  7 days) from the date of randomization using the same modality used to confirm the bone lesions at baseline. Areas that have received palliative radiotherapy on study cannot be used to assess response to study treatment.
    - Bone scans every 24 weeks ( $\pm$  7 days) from the date of randomization and to confirm complete response. Abnormalities found on subsequent bone scans must also be confirmed by X-ray, CT scan, or MRI.
  - If no bone lesions were identified at baseline, bone scans should be performed as clinically indicated (ie, patient describes new or worsening bone pain, or has increasing alkaline phosphatase level, or other signs and symptoms of new/progressing bone metastases) but are required to confirm complete response. Abnormalities found on subsequent bone scans must also be confirmed by X-ray, CT scan, or MRI.
  - Repeat brain scans will be required only if metastases are suspected.

The CT scans, including brain CT scan if applicable, should be performed with contrast agents unless contraindicated for medical reasons. If IV contrast is medically contraindicated, the imaging modality to be used to follow the disease (either CT without contrast or MRI) should be the modality which best evaluates the disease, and the choice should be determined by the investigator in conjunction with the local radiologist. MRI of the abdomen and pelvis can be substituted for CT if MRI adequately depicts the disease.

However, MRI of the chest should not be substituted for CT of chest even if IV contrast is contraindicated. In such case CT will be performed without contrast. If MRI is used to follow-up bone lesion(s) it must be performed before any treatment that may affect bone-marrow cellularity (eg, G-CSF).<sup>75</sup>

The same method and technique should be used to characterize each lesion identified and reported at baseline, during the study treatment period and during follow-up. The use of plain-film X-rays (with the exception of bone X-rays as detailed above) is discouraged. The use of positron emission tomography (PET) imaging as the only imaging modality is not permitted.

For patients having effusions or ascites, cases having cytological proof of malignancy should be recorded as non-target lesions on the tumor assessment CRFs. Effusions that have not been evaluated using cytology or were found to be non-malignant should not be recorded on the non-target lesion CRF.

Objective tumor response will be measured using the Response Evaluation Criteria in Solid Tumors (RECIST Version 1.1, see <http://www.eortc.be/recist/default.htm>). Also please refer to [Appendix 7](#). All measurements should be recorded in metric notation using a ruler or calipers.

**For patients with bone-only disease:**

- Treatment outcome will be recorded in the CRF as complete response (CR), stable disease (SD) or progression (PD).

Interpretation will be PD if:

- The malignant nature of one or more new lesions identified with bone scan is confirmed with X-ray, or CT, or MRI scan,
- Flare observed in bone scan is followed by confirmation of progression with other imaging modalities,
- Clinical worsening of the disease is assessed by bone scan and disease progression (ie, new lesion(s)) is confirmed with other imaging modalities.
- Unequivocal progression of existing bone lesions.

Interpretation will be SD if:

- The malignant nature of all the new lesions identified with bone scan is not confirmed.

In the following cases the patient will be censored at the date of prior tumor assessment with no PD: 1) on-study fracture; 2) on-study management of pain (palliative radiation therapy, palliative surgery), 3) clinical worsening not objectively confirmed; 4) on-study change of therapy. In all the censored cases (no objectively documented PD) tumor assessment will be performed until PD. Also, it will be at the discretion of the investigator to discontinue the study treatment.

It is suggested to institute palliative radiotherapy (eg, lesions at risk for spontaneous micro-fractures or painful lesions) before study initiation as well as palliative surgery if possible and clinically appropriate.

### 7.1.3. Overall Survival

Following the End of Treatment visit, survival status will be collected in all patients (telephone contact is acceptable) every 6 months ( $\pm$  7 days) from the last dose of study treatment. Information on subsequent anticancer therapy will also be collected.

## 7.2. Safety assessments

Safety assessment will consist of monitoring of all adverse events (AEs), including serious adverse events (SAEs), regular monitoring of hematology, serum chemistry, and routine monitoring of ECGs, physical examinations, vital signs, ECOG performance status, and chest CTs.

Adverse event assessment will include type, incidence, severity (graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE], Version 4.0, see [Severity Assessment](#) section), timing, seriousness, and relatedness.

Baseline tumor-related signs and symptoms will be recorded at the Cycle 1 Day 1 visit and then reported as adverse events during the trial if they worsen in severity or increase in frequency.

### 7.2.1. Laboratory Safety Assessments

Blood tests will include the following:

Hematology Panel		Blood Chemistry Panel	
1	Hemoglobin	1	ALT
2	Platelets	2	AST
3	WBC	3	Alkaline Phosphatase
4	Absolute Neutrophils	4	Sodium
		5	Potassium
		6	Total Calcium
		7	Magnesium
		8	Total Bilirubin
		9	BUN or Urea
		10	Serum Creatinine
		11	Albumin

Blood tests will be drawn at the time points described in the Schedule of Activities table. Additional blood tests may be performed at the investigator's discretion as clinically indicated for the purpose of planning treatment administration, dose modification, or following adverse events.

### **7.2.2. Electrocardiogram (ECG)**

12-lead ECG monitoring will be undertaken in all patients enrolled in the trial. At each time point (see SCHEDULE OF ACTIVITIES), 3 consecutive ECGs will be performed approximately 2 minutes apart to determine the mean machine-read QTc interval. If the mean QTc interval is prolonged (>500 msec), then the ECGs should be re-evaluated by a qualified person at the site for confirmation. Additional triplicate ECGs may be performed as clinically indicated.

### **7.2.3. Ocular Safety Assessments**

#### **7.2.3.1. Snellen Best Corrected Visual Acuity and Refraction**

Snellen visual acuity will be assessed by using a standard wall or projection chart before implementing any procedures that can affect vision (eg, pupil dilation, tonometry, and gonioscopy). The same optotype will be used throughout the study for a specific patient, and the right eye should be tested first. The refractive error will be determined at the Screening visit. The examiner should ensure that patients are seated comfortably and that they do not move their head forward or backward during testing. Patients will be told that the chart contains only letters.

The line read with 2 or fewer errors will be recorded. If 3 of the 5 letters on a line are read correctly, the patient will be given credit for that line. For example, if the patient reads 20/25 +3, 20/20 will be recorded.

A decrease in best-corrected visual acuity of 3 lines or more from the Screening visit will be reported as an adverse event. An adverse event of visual acuity will be counted from the following lines: 20/20 or better, 20/25, 20/30, 20/40, 20/50, 20/60, 20/70, 20/80, 20/100, 20/125, 20/150, and 20/200. If the acuity at screening is better than 20/20, the decrease will be calculated from 20/20.

In the event of a decrease in visual acuity of 3 lines or more from screening, refraction will be rechecked at all subsequent study visits. A change in refraction power (spherical or cylindrical) of  $\pm 1.25$  diopters compared with the screening examination will be reported as an adverse event.

### 7.2.3.2. Intraocular Pressure Measurement

Intraocular pressure (IOP) will be measured using a calibrated Goldmann applanation tonometer. Both eyes will be tested, with the right eye preceding the left eye. The operator will initially set the dial at 10 mm Hg, then look through the slit lamp and adjust the dial to take the reading, and then record the results, including the time assessment is made.

Any IOP increase of greater than 10 mmHg above baseline or any IOP that increases above 25 mm Hg will be reported as an adverse event (AE).

### 7.2.3.3. Slit-lamp Biomicroscopy

Slit-lamp biomicroscopy with fluorescein will be performed. At each scheduled visit, deposition of pigment on the corneal endothelial layer or the lens capsule or any abnormalities of the lids, conjunctivae, cornea, anterior chamber, iris, or lens (see lens grading) will be graded as mild, moderate, or severe. Slit-lamp biomicroscopy should precede IOP measurement and the administration of any pupil-dilating agent for ophthalmoscopy.

Cells and flare in the anterior chamber should be noted during the slit-lamp examination.

Intraocular Inflammation Grading Scale for Biomicroscopy:

	Grade				
	0	1	2	3	4
Grading of aqueous flare <sup>a</sup>	Completely Absent	Barely Detectable	Moderate (iris and lens details clear)	Marked (iris and lens details hazy)	Intense (formed fibrin in aqueous)
Grading of cells in the aqueous <sup>a,b</sup>	No cells	1 to 5 cells	6 to 10 cells	11 to 20 cells	>20 cells

<sup>a</sup> Evaluation of Anterior Chamber Inflammation:

1. Examination of the anterior chamber for cells must be performed before either dilation or applanation tonometry.
2. The light intensity of the slit lamp is turned to the maximum tolerated by the patient.
3. High magnification and 1 x 2 mm slit are used.
4. The ray of light as directed at an angle of approximately 45° to the plane of the iris.

<sup>b</sup> Modified from Hogan et al. 1959<sup>76</sup>.

During the study, any new finding or deterioration from baseline findings should be reported as an adverse event.

#### **7.2.3.4. Lens Grading**

When doing lens grading, graders must be aware of their bias, either conscious or subconscious, that cataract is a unidirectional disease that steadily gets worse with age. Because of this bias, if one knows the baseline or any prior lens grade, it is likely that the grade assigned at a follow-up visit will be higher. To avoid this potential observation bias, the grader will remain masked to earlier lens grading and should always start with a blank case report form (CRF). The Wisconsin AREDS 2008 Clinical Lens Opacity Grading Procedure will be used.<sup>74</sup> Once the pupils are dilated to at least 5 mm, use slit lamp with ~10X magnification and brightest beam intensity.

- Nuclear opacity:
  - Orient beam at 45° to viewing axis;
  - Adjust slit beam to standard parameters: 8 mm height and 0.3 mm width;
  - Compare opalescence of nucleus with those on the provided pocket card of standard photos.
  
- Cortical and Posterior Subcapsular Cataract (PSC) opacities:
  - Select wide slit beam setting optimum for retro-illumination of lens;
  - Visualize lens opacities against red fundus reflex background;
  - Count only opacities definitely visible against red reflex;
  - Mentally combine all cortical opacities into one contiguous area;
  - Compare total opacity area with those on the provided pocket card of standard photos;
  - Grade each type of opacity in half steps from <1 to >3 (1=mild, 2=moderate and 3=severe) using the scale defined on the provided pocket card of standard photos.

#### **7.2.3.5. Funduscopy (Ophthalmoscopy)**

Funduscopy (Ophthalmoscopy) will be performed after dilation of the pupils to examine the vitreous body, retina, and optic nerve head. At screening, any abnormalities and pathologic findings will be graded as mild, moderate, or severe.



Any new findings or deterioration from baseline findings will be reported as an adverse event.

#### **7.2.4. Other Safety Assessments**

A full physical examination including an examination of all major body systems, 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, will be required at screening, and Day 1 of Cycles 1 and 2.

Symptom directed physical examinations, blood pressure and pulse rate will be performed at subsequent visits.

Performance Status: The Eastern Cooperative Oncology Group (ECOG) performance status scale will be used (see [Appendix 1](#)).

A recent publication by Lee et al., (2014)<sup>77</sup> suggests a potential role of Cyclin D1-CDK4 in controlling glucose metabolism; accordingly glucose levels will be monitored in all patients (fasting glucose, fasting insulin and HgbA1c) at various intervals as outlined in the Schedule of Activities. Fasting lipid panel [including total Cholesterol, HDL (High Density Lipoprotein), LDL( Low Density Lipoprotein) and triglycerides] will also be monitored at baseline and at the End of Treatment visit as outlined in the Schedule of Activities.

#### **7.3. Pharmacokinetic Assessments**

All efforts will be made to obtain the pharmacokinetic samples at the scheduled nominal time relative to dosing. However, samples obtained within 10% of the nominal time AND collected prior to administration of the investigational product on that day will be considered protocol compliant. Patients must be instructed to withhold their daily dose of study drugs on PK sampling days until the pre-dose PK sample and safety assessments (ie hematology, blood chemistry, and ECGs) have been completed. The exact time of the sample collection and the most recent dosing time will be recorded on the CRF. The date of any missing dose(s) should also be recorded in the CRF. One 3 mL sample of venous blood will be collected in appropriately labeled K2 EDTA collection tubes for assessment of Palbociclib (PD-0332991) levels at the protocol-specified times. Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures.

Blood samples will be collected from all participating patients for PK assessments of Palbociclib on Day 14 of Cycles 1 and Cycle 2 before administration of investigational product on that day (24 hours after the dose on previous day). In the event a pre-dose sample cannot be/is not collected on Day 14 of Cycle 1 or Cycle 2 as scheduled, every effort should be made to collect a makeup pre-dose sample between Day 15 and Day 21 of the same cycle or between Day 14 and Day 21 of any subsequent cycles beyond Cycle 2 following the same rules described above.

Additional blood samples may be requested from patients experiencing unexpected or serious adverse events, or adverse events that lead to discontinuation.

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Refer to the Study Manual for detailed collection, processing and shipping procedures.

#### **7.4. Patient Reported Outcomes**

Patient reported outcomes of health-related quality of life and health status will be assessed using the Functional Assessment of Cancer Therapy-Breast (FACT-B) and EuroQol-5D (EQ-5D) instruments.

Patients will complete each instrument pre-dose on Day 1 of Cycle 1 through 3, then on Day 1 of every other subsequent cycles starting with Cycle 5 (eg, cycles 5, 7, 9, etc), and then at the end of treatment visit. Completed questionnaires are always considered source document and must be filed accordingly.

Patients must complete these instruments in clinic (cannot be taken home) and prior to having any tests and to any discussion of their progress with healthcare personnel at the site. Interviewer administration in clinic may be used under special circumstances (eg, patient forgot their glasses or feels too ill). The FACT-B and EQ-5D will be given to the patient in the appropriate language for the site.

##### **7.4.1. EuroQol Health Utilities Index EQ-5D (Appendix 5)**

The EuroQol-5D (EQ-5D) is a 6 item instrument designed to assess health status in terms of a single index value or utility score. It consists of 5 descriptors of current health state

(mobility, self care, usual activities, pain/discomfort, and anxiety/depression); a patient is asked to rate each state on a three level scale (1=no problem, 2=some problem, and 3=extreme problem) with higher levels indicating greater severity/impairment. It also includes a visual analogue scale: the EQ VAS. The EQ VAS records the patient's self rated health on a scale from 0 (worst imaginable health state) to 100 (best imaginable health state). Published weights are available that allow for the creation of a single summary score. Overall scores range from 0 to 1, with low scores representing a higher level of dysfunction and 1 as perfect health.

#### **7.4.2. Functional Assessment of Cancer Therapy-Breast (FACT-B) [Version 4] (Appendix 6)**

The Functional Assessment of Cancer Therapy (FACT) is a modular approach to assess patient health-related quality of life using a 'core' set of questions (FACT-G) as well as a cancer site-specific module.

The FACT-G is a 27-item compilation of general questions divided into 4 domains: Physical Well-Being, Social/Family Well-Being, Emotional Well-Being, and Functional Well-Being.

The FACT-B consists of the FACT-G (27-items) and a breast-specific module: a 10-item instrument designed to assess patient concerns relating to breast cancer. Patients are asked to respond to a likert scale where 0=not at all, 1=a little bit, 2=somewhat, 3=quite a bit, and 4=very much.

#### **7.5. Biomarker Assessment**

Tumor tissues are required from all patients for study participation.

Retrospective confirmatory testing of tumor tissue samples for ER status will be performed in a central laboratory designated by the sponsor using an FDA-cleared (local standard) test. Results from this testing will be used for sensitivity analyses and will not be made available to the sites. In addition, tumor tissue biomarkers, including DNA, RNA and protein analytes, will be analyzed to investigate possible associations with resistance/sensitivity to treatment with study drugs. Biomarkers that will be analyzed will be selected based on their known relevance to mechanisms involved in cell cycle regulation. Examples of such biomarkers include but not limited to Ki67, ER protein expression.

Submission of formalin-fixed paraffin embedded (FFPE) tumor samples (blocks) of adequate size to allow for three 0.6 mm diameter x 5 mm deep cores that will be used to generate a tissue microarray are needed. If FFPE tissue block cannot be provided, 12 glass slides each containing an unstained 5-micron FFPE tissue section (highly recommend to submit tissue block or 12 unstained slides, but if there would be technical difficulties or other issues refraining from obtaining tissue block or 12 unstained slides, however, it is still mandatory to collect a minimum 7 unstained slides), will be required for patient participation. Archived FFPE specimen from the original diagnostic tumor tissue will be collected and sent to the sponsor-designated central laboratories for assessment of biomarkers associated with sensitivity and/or resistance to Palbociclib (eg, Ki67, ER). Tissue sample from a metastatic or recurrent tumor lesion, if available, will also be collected for retrospective confirmation of ER status by the central laboratory. If a tissue sample from a recurrent tumor or distant metastasis is unavailable, a de novo fresh biopsy is recommended when, in the investigator's judgment, such biopsy is feasible and can be safely performed. Original diagnostic tumor tissue will be used for confirmation of ER status in the event that a recurrent/metastatic tissue sample is not available and a fresh biopsy of the recurrent/metastatic lesion is not feasible.

Tissue samples from all patients will be used for additional biomarker analyses. Detailed information about biomarker sample collection, preparation, storage, labeling, and shipment is indicated in the Study Reference Manual.

#### **7.5.1. Optional Tumor Tissue Biopsy for Molecular Profiling**

An optional fresh metastatic/recurrent tumor biopsy sample should be collected at the end of treatment visit for patients who discontinue treatment due to disease progression. The tumor tissue will be used to determine possible mechanisms of resistance to study treatment.

#### **7.6. CDK6 Genotyping**

In order to explore the relationship between CDK6 polymorphism and the neutropenia associated with Palbociclib treatment, germline polymorphism of CDK6 will be analyzed. A single 4 mL blood sample (Prep D1; K2 EDTA whole blood collection optimized for DNA analysis) will be collected pre-dose at the Cycle 1 Day 1. A SNP rs445 as defined in the NCBI database in the CDK6 gene will be analyzed.

## **7.7. Banked Biospecimen**

### **7.7.1. Markers of Drug Response**

Variation in genetic markers and other biomarkers may help to explain some of the variability in response seen with some drugs among different individuals. This is referred to as pharmacogenomic/biomarker research. Comparing the DNA, RNA, protein, and metabolite variation patterns of patients who respond well and those who respond poorly to treatment may help to better define the most appropriate group of patients in which to target a given treatment. Collecting biospecimens for pharmacogenomic/biomarker analyses and retaining them in a Pfizer BioBank makes it possible to better understand the drug's mechanism of action and to seek explanations for differences in, for example, exposure, efficacy, tolerability, or safety not anticipated prior to the beginning of the study. Providing these biospecimens is a required study activity for study sites and subjects, unless prohibited as such by local regulations or ethics committee decision.

To protect subjects' confidentiality, the banked biospecimens and data generated from them will be coded with the subject's study ID number. Samples will be kept in a facility accessible only by badge-swipe. Data will be stored on password-protected computer systems. The key between the code and the subject's personal identifiers will be held at the study site; the researchers using the biospecimens and data generated from them will not have access to the key nor any personally identifying information. Biospecimens will only be used for the purposes described here and in the informed consent document/patient information sheet; any other uses require additional ethical approval. Unless a time limitation is required by local regulations or ethical requirements, biospecimens will be stored indefinitely to allow for future research on the topics described here, including research conducted during the lengthy drug development process and also post-marketing research. Subjects can withdraw their consent for the use of their biospecimens at any time by making a request to the investigator, in which event any remaining biospecimen will be destroyed; data already generated from the biospecimens will continue to be stored to protect the integrity of existing analyses. It is very unlikely that results generated from the biospecimens will have any clinical, diagnostic, or therapeutic implications for the individual study participants. Subjects are notified in the informed consent document/patient information sheet that their results will not be given to them, unless required by local laws or regulations, in which case results will be returned via the investigator. Results will not be provided to family members or other physicians; nor will they be recorded in the subject's medical record. There is no intention to contact subjects after completion of the clinical trial.

A 4 mL blood biospecimen Prep D1 (K<sub>2</sub> edetic acid (ethylenediaminetetraacetic acid) (EDTA) whole blood collection optimized for DNA analysis) will be collected at the pre-dose at the Cycle 1, Day 1 visit to be retained for potential pharmacogenomic/biomarker analyses related to drug response or adverse drug reactions, unless prohibited by local regulations or ethics committee decision.

The Banked biospecimen will be collected from all patients unless prohibited by local regulations or ethics committee decision. Detailed collection, processing, storage and shipment instructions are provided in the central laboratory manual.

It is possible that the use of these biospecimens may result in commercially viable products. Subjects will be advised in the informed consent document/patient information sheet that they will not be compensated in this event.

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[REDACTED]

[REDACTED]

- [REDACTED]
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[REDACTED]

[REDACTED]

## 8. ADVERSE EVENT REPORTING

### 8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as a serious adverse event (SAE) requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any non-serious adverse event that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

## **8.2. Reporting Period**

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the patient provides informed consent, which is obtained prior to the patient's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. Serious adverse events occurring to a subject after the active reporting period has ended should be reported to the Sponsor if the investigator becomes aware of them; at a minimum, all serious adverse events that the investigator believes have at least a reasonable possibility of being related to study drug are to be reported to the Sponsor.

AEs (serious and non-serious) should be recorded on the Case Report Form (CRF) from the time the patient has taken at least one dose of study treatment through last patient visit.

If a patient begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started. Death must be reported if it occurs during the SAE reporting period after the last dose of investigational product, irrespective of any intervening treatment.

### **8.3. Definition of an Adverse Event**

An AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Drug abuse;
- Drug dependency.

Additionally, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breast feeding;
- Medication error;
- Occupational exposure.

Worsening of signs and symptoms of the malignancy under study should be reported as AEs in the appropriate section of the CRF. Disease progression assessed by measurement of malignant lesions on radiographs or other methods should not be reported as AEs.



#### **8.4. Abnormal Test Findings**

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing (*outside of protocol-stipulated dose adjustments*) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an AE by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

#### **8.5. Serious Adverse Events**

An SAE is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Progression of the malignancy under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal within the safety reporting period. Hospitalization due to signs and symptoms of disease progression should not be reported as an SAE. If the malignancy has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as an

SAE with Common Terminology Criteria (CTC) Grade 5 (see Section on [Severity Assessment](#)).

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

#### **8.5.1. Protocol-Specified Serious Adverse Events**

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see Section on SAE Reporting Requirements)

#### **8.5.2. Potential Cases of Drug-Induced Liver Injury**

Abnormal values in aspartate transaminase (AST) and/or alanine transaminase (ALT) levels concurrent with elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Patients with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values  $\geq 3$  times the upper limit of normal (X ULN) concurrent with a total bilirubin values  $\geq 2$  X ULN with no evidence of hemolysis and an alkaline phosphatase values  $\leq 2$  X ULN or not available.
- For patients with preexisting ALT **or** AST **or** total bilirubin values above the upper limit of normal, the following threshold values should be used in the definition mentioned above:

- For patients with pre-existing AST or ALT baseline values above the normal range: AST or ALT values  $\geq 2$  times the baseline values and  $\geq 3$  X ULN, or  $\geq 8$  X ULN (whichever is smaller).

Concurrent with

- For patients with pre-existing values of total bilirubin above the normal range: Total bilirubin increased from baseline by an amount of at least one time the upper limit of normal or if the value reaches  $\geq 3$  times the upper limit of normal (whichever is smaller).

The patient should return to the investigational site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history and physical assessment. The possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/ international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen (paracetamol), recreational drug and supplement consumption, family history, occupational exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C and E infection and liver imaging (eg, biliary tract) may be warranted. Acetaminophen levels may be indicated. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for liver function test (LFT) abnormalities identified at the time should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's Law cases should be reported as SAEs.

## **8.6. Hospitalization**

Hospitalization is defined as any initial admission (even less than 24 hours) in a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a

tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, the event leading to the emergency room visit should be assessed for medical importance. Hospitalization does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same day surgeries (as outpatient/same day/ambulatory procedures).

Hospitalization or prolongation of hospitalization in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for work-up of persistent pre-treatment laboratory abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);
- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Pre-planned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual patient.
- Admission exclusively for the administration of blood products.

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

### **8.7. Severity Assessment**

As required on the AE CRFs, the investigator will report adverse events using concise medical terminology (verbatim) as well as collect on the CRF the appropriate Common Terminology Criteria for Adverse Events (CTCAE) (version 4.0, Publish Date: May 28, 2009, <http://ctep.cancer.gov/reporting/ctc.html>) and will use the following definitions of severity to describe the maximum intensity of the adverse event.

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 4.0 document but may be used in certain circumstances.)
1	MILD Adverse Event
2	MODERATE Adverse Event
3	SEVERE Adverse Event
4	LIFE-THREATENING consequences; urgent intervention indicated
5	DEATH RELATED TO Adverse Event

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

### **8.8. Causality Assessment**

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the serious adverse reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused

the event, then the event will be handled as “related to investigational product” for reporting purposes, as defined by the sponsor (see Section on [Reporting Requirements](#)). If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on study records.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

### **8.9. Exposure During Pregnancy**

For investigational products and for marketed products, an exposure during pregnancy occurs if:

- A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes, or is found to be pregnant after discontinuing and/or being exposed to the investigational product ;

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

- A male subject has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner’s pregnancy.

If a study patient becomes or is found to be pregnant during the study patient’s treatment with the investigational product, the investigator must submit this information to the Pfizer Drug Safety Unit on a Serious Adverse Event Form and Exposure in Utero (EIU). In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a patient reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EIU Form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EIU reports with an unknown outcome. The investigator will follow the pregnancy until completion or until pregnancy termination) and notify Pfizer of the outcome as a follow up to the initial EIU Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as serious adverse events when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study patient with the Pregnant Partner Release of Information Form to deliver to his partner. The Investigator must document in the source documents that the patient was given the Pregnant Partner Release of Information Form to provide to his partner.

### **8.10. Occupational Exposure**

An occupational exposure occurs when during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product, which may or may not lead to the occurrence of an adverse event.

An occupational exposure is reported to safety within 24 hours of Investigator's awareness, using the SAE Report form, regardless of whether there is an associated AE/SAE. Since the information does not pertain to a subject enrolled in the study, the information is not reported on a Case Report Form (CRF); however, a copy of the completed SAE Report form is maintained in the study master file.

#### **8.11. Withdrawal Due to Adverse Events (See Also [Section 6.5 Patient Withdrawal](#))**

Withdrawal due to AE should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a patient withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

#### **8.12. Eliciting Adverse Event Information**

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient. In addition, each study patient will be questioned about AEs.

#### **8.13. Reporting Requirements**

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

##### **8.13.1. Serious Adverse Event Reporting Requirements**

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This timeframe also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of exposure during pregnancy, and exposure via breastfeeding and occupational exposure cases.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study patient initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his/her first awareness of the AE.



For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the timeframes for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

### **8.13.2. Non-Serious Adverse Event Reporting Requirements**

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

### **8.13.3. Sponsor Reporting Requirements to Regulatory Authorities**

Adverse event reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

## **9. DATA ANALYSIS/STATISTICAL METHODS**

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated and maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition and/or its analysis will also be reflected in a protocol amendment.

### **9.1. Sample Size Determination**

The primary purpose of this study is to compare the combination of Palbociclib with letrozole versus placebo plus letrozole in prolonging PFS in Asian postmenopausal women with ER (+), HER2 (-) ABC who have not received any prior systemic anti-cancer treatment for advanced disease.

The sample size for this study is determined based on the assumptions that the median PFS for ABC patients receiving placebo plus letrozole in the first-line treatment setting is 9 months and it is desired to detect a risk reduction of 36% (hazard ratio 0.64), equivalent to an improvement in median PFS to 14 months in subjects receiving Palbociclib plus letrozole treatment. A total of approximately 213 events are required in the 2 arms of the study based on a 1:1 randomization to have 90% power to detect a difference assuming a true hazard ratio of 0.64 in favor of the Palbociclib plus letrozole arm using a one-sided, log-rank test at a significance level of 0.025. Assuming a 10% drop-out rate on either treatment arm, an accrual accomplished over a 19-month period and follow-up for about 12 months after the last patient is enrolled, a total sample size of approximately 330 patients (approximately 165 in the Palbociclib plus letrozole arm and approximately 165 in the placebo plus letrozole arm) is required.

The sample size described above will also allow the assessment of differences in the secondary endpoint of OS. The OS outcomes of a Phase 3 clinical trial in a similar patient population demonstrated a median OS of 34 months for the arm receiving letrozole. Using this value as an assumption with a hypothesized 30% risk reduction (a hazard ratio of 0.7) or 43% improvement in median OS (from 34 months to 48.6 months) in patients randomized to receive palbociclib plus letrozole and a follow-up period of approximately 61 months, 330 patients will provide approximately 247 events for 80% power to detect such a difference using a 1-sided, log-rank test at a significance level of 0.025.

## **9.2. Analysis Population**

### **9.2.1. Intent-to-Treat Population (ITT)**

The ITT population will include all patients who are randomized, with study drug assignment designated according to initial randomization. The ITT population will be the primary population for evaluating all efficacy endpoints and patient characteristics.

### **9.2.2. As-Treated Population (AT)**

The AT population will include all patients who receive at least 1 dose of study treatment (ie, Palbociclib/letrozole or placebo/letrozole ), with treatment assignments designated according to actual study treatment received. The AT population will be the primary population for evaluating treatment administration/compliance and safety. Efficacy endpoints may be assessed in this population as well.

### **9.3. Efficacy Analysis**

All efficacy analyses will be based on intent-to-treat (ITT) population. Some efficacy analyses will also be performed on the AT population. All primary and secondary endpoints based on radiological (and photographic where applicable) assessments of tumor burden (ie, PFS, OR, DR, DC) will be derived using the local radiologist's/investigator's assessment. Radiographic images and clinical information collected on-study will also be reviewed retrospectively by a blinded independent third-party core imaging laboratory to verify investigator reported tumor assessments. This information will be used for supportive analyses.

#### **9.3.1. Analysis of Primary Endpoint**

The primary endpoint is PFS based on investigator's assessment which is 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 occurs first. PFS data will be censored on the date of the last tumor assessment on study for patients who do not have objective tumor progression and who do not die while on study. Patients lacking an evaluation of tumor response after randomization will have their PFS time censored on the date of randomization with a duration of 1 day. Additionally, patients who start a new anti-cancer therapy prior to documented PD will be censored at the date of the last tumor assessment prior to the start of the new therapy.

The primary analyses of PFS will be performed in the ITT population. A stratified log-rank test (one-sided) will be 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 (one-sided). The stratification factor(s) will be specified in the SAP. PFS time associated with each treatment arm will be summarized for the ITT population using the Kaplan-Meier method and displayed graphically where appropriate. Confidence intervals (CIs) for the 25th, 50th and 75th percentiles of the event-free time will be reported. The Cox proportional hazards model will be fitted to compute the treatment hazard ratio and the corresponding 95% CI.

PFS will also be evaluated in the AT population.

As the emphasis of the study is on the estimation of treatment effect in Asia region, various analysis methods might be used to obtain more information about the treatment effect. Data from Asian patients in global study A5481008 will be used with A5481027 data for the

combined analysis. Other methods (for example, the weighted Z-test proposed by Lan et al. 2005) may also be explored to combine the global study data and the regional study data. Details about these analyses will be specified in the SAP.

### **9.3.2. Analysis of Secondary Endpoints**

PFS analyses will be repeated on ITT population based on the review of the blinded independent third-party core imaging laboratory as secondary supportive analysis.

The other secondary efficacy endpoints are:

#### **Overall Survival**

Overall Survival (OS) is 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 will be censored to last date the patient is known to be alive.

All patients randomized will be considered evaluable for OS. A stratified log-rank test (using the same stratification factors as for the PFS analysis) will be used to compare OS between the treatment arms. OS for the two arms will be assessed using Kaplan-Meier methods and displayed graphically where appropriate. The median event times and 95% CIs will be estimated. Cox regression models will be used to estimate the treatment hazard ratio and its 95% confidence interval.

The 1-year survival probability will be estimated using the Kaplan-Meier method and a two sided 95% CI for the log [-log(1 year survival probability)] will be calculated using a normal approximation, and then back transformed to give a CI for the 1-year survival probability itself. The 2-year, and 3-year survival probabilities will be estimated similarly.

#### **Objective Response (OR)**

Objective response is defined as a complete response (CR) or partial response (PR) according to the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1; [Appendix 7](#)) recorded from randomization until disease progression or death due to any cause.

A patient will be considered to have achieved an OR if the patient has a sustained complete response (CR) or partial response (PR) according to RECIST v.1.1 definitions. Otherwise, the patient will be considered as non-responders in the OR rate analysis. Additionally, patients with inadequate data for tumor assessment (eg, no baseline assessment or no follow-up assessments) will be considered as non-responders in the OR rate analysis.

The OR rate (ORR) on each randomized treatment arm will be estimated by dividing the number of patients with objective response (CR or PR) by the number of patients randomized to the respective treatment arm (“response rate”). A 95% CI for the response rates will be provided. Response rate comparisons between the 2 treatment arms as randomized will be assessed using Cochran-Mantel-Haenszel (CMH) test with the same stratification factors as for the PFS analysis.

Analyses for ORR will be performed on the ITT population based on the investigator’s assessment as well and also on the review of the blinded independent third-party core imaging laboratory.

In addition, the best overall response for each patient will be summarized by treatment arm.

### **Disease Control (DC)**

Disease control (DC) is defined as complete response (CR), partial response (PR), or stable disease (SD)  $\geq 24$  weeks according to the RECIST version 1.1 ([Appendix 7](#)) recorded in the time period between randomization and disease progression or death to any cause.

The DC rate (DCR) on each randomized treatment arm will be estimated by dividing the number of patients with CR, PR, or SD  $\geq 24$  weeks by the number of patients randomized to the treatment arm. A 95% CI for the DC rates will be provided. DC rate comparison between the two treatment arms as randomized will be assessed using CMH test with the same stratification factors as for the PFS analysis.

Analyses for DCR will be performed on the ITT population based on the investigator’s assessment as well and also on the review of the blinded independent third-party core imaging laboratory.

### **Duration of Response (DR)**

Duration of response (DR) is 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 occurs first. DR data will be censored on the date of the last tumor assessment on study for patients who do not have objective tumor progression and who do not die due to any cause while on study.

DR will only be calculated for the subgroup of patients with an objective response.

DR for the two treatment arms will be summarized using Kaplan-Meier methods and displayed graphically, where appropriate. The median event time and 95% CI for the median will be provided for each endpoint.

Additional sensitivity analyses will be outlined in the SAP.

Additional secondary endpoints include:

### **Patient Reported Outcomes (PRO)**

Breast cancer-specific quality of life scores and change from baseline scores will be compared between the treatment arms at various time points using a mixed model repeated measures (MMRM) approach adjusting for specified covariates. In addition, analyses will be performed to determine if the change from baseline scores achieve the appropriate minimally important difference (MID) cut-off for the scale being examined. Patients from the ITT population who completed a baseline assessment and at least one post-baseline assessment will be considered evaluable for the patient reported outcome analysis.

### **Pharmacokinetic Analysis**

Individual and Average Palbociclib trough concentrations will be listed by patient. Summary statistics will be provided for trough concentrations by study cycle and for average trough concentrations by patient. The relationship between trough concentration and potential covariates may be evaluated. All patients treated with Palbociclib and for whom drug plasma concentration results (from at least 1 visit) are available will be included in the analysis.

Exposure/Response Analysis: In addition, the relationship between exposure and efficacy/safety endpoints will be explored, as necessary, based on emerging efficacy and safety data. Refer to the SAP for details of the analyses. The results of these modeling analyses may be reported separately from the the clinical study report.

### **9.4. Analysis of Other Endpoints**

Descriptive statistics will be used to summarize all patient characteristics, treatment administration/compliance, efficacy endpoints, safety parameters, and biomarkers. Data will also be displayed graphically, where appropriate.

## **9.5. Safety Analysis**

The AT population will be the primary population for safety evaluation. Summaries of AEs and other safety parameters will be provided as appropriate.

### **Adverse Events**

Adverse events will be classified using the medical dictionary for regulatory activities (MedDRA) classification system. The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible (<http://ctep.info.nih.gov/reporting/ctc.html>).

Adverse events will be summarized by treatment and by the frequency of patients experiencing treatment emergent adverse events corresponding to body systems and MedDRA preferred term. Adverse events will be graded by worst NCI CTCAE v4.0 Grade. Adverse events will be summarized by cycle and by relatedness to trial treatment. Detailed information collected for each AE will include a description of the event, duration, whether the AE was serious, intensity, relationship to study drug, action taken, and clinical outcome. Emphasis in the analysis will be placed on AEs classified as treatment emergent.

Adverse events leading to death or discontinuation of trial treatment, events classified as NCI CTCAE v4.0 Grade 3 or higher, trial drug-related events, and serious adverse events will be considered with special attention.

### **Laboratory Abnormalities**

Hematology and chemistry laboratory data will be summarized by treatment and by cycle. The laboratory results will be graded according to the NCI CTCAE v4.0 severity grade. The frequencies of the worst severity grade observed will be displayed by study treatment. Shift tables will be provided to examine the distribution of laboratory toxicities. For parameters for which an NCI CTCAE v4.0 scale does not exist, the frequency of patients with values below, within, and above the normal ranges will be summarized by treatment.

### **Ocular Events**

Ocular events will be reported as part of the adverse event analysis described above.

Additionally, changes in lens grading while on study treatment will be analyzed as described in the Statistical Analysis Plan.

## **Analysis of Electrocardiogram Measurements**

ECG measurements (an average of the triplicate measurements) will be used for the statistical analysis and all data presentations. QT measurements corrected for heart rate (QTc) using Bazett's (QTcB) and Fridericia's (QTcF) method will be used for the data analysis and interpretation. Data will be summarized and listed for QT, HR, RR, PR, QRS and QTcF by treatment and dose. Individual QTc (all evaluated corrections) intervals will be listed by time and dose. Descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be used to summarize the absolute QTc value and changes from baseline in QTc after treatment by day and time point.

### **9.6. Interim Analysis**

The study is designed to have one interim analysis and the final analysis based on the primary PFS endpoint. The purposes of the interim analysis are to allow early stopping of the study for efficacy, and to assess safety of the combination regimen. The analysis will be performed after approximately 139 patients have documented progressive disease or die (approximately 65% of the total events expected).

A formal efficacy boundary for rejecting the null hypothesis is constructed by using the spending function methodology of the power family design with  $\Delta = -0.5$ . To protect the integrity of the study and to preserve the type-1 error rate, a fraction of alpha for efficacy will be spent at the interim analysis and accounted for in the overall type I error rate. For logistical and administrative reasons the actual number of events at the interim and final analyses might differ slightly from those that have been pre-specified above. In that case appropriate adjustments will be made to the efficacy boundaries based on the power family spending functions. The overall significance level for the efficacy analysis of PFS will be preserved at 0.025 (1-sided test).

At the interim analysis, if the result exceeds the efficacy boundary, the trial may be stopped for efficacy. Alternatively, as appropriate, the sample size of the study may be adjusted using the method outlined by Cui et al.

If the results of the interim analysis indicate serious safety concerns, the sponsor will communicate with the Health Authorities regarding stopping the clinical trial.



An interim analysis of efficacy is also planned for the secondary endpoint OS. The analysis will be performed at the same time of the final analysis of PFS. Even if the improvement in PFS is significant at its interim and the study is stopped due to the overwhelming results, the interim OS analysis will still be performed at the approximately planned PFS final analysis time. The nominal significance levels for the interim analysis of OS will be determined by using the Lan-Demets procedure with an O'Brien-Flemming stopping rule. The overall significance level for the efficacy analysis of OS will be preserved at 0.025 (one-sided test). Details of the analysis will be provided in the SAP.

In order to control the overall type I error rate, OS will be hierarchically tested for significance at the time of final PFS analysis, provided the primary endpoint PFS is statistically significant at the interim or final PFS analysis. If OS does not yield a significant result at this analysis, OS will be tested at the final OS analysis. If PFS is not significant at the final PFS analyses, OS will not be statistically evaluated.

#### **9.7. Data Monitoring Committees**

An independent third party External Data Monitoring Committee (E-DMC) will monitor the safety data on a periodic basis. The E-DMC will make recommendation as to whether the trial should continue based on ongoing reviews of safety data. The E-DMC will also evaluate efficacy at the interim analysis and make a recommendation regarding study continuation based on observed results of the study. The Sponsor will designate an external third-party biostatistician not affiliated with the project to prepare data for DMC review which will be kept confidential to the EDMC. The E-DMC membership and governance is outlined in a separate charter.

The DMC will be responsible for ongoing monitoring of the efficacy and safety of subjects in the study according to the Charter. The recommendations made by the DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate.

The recommendations made by the E-DMC to alter the conduct of the study will be forwarded to Pfizer for final decision. Pfizer will forward such decisions, to regulatory authorities, as appropriate. Clinical sites will be restricted from access to study results until the conclusion of the study.

## **10. QUALITY CONTROL AND QUALITY ASSURANCE**

During study conduct, Pfizer or its agents will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs is accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study site may be subject to review by the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

## **11. DATA HANDLING AND RECORD KEEPING**

### **11.1. Case Report Forms/Electronic Data Record**

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A CRF is required and should be completed for each included patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

## **11.2. Record Retention**

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain study records for the required period (eg, retirement, relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

## **12. ETHICS**

### **12.1. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)**

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/IEC approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the investigator must notify the IRB/IEC and Pfizer in writing immediately after the implementation.

## **12.2. Ethical Conduct of the Study**

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Patients (Council for International Organizations of Medical Sciences 2002), Guidelines for Good Clinical Practice (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

## **12.3. Patient Information and Consent**

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws.

Patient names, address, birth date and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify the trial patient. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent document must be in compliance with ICH GCP, local regulatory requirements, and legal requirements.

The informed consent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC before use, and available for inspection.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient or the patient's legal representative before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent document. The patient will be provided with a copy of the signed informed consent form(s).

#### **12.4. Patient Recruitment**

Advertisements approved by ethics committees and investigator databases may be used as recruitment procedures.

#### **12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP**

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable Competent Authority in any area of the World, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

### **13. DEFINITION OF END OF TRIAL**

#### **13.1. End of Trial in a Member State**

End of Trial in a Member State of the European Union is defined as the time at which it is deemed that sufficient patients have been recruited and completed the study as stated in the regulatory application (ie, Clinical Trial Application (CTA)) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

#### **13.2. End of Trial in all other Participating Countries**

End of Trial in all other participating countries is defined as Last Patient Last Visit.

### **14. SPONSOR DISCONTINUATION CRITERIA**

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of Pfizer. In addition, Pfizer retains the right to discontinue development of Palbociclib at any time.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating patients and the hospital pharmacy (if applicable) within a week of notification. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

## 15. PUBLICATION OF STUDY RESULTS

### 15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (ClinicalTrials.gov), [www.pfizer.com](http://www.pfizer.com), and/or the European Clinical Trials Database (EudraCT), and other public registries in accordance with applicable local laws/regulations.

[www.clinicaltrials.gov](http://www.clinicaltrials.gov)

Pfizer posts clinical trial Basic Results on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) for all Pfizer-sponsored interventional studies that evaluate the safety and/or efficacy of a Pfizer product.

The timing of the posting depends on whether the Pfizer product is approved for marketing in any country at the time the study is completed:

For studies involving products applicable under the US Food and Drug Administration Amendments Act of 2007 (FDAAA), ie, FDA approved products, Pfizer posts results within one year of the primary completion date (PCD). For studies involving products approved in any country, but not FDA approved, Pfizer posts results one year from last subject, last visit (LSLV);

For studies involving products that are not yet approved in any country, Pfizer posts the results of already-completed studies within 30 days of US regulatory approval, or one year after the first ex-US regulatory approval of the product (if only submitted for approval ex-US);

For studies involving products whose drug development is discontinued before approval, Pfizer posts the results within one year of discontinuation of the program (if there are no plans for outlicensing or within two years if outlicensing plans have not completed).

Primary Completion Date is defined as the date that the final patient was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical study concluded according to the pre-specified protocol or was terminated.

[www.pfizer.com](http://www.pfizer.com)

Pfizer posts clinical trial results on [www.pfizer.com](http://www.pfizer.com) for all Pfizer-sponsored interventional studies in patients that assess the safety and/or efficacy of an FDA-approved Pfizer product with a LSLV on or after 27-Sep-2007 for which Basic Results were posted on [www.clinicaltrials.gov](http://www.clinicaltrials.gov).

#### EudraCT

Pfizer posts clinical trial results on EudraCT in accordance with Commission Guideline 2012/C 302/03 *Guidance on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006* for studies with centers in the European Economic Area and with LSLV on or after 01-May-2004, regardless of the marketing status of the compound.

#### **15.2. Publications by Investigators**

Pfizer has no objection to publication by Investigators of any information collected or generated by Investigators, whether or not the results are favorable to the Investigational Product. However, to ensure against inadvertent disclosure of Confidential Information or unprotected Inventions, Investigators will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigators will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigators agree to delay the disclosure for a period not to exceed an additional 60 days.

Investigators will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-centre study, Investigators agree that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigators are free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institutions will comply with recognized ethical standards concerning publications and authorship, including Section II - “Ethical Considerations in the Conduct and Reporting of Research” of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, <http://www.icmje.org/index.html#authorship>, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the Institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.



## 16. REFERENCES

1. Boyles P., Levin B., Editors. World Health Organization. World Cancer Report 2008: Breast Health Care Delivery in Low- and Middle-income Countries. International Agency for Research on Cancer. Lyon: IARC Press 2008; 100-103.
2. Wood WC, Muss HB, Solin LJ, Olopade OI. Malignant Tumors of the Breast. In: De Vita VT Jr, Hellmann S, Rosenberg SA, editors. Cancer, Principle and Practice of Oncology, 7th Edition, Lippincott Williams and Wilkins; 2005; 1415-1477.
3. Harvey JM, Clark GM, Osborne CK, Allred DC. Estrogen Receptor Status by Immunohistochemistry Is Superior to the Ligand-Binding Assay for Predicting Response to Adjuvant Endocrine Therapy in Breast Cancer. *Journal of Clinical Oncology*, 17, 5, 1999; 1474-1481.
4. Mouridsen H, Gershanovich M, Sun Y, Pérez-Carrión R, Boni C, Monnier A, et al. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the international Letrozole Breast Cancer Group. *Journal of Clinical Oncology* 2003; 2101-2109.
5. Leung, BS, Potter AH. Mode of estrogen action on cell proliferation in CAMA-1 cells. II. Sensitivity of G1 phase population. *J. Cell. Biochem.* 1987; 34:213-225.
6. Sutherland RL, Hall RE, Taylor IW. Cell proliferation kinetics of MCF-7 human mammary carcinoma cells in culture and effects of tamoxifen on exponentially growing and plateau-phase cells. *Cancer Res.* 1983; 43:3998-4006.
7. Sherr CJ. Cancer cell cycles. *Science* 1996; 274:1672-1677.
8. Sherr CJ, Roberts JM. CDK inhibitors: positive and negative regulators of G1-phase progression. *Genes Dev.* 1999; 13:1501-1512.
9. van den Heuvel S, Harlow E. Distinct roles for cyclin-dependent kinases in cell cycle control. *Science* 1993; 262:2050-2054.
10. Weinberg, RA. The retinoblastoma protein and cell cycle control. *Cell* 1995; 81:323-330.

11. Roussel MF, Theodoras AM, Pagano M, Sherr CJ. Rescue of defective mitogenic signaling by D-type cyclins. *Proc. Natl. Acad. Sci. USA* 1995; 92:6837-6841.
12. Sherr CJ. D-type cyclins. *Trends Biochem. Sci.* 1995; 20:187-190.
13. Altucci L, Addeo R, Cicatiello L, Germano D, Pacilio C, Battista T, Cancemi M, Petrizzi VB, Bresciani F, Weisz A. Estrogen induces early and timed activation of cyclin-dependent kinases 4, 5, and 6 and increases cyclin messenger ribonucleic acid expression in rat uterus. *Endocrinology* 1997; 138:978-984.
14. Geum D, Sun W, Paik SK, Lee CC, Kim K. Estrogen-induced cyclin D1 and D3 gene expressions during mouse uterine cell proliferation in vivo: differential induction mechanism of cyclin D1 and D3. *Mol. Reprod. Dev.* 1997; 46:450-458.
15. Said TK, Conneely OM, Medina D, O'Malley BW, Lydon JP. Progesterone, in addition to estrogen, induces cyclin D1 expression in the murine mammary epithelial cell, in vivo. *Endocrinology* 1997; 138:3933-3939.
16. Tong W, Pollard JW. Progesterone inhibits estrogen-induced cyclin D1 and cdk4 nuclear translocation, cyclin E- and cyclin A-cdk2 kinase activation, and cell proliferation in uterine epithelial cells in mice. *Mol. Cell. Biol.* 1999; 19:2251-2264.
17. Hui R, Cornish AL, McClelland RA, Robertson JF, Blamey RW, Musgrove EA, Nicholson RI, Sutherland RL. Cyclin D1 and estrogen receptor messenger RNA levels are positively correlated in primary breast cancer. *Clin. Cancer Res.* 1996; 2:923-928.
18. Michalides R, Hageman P, van Tinteren H, Houben L, Wientjens E, Klompaker R, Peterse J. A clinicopathological study on overexpression of cyclin D1 and of p53 in a series of 248 patients with operable breast cancer. *Br. J. Cancer* 1996; 73:728-734.
19. Nielsen NH, Emdin SO, Cajander J, Landberg G. Deregulation of cyclin E and D1 in breast cancer is associated with inactivation of the retinoblastoma protein. *Oncogene* 1997; 14:295-304.
20. Altucci L, Addeo R, Cicatiello L, Dauvois S, Parker MG, Truss M, Beato M, Sica V, Bresciani F, Weisz A. 17beta-Estradiol induces cyclin D1 gene transcription, p36D1-p34cdk4 complex activation and p105Rb phosphorylation during mitogenic stimulation of G(1)-arrested human breast cancer cells. *Oncogene* 1996; 12:2315-2324.

21. Foster JS, Wimalasena J. Estrogen regulates activity of cyclin-dependent kinases and retinoblastoma protein phosphorylation in breast cancer cells. *Mol. Endocrinol.* 1996; 10:488-498.
22. Planas-Silva MD, Weinberg RA. Estrogen-dependent cyclin E-cdk2 activation through p21 redistribution. *Mol. Cell. Biol.* 1997; 17:4059-4069.
23. Prall OWJ, Sarcevic B, Musgrove EA, Watts CKW, Sutherland RL. Estrogen-induced activation of Cdk4 and Cdk2 during G1-S phase progression is accompanied by increased cyclin D1 expression and decreased cyclin-dependent kinase inhibitor association with cyclin E-Cdk2. *J. Biol. Chem.* 1997; 272:10882-10894.
24. Lukas J, Bartkova J, Bartek J. Convergence of mitogenic signalling cascades from diverse classes of receptors at the cyclin D-cyclin-dependent kinase-pRb-controlled G1 checkpoint. *Mol. Cell. Biol.* 1996; 16:6917-6925.
25. Watts CK, Brady A, Sarcevic B, DeFazio A, Musgrove EA, Sutherland RL. Antiestrogen inhibition of cell cycle progression in breast cancer cells is associated with inhibition of cyclin-dependent kinase activity and decreased retinoblastoma protein phosphorylation. *Mol. Endocrinol.* 1995; 9:1804-1813.
26. McMahon C, Suthiphongchai T, DiRenzo J, Ewen ME. P/CAF associates with cyclin D1 and potentiates its activation of the estrogen receptor. *Proc. Natl. Acad. Sci. USA* 1999; 96:5382-5387.
27. Neuman E, Ladha MH, Lin N, Upton TM, Miller SJ, DiRenzo J, Pestell RG, Hinds PW, Dowdy SF, Brown M, Ewen ME. Cyclin D1 stimulation of estrogen receptor transcriptional activity independent of cdk4. *Mol. Cell. Biol.* 1997; 17:5338-5347.
28. Zwijsen RM, Buckle RS, Hijmans EM, Loomans CJ, Bernards R. Ligand-independent recruitment of steroid receptor coactivators to estrogen receptor by cyclin D1. *Genes Dev.* 1998; 12:3488-3498.
29. Zwijsen RM, Wientjens E, Klompaker R, van der Sman J, Bernards R, Michalides RJ. CDK-independent activation of estrogen receptor by cyclin D1. *Cell* 1997; 88:405-415.

30. Harper JW, Adami GR, Wei N, Keyomarsi K, Elledge SJ. The p21 Cdk-interacting protein Cip1 is a potent inhibitor of G1 cyclin-dependent kinases. *Cell* 1993; 75:805-816.
31. Koff A, Ohtsuki M, Polyak K, Roberts JM, Massague J. Negative regulation of G1 in mammalian cells: inhibition of cyclin E-dependent kinase by TGF-beta. *Science* 1993; 260:536-539.
32. Polyak K, Kato JY, Solomon MJ, Sherr CJ, Massague J, Roberts JM, Koff A. p27Kip1, a cyclin-Cdk inhibitor, links transforming growth factor-beta and contact inhibition to cell cycle arrest. *Genes Dev.* 1994; 8:9-22.
33. Toyoshima H, Hunter T. p27, a novel inhibitor of G1 cyclin-Cdk protein kinase activity, is related to p21. *Cell* 1994; 78:67-74.
34. Lukas J, Parry D, Aagaard L, Mann DJ, Bartkova J, Strauss M, Peters G, Bartek J. Retinoblastoma-protein-dependent cell-cycle inhibition by the tumour suppressor p16. *Nature* 1995; 375:503-506.
35. Medema RH, Herrera RE, Lam F, Weinberg RA. Growth suppression by p16ink4 requires functional retinoblastoma protein. *Proc. Natl. Acad. Sci. USA* 1995; 92:6289-6293.
36. Parry D, Bates S, Mann DJ, Peters G. Lack of cyclin D-Cdk complexes in Rb-negative cells correlates with high levels of p16INK4/MTS1 tumour suppressor gene product. *EMBO J.* 1995; 14:503-511.
37. Jiang H, Chou HS, Zhu L. Requirement of cyclin E-Cdk2 inhibition in p16INK4a-mediated growth suppression. *Mol. Cell. Biol.* 1998; 18:5284-5290.
38. McConnell BB, Gregory FJ, Stott FJ, Hara E, Peters G. Induced expression of p16INK4a inhibits both CDK4- and CDK2-associated kinase activity by reassembly of cyclin-CDK-inhibitor complexes. *Mol. Cell. Biol.* 1999; 19:1981-1989.
39. Mitra J, Dai CY, Somasundaram K, El-Deiry WS, Satyamoorthy K, Herlyn M, Enders GH. Induction of p21WAF1/CIP1 and inhibition of Cdk2 mediated by the tumor suppressor p16INK4a. *Mol. Cell. Biol.* 1999; 19:3916-3928.

40. Craig C, Kim M, Ohri E, Wersto R, Katayose D, Choi ZLiYH, Mudahar B, Srivastava S, P. Seth, Cowan K. Effects of adenovirus-mediated p16INK4A expression on cell cycle arrest are determined by endogenous p16 and Rb status in human cancer cells. *Oncogene* 1998; 16:265-272.
41. Craig C, Kim M, Ohri E, Wersto R, Katayose D, Lee SJ, Trepel J, Cowan K, Seth P. A recombinant adenovirus expressing p27Kip1 induces cell cycle arrest and loss of cyclin-Cdk activity in human breast cancer cells. *Oncogene* 1997; 14:2283-2289.
42. Foster JS, Henley DC, Bukovsky A, Seth P, Wimalasena J. Multifaceted regulation of cell cycle progression by estrogen: regulation of Cdk inhibitors and Cdc25A independent of cyclin D1-Cdk4 function. *Molecular and cellular biology*, 2001; 21, 3: 794-810.
43. Buckley MF, Sweeney KJ, Hamilton JA, Sini RL, Manning DL, Nicholson RI, de Fazio A, Watts CK, Musgrove EA, Sutherland RL. Expression and amplification of cyclin genes in human breast cancer, *Oncogene*, 1993; 8, pp. 2127–2133.
44. Dickson C, Fantl V, Gillett C, Brookes S, Bartek J, Smith R, Fisher C, Barnes D, Peters G. Amplification of chromosome band 11q13 and a role for cyclin D1 in human breast cancer, *Cancer Lett.* 1995; 90, pp. 43–50.
45. Lammie GA, Fantl V, Smith R, Schuurin E, Brookes S, Michalides R, Dickson C, Arnold A, Peters G. D11S287, a putative oncogene on chromosome 11q13, is amplified and expressed in squamous cell and mammary carcinomas and linked to BCL-1, *Oncogene* 1991; 6, pp. 439–444.
46. Bartkova J, Lukas J, Muller H, Lutzhoft D, Strauss M, Bartek J. Cyclin D1 protein expression and function in human breast cancer, *Int. J. Cancer*, 1994; 57, pp. 353–361.
47. Gillett C, Fantl V, Smith R, Fisher C, Bartek J, Dickson C, Barnes D, Peters G. Amplification and overexpression of cyclin D1 in breast cancer detected by immunohistochemical staining, *Cancer Res.* 1994; 54, pp. 1812–1817.
48. McIntosh GG, Anderson JJ, Milton I, Steward M, Parr AH, Thomas MD, Henry JA, Angus B, Lennard TW, Horne CH. Determination of the prognostic value of cyclin D1 overexpression in breast cancer, *Oncogene* 1995; 11, pp. 885–891.

49. Gillett C, Smith P, Gregory W, Richards M, Millis R, Peters G, Barnes D. Cyclin D1 and prognosis in human breast cancer, *Int. J. Cancer* 1996; 69, pp. 92–99.
50. Khatib ZA, Matsushime H, Valentine M, Shapiro DN, Sherr CJ, Look AT. Coamplification of the CDK4 gene with MDM2 and GLI in human sarcoma, *Cancer Res.* 1993; 53, pp. 5535-5541.
51. An HX, Beckmann MW, Reifenger G, Bender HG, Niederacher D. Gene amplification and overexpression of CDK4 in sporadic breast carcinomas is associated with high tumor cell proliferation, *American J of Pathology* 1999; 154, pp. 113-118.
52. Yu Q, Sicinska E, Geng Y, Ahnström M, Zagozdzon A, Kong Y, Gardner H, Kiyokawa H, Harris LN, Stål O, Sicinski P. Requirement for CDK4 kinase function in breast cancer. *Cancer Cell* 2006; 9: 23-32.
53. Pietilainen T, Lipponen P, Aaltomaa S, Eskelinen M, Kosma VM, Syrjanen K. Expression of retinoblastoma gene protein (Rb) in breast cancer as related to established prognostic factors and survival. *Eur J Cancer* 1995; 31A:329-33.
54. Borg A, Zhang QX, Alm P, Olsson H, Sellberg G. The retinoblastoma gene in breast cancer: Allele loss is not correlated with loss of gene protein expression. *Cancer Res* 1992; 52: 2991-2994.
55. Oesterreich S, Fuqua SA. Tumor suppressor genes in breast cancer. *Endocr Relat Cancer* 1999; 6: 405-419.
56. Chano T, Kontani K, Teramoto K, Okabe H, Ikegawa S. Truncating mutations of RB1CC1 in human breast cancer. *Nat Genet* 2002; 31: 285-288.
57. Bosco EE, Wang Y, Xu H, Zilfou JT, Knudsen KE, Aronow BJ, Lowe SW, Knudsen ES. The retinoblastoma tumor suppressor modifies the therapeutic response of breast cancer. *The Journal of Clinical Investigation.* 2007; 117, 1: 218-28.
58. Musgrove EA, Lilischkis R, Cornish AL, Lee CS, Setlur V, Seshadri R, Sutherland RL. Expression of the cyclin-dependent kinase inhibitors p16INK4, p15INK4B and p21WAF1/CIP1 in human breast cancer. *Int J Cancer* 1995; 63:584-591.

59. Zhou R, Frum R, Deb S, Deb SP. The growth arrest function of the human oncoprotein mouse double minute-2 is disabled by downstream mutation in cancer cells. *Cancer Res* 2005; 65:1839-48.
60. Amir E, Miller N, Geddie W, Freedman O, Kassam F, Simmons C, Oldfield M, Dranitsaris G, Tomlinson G, Laupacis A, Tannock IF, Clemons M. Prospective study evaluating the impact of tissue confirmation of metastatic disease in patients with breast cancer, *J. Clin. Oncol.* 2012; 30, pp. 587-592.
61. Niikura N, Liu J, Hayashi N, Mittendorf EA, Gong Y, Palla SL, Tokuda Y, Gonzalez-Angulo AM, Hortobagyi GN, Ueno NT. Loss of human epidermal growth factor receptor 2 (HER2) expression in metastatic sites of HER2-overexpressing primary breast tumors, *J. Clin. Oncol.* 2012; 30, pp. 593-599.
62. Badve SS, Baehner FL, Gray RP, Childs BH, Maddala T, Liu ML, Rowley SC, Shak S, Perez EA, Shulman LJ, Martino S, Davidson NE, Sledge GW, Goldstein LJ, Sparano JA. Estrogen- and progesterone-receptor status in ECOG 2197: comparison of immunohistochemistry by local and central laboratories and quantitative reverse transcription polymerase chain reaction by central laboratory, *J. Clin. Oncol.* 2008; 26, pp. 2473-2481.
63. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, Francis G, Goldstein NS, Hayes M, Hicks DG, Lester S, Love R, Mangu PB, McShane L, Miller K, Osborne CK, Paik S, Perlmutter J, Rhodes A, Sasano H, Schwartz JN, Sweep FC, Taube S, Torlakovic EE, Valenstein P, Viale G, Visscher D, Wheeler T, Williams RB, Wittliff JL, Wolff AC. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. *J Clin Oncol.* 2010;28:2784-95.
64. Finn RS, Dering J, Conklin D, et al. Palbociclib, a selective cyclin D kinase 4/6 inhibitor, preferentially inhibits proliferation of luminal estrogen receptor-positive human breast cancer cell lines in vitro. *Breast Cancer Research* 2009; 11(5):R77.
65. Gao CY, Rampalli AM, Cai H-C, et al. Changes in cyclin dependent kinase expression and activity accompanying lens fiber cell differentiation. *Exp Eye Res* 1999;69:695-703.

66. Bhat SP. The ocular lens epithelium. *Bioscience Reports* 2002;21(4):537-63.
67. N. Awasthi, B.J. Wagner – Suppression of Human Lens Epithelial Cell Proliferation by Proteasome Inhibition, a Potential Defense against Posterior Capsular Opacification. *Invest Ophthalmol Vis Sci.*, 2006; 47: 4482–4489.
68. UK Summary of Product Characteristics for Femara ®  
<http://emc.medicines.org.uk/emc/industry/default.asp?page=displaydoc.asp&documentid=1285>.
69. Fisher B., Constantino J.P., Wickerham D.L., et al. “Tamoxifen for the Prevention of Breast Cancer: Current Status of the National Surgical Adjuvant Breast and Bowel Project P-1 Study.” *J. Natl. Cancer Inst.*, 2005:97:165-62.
70. D. J. Slamon, S. A. Hurvitz, S. Applebaum, J. A. Glaspy, M. K. Allison, B. A. DiCarlo, R. D. Courtney, S. T. Kim, S. Randolph, R. S. Finn. Phase I study of Palbociclib, cyclin-D kinase (CDK) 4/6 inhibitor in combination with letrozole for first-line treatment of patients with ER-positive, HER2-negative breast cancer. *J Clin Oncol* 28:15s, 2010 (suppl; abstr 3060).
71. RS Finn, JP Crown, I Lang, K Boer et.al Final results of a Randomized Phase 2 Study of PD 0332991, a Cyclin-Dependent Kinase (CDK) 4/6 Inhibitor, in Combination with Letrozole vs Letrozole Alone for First-Line Treatment of ER+, HER2– Advanced Breast Cancer (PALOMA-1/TRIO-18) Abstract CT101, Presented at AACR 2014; April 6, 2014; San Diego, CA, USA
72. Craig Jordan, Historical perspective on hormonal therapy of advanced breast cancer, *Clinical Therapeutics*, Volume 24, Supplement 1, 2002, Pages A3-A16, ISSN 0149-2918, 10.1016/S0149-2918(02)85031-7.
73. Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, Benner CL, Cantor SB, Crawford J, Cross SJ, Demetri G, Desch CE, Pizzo PA, Schiffer CA, Schwartzberg L, Somerfield MR, Somlo G, Wade JC, Wade JL, Winn RJ, Wozniak AJ, Wolff AC. 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. *Journal of Clinical Oncology* 2006; 24, 19: 3187-3205.



74. Chew EY, Kim J, Sperduto RD, Datiles MB 3rd, Coleman HR, Thompson DJ, Milton RC, Clayton JA, Hubbard LD, Danis RP, Ferris FL 3rd. Evaluation of the age-related eye disease study clinical lens grading system AREDS report No. 31. *Ophthalmology*. 2010 Nov;117(11):2112-9.
75. Ciray I, Lindman H, Astrom GKO, et al. Effect of granulocyte colony-stimulating factor (G-CSF)-supported chemotherapy on MR imaging of normal red bone marrow in breast cancer patients with focal bone metastases. *Acta Radiol* 2003; 44: 472-484.
76. Hogan MJ, Kimura SJ, Thygeson P: Signs and symptoms of uveitis: I. Anterior uveitis. *Am J Ophthalmol* 1959;47:155-70.
77. Lee Y , Dominy JE , Choi YJ: Cyclin D1-Cdk4 controls glucose metabolism independently of cell cycle progression. *Nature*. Published online 25 May 2014.; doi:10.1038/nature13267.

**Appendix 1. Eastern Cooperative Oncology Group (ECOG) Performance Status**

<b>Description</b>	<b>Grade</b>
Fully active, able to carry on all pre-disease performance without restriction.	0
Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature, ie, light house work, office work.	1
Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4

**Appendix 2. Sponsor Approved HER2 Assays**

**HER2 results based on 1 of the following commercial kit assays are acceptable (for the purposes of study entry)**

<b>IHC Approved Assay</b>	<b>FISH Approved Assay</b>	<b>CISH Approved Assay</b>
HercepTest	Pathvysion HER2 DNA Probe Kit	SPOT-Light® HER2 CISH™ Kit
Pathway	INFORM HER2/neu Probe	-
-	HER2 FISH PharmDx™ Kit	-

### Appendix 3. List of Drugs Known to Predispose to Torsade de Pointes

<b>Generic Name</b>	<b>Brand Name(s)</b>
Amiodarone	Cordarone®, Pacerone®
Arsenic trioxide	Trisenox®
Astemizole	Hismanal®
Azithromycin	Zithromax®
Bepidil	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Cisapride	Propulsid®
Citalopram	Celexa®
Clarithromycin	Biaxin®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone	Motilium®
Droperidol	Inapsine®
Erythromycin	Erythrocin®, E.E.S.®
Flecainide	Tambocor®
Halofantrine	Halfan®
Haloperidol	Haldol®
Ibutilide	Corvert®
Levomethadyl	Orlaam®
Mesoridazine	Serentil®
Methadone	Dolophine®, Methadose®
Moxifloxacin	Avelox®
Pentamidine	Pentam®, NebuPent®
Pimozide	Orap®
Probucol	Lorelco®
Procainamide	Pronestyl®, Procan®
Quinidine	Cardioquin®, Quinaglute®
Sotalol	Betapace®
Sparfloxacin	Zagam®
Terfenadine	Seldane®
Thioridazine	Mellaril®
Vandetanib	Caprelsa®

Adapted from the University of Arizona Cancer Center for Education and Research on Therapeutics: "Torsades List: Drugs with a Risk of Torsades de Pointes," drugs that are generally accepted by the QTdrugs.org Advisory Board to carry a risk of Torsades de Pointes on the University of Arizona CERT website: <http://www.crediblemeds.org/>. This list is not meant to be considered all inclusive. See website for current list.

**Appendix 4. Bone Marrow Reserve in Adult**

*Adapted from R.E. ELLIS: The Distribution of Active Bone Marrow in the Adult, Phy. Med. Biol. 5, 255-258, 1961*

**MARROW DISTRIBUTION OF THE ADULT**

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
<b>CRANIUM AND MANDIBLE</b>	Head:			136.6		
	Cranium	165.8	0.75	124.3	13.1	<b>13.1</b>
	Mandible	16.4	0.75	12.3		
<b>HUMERI, SCAPULAE, CLAVICLES</b>	Upper Limb Girdle :			86.7		
	2 Humerus,	26.5	0.75	20.0	8.3	
	head & neck					8.3
	2 Scapulae	67.4	0.75	50.5		
	2 Clavicles	21.6	0.75	16.2		
<b>STERNUM AND RIBS</b>	Sternum	39.0	0.6	23.4	2.3	
	Ribs:			82.6		
	1 pair	10.2	All 0.4	4.1		
	2	12.6		5.0		
	3	16.0		6.4		
	4	18.6		7.4		
	5	23.8		9.5	7.9	<b>10.2</b>
	6	23.6		9.4		
	7	25.0		10.0		
	8	24.0		9.6		
	9	21.2		8.5		
	10	16.0		6.4		
	11	11.2		4.5		
12	4.6		1.8			
<b>PELVIC BONES</b>	Sacrum	194.0	0.75	145.6	13.9	
	2 os coxae	310.6	0.75	233.0	22.3	<b>36.2</b>
<b>FEMUR</b>	2 Femoral head and neck	53.0	0.75	40.0		<b>3.8</b>

**MARROW DISTRIBUTION OF THE ADULT (CONT'D)**

SITE		MARROW wt. (g)	FRACTION RED MARROW AGE 40	RED MARROW wt. (g) AGE 40	% TOTAL RED MARROW	
<b>VERTEBRAE</b>	Vertebrae (Cervical):			35.8		<b>28.4</b>
	1	6.6	All 0.75	5.0	3.4	
	2	8.4		6.3		
	3	5.4		4.1		
	4	5.7		4.3		
	5	5.8		4.4		
	6	7.0		5.3		
	7	8.5		6.4		
	Vertebrae (Thoracic):			147.9		
	1 pair	10.8	All 0.75	8.1	14.1	
	2	11.7		8.8		
	3	11.4		8.5		
	4	12.2		9.1		
	5	13.4		10.1		
	6	15.3		11.5		
	7	16.1		12.1		
	8	18.5		13.9		
	9	19.7		14.8		
	10	21.2		15.9		
	11	21.7		16.3		
	12	25.0		18.8		
Vertebrae (Lumbar):			114.1			
1 pair	27.8	All 0.75	20.8	10.9		
2	29.1		21.8			
3	31.8		23.8			
4	32.1		24.1			
5	31.4		23.6			
<b>TOTAL</b>		1497.7		1045.7	100.0	<b>100.0</b>

## Appendix 5. EuroQol Health Utilities Index EQ-5D



**Health Questionnaire**

*English version for the UK  
(validated for Ireland)*

SAMPLE

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By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

**Mobility**

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

**Self-Care**

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

**Usual Activities** (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

**Pain/Discomfort**

- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

**Anxiety/Depression**

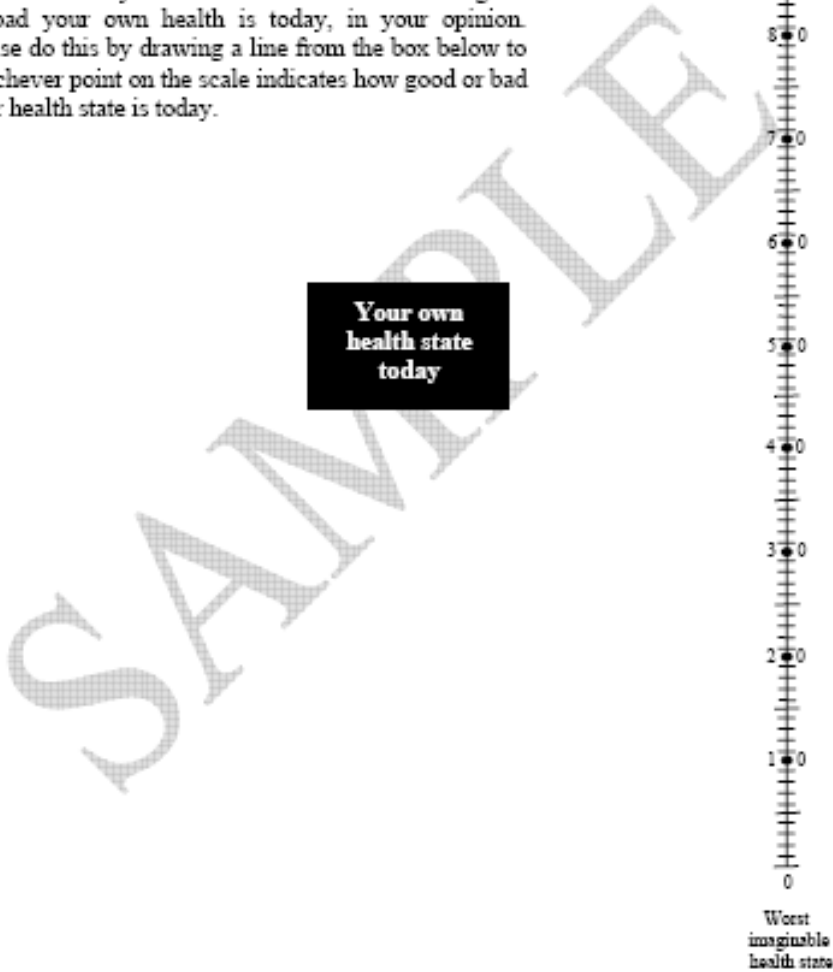
- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed



To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

**Your own  
health state  
today**



**Appendix 6. Functional Assessment of Cancer Therapy-Breast (FACT-B) [Version 4]**

Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<b><u>PHYSICAL WELL-BEING</u></b>		Not at all	A little bit	Some- what	Quite a bit	Very much
GP1	I have a lack of energy .....	0	1	2	3	4
GP2	I have nausea .....	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family .....	0	1	2	3	4
GP4	I have pain .....	0	1	2	3	4
GP5	I am bothered by side effects of treatment .....	0	1	2	3	4
GP6	I feel ill .....	0	1	2	3	4
GP7	I am forced to spend time in bed .....	0	1	2	3	4

<b><u>SOCIAL/FAMILY WELL-BEING</u></b>		Not at all	A little bit	Some- what	Quite a bit	Very much
GS1	I feel close to my friends .....	0	1	2	3	4
GS2	I get emotional support from my family .....	0	1	2	3	4
GS3	I get support from my friends .....	0	1	2	3	4
GS4	My family has accepted my illness .....	0	1	2	3	4
GS5	I am satisfied with family communication about my illness .....	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support) .....	0	1	2	3	4
Q1	<i>Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box <input type="checkbox"/> and go to the next section.</i>					
GS7	I am satisfied with my sex life .....	0	1	2	3	4

**FACT-B (Version 4)**

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<b><u>EMOTIONAL WELL-BEING</u></b>		Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad .....	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness .....	0	1	2	3	4
GE3	I am losing hope in the fight against my illness .....	0	1	2	3	4
GE4	I feel nervous .....	0	1	2	3	4
GE5	I worry about dying .....	0	1	2	3	4
GE6	I worry that my condition will get worse .....	0	1	2	3	4

<b><u>FUNCTIONAL WELL-BEING</u></b>		Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home) .....	0	1	2	3	4
GF2	My work (include work at home) is fulfilling .....	0	1	2	3	4
GF3	I am able to enjoy life .....	0	1	2	3	4
GF4	I have accepted my illness .....	0	1	2	3	4
GF5	I am sleeping well .....	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun .....	0	1	2	3	4
GF7	I am content with the quality of my life right now .....	0	1	2	3	4

**FACT-B (Version 4)**

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

<u>ADDITIONAL CONCERNS</u>		Not at all	A little bit	Some- what	Quite a bit	Very much
011	I have been short of breath.....	0	1	2	3	4
012	I am self-conscious about the way I dress.....	0	1	2	3	4
013	One or both of my arms are swollen or tender.....	0	1	2	3	4
014	I feel sexually attractive .....	0	1	2	3	4
015	I am bothered by hair loss .....	0	1	2	3	4
016	I worry that other members of my family might someday get the same illness I have .....	0	1	2	3	4
017	I worry about the effect of stress on my illness .....	0	1	2	3	4
018	I am bothered by a change in weight .....	0	1	2	3	4
019	I am able to feel like a woman .....	0	1	2	3	4
020	I have certain parts of my body where I experience pain....	0	1	2	3	4

## **Appendix 7. RECIST (Response Evaluation Criteria In Solid Tumors) version 1.1 Guidelines**

*Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247*

Categorizing Lesions at Baseline.

### **Measurable Lesions**

- Lesions that can be accurately measured in at least one dimension.
- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

### **Non-measurable disease**

Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.

- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion subjected to other local treatment) is non-measurable unless it has progressed since completion of treatment.

### **Normal sites**

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific definition above. If non-cystic lesions are also present, these are preferred as target lesions.
- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

### **Recording Tumor Assessments**

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

### **Target lesions**

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.
- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

### **Non-target disease**

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

### **OBJECTIVE RESPONSE STATUS AT EACH EVALUATION**

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

### **Target disease**

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis < 10 mm). All target lesions must be assessed.
- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.
- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.
- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.
- Indeterminate. Progression has not been documented, and
  - one or more target measurable lesions have not been assessed,

- or assessment methods used were inconsistent with those used at baseline,
- or one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure),
- or one or more target lesions were excised or irradiated and have not reappeared or increased.

### **Non-target disease**

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).
- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.
- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.
- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.



### **New Lesions**

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

### **Supplemental Investigations**

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.
- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

### **Subjective progression**

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

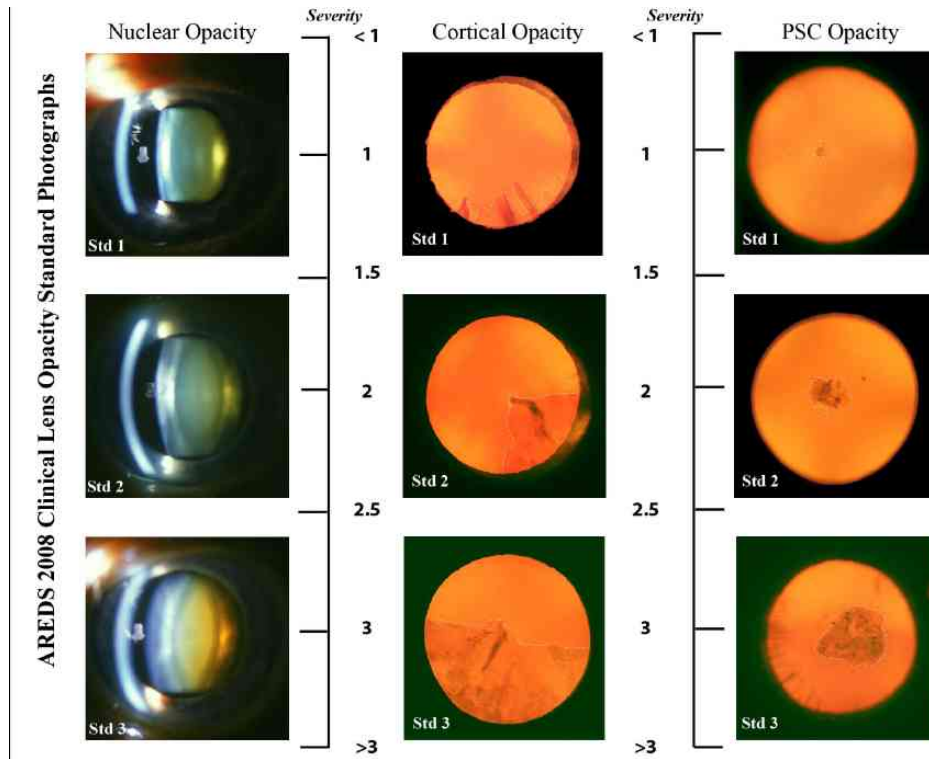
<b>Table 1. Objective Response Status at each Evaluation</b>			
<b>Target Lesions</b>	<b>Non-target Disease</b>	<b>New Lesions</b>	<b>Objective status</b>
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If the protocol allows enrollment of patients with only non-target disease, the following table will be used:

<b>Table 2. Objective Response Status at each Evaluation for Patients with Non-Target Disease Only</b>		
<b>Non-target Disease</b>	<b>New Lesions</b>	<b>Objective status</b>
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD

## **Appendix 8. Wisconsin Age-Related Eye Disease Study (AREDS) 2008 Clinical Lens Opacity Grading Procedure**

- Dilate pupils to at least 5 mm diameter;
- Use slit lamp with ~10X magnification;
- Use brightest beam intensity.
- Nuclear opacity:
  - Orient beam at 45° to viewing axis;
  - Adjust slit beam to standard parameters: 8 mm height and 0.3 mm width;
  - Compare opalescence of nucleus with that in standard photos.
- Cortical and PSC opacities:
  - Select wide slit beam setting optimum for retro-illumination of lens;
  - Visualize lens opacities against red fundus reflex background;
  - Count only opacities definitely visible against red reflex;
  - Mentally combine all cortical opacities into one contiguous area;
  - Compare total opacity area with that in standard photos.
- Classify each opacity with scale defined by 3 standard photos.
- Select nearest half-step:
  - Similar to standard or between two standards;
  - Obviously less than mildest standard or greater than most severe.



## Appendix 9. List of Abbreviation

ABC	Advanced Breast Cancer
ASCO	American Society of Clinical Oncology
AE	Adverse Event
ALT	Alanine Aminotransferases
AI	Aromatase Inhibitor
ANC	Absolute Neutrophil Count
AREDS	Age-Related Eye Disease Study
AST	Aspartate Aminotransferases
AT	As Treated
AUC	Area Under the Curve
BC	Breast Cancer
BUN	Blood Urea Nitrogen
CAP	Chest, Abdomen, Pelvis OR College of American Pathologists depending on context.
CCND1	Cyclin D1
CDK	Cyclin-Dependent Kinase
CDKN2A, p16 <sup>Ink4A</sup>	Cyclin-Dependent Kinase Inhibitor 2A
CFDA	China Food and Drug Administration
CI	Confidence Interval
CISH	Chromogenic In Situ Hybridization
CLIA	Clinical Laboratory Improvement Amendments
C <sub>max</sub>	Maximum Plasma Concentration
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CSA	Clinical Study Agreement
CSF	Colony-Stimulating Factors
CT	Computed Tomography
CTA	Clinical Trial Application
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P-450
DC	Disease Control
DCR	Disease Control Rate
DFI	Disease Free Interval
DICOM	Digital Imaging and Communications in Medicine
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

E-DMC	External Data Monitoring Committee
EDTA	Ethylenediaminetetraacetic acid
EIU	Exposure In Utero
EQ-5D	Dimension Health State EuroQoL Score
ER	Estrogen Receptor
FACT	Functional Assessment of Cancer Therapy
FACT-B	Functional Assessment of Cancer Therapy - Breast
FACT-G	Functional Assessment of Cancer Therapy - General
FDA	US Food and Drug Administration
FDAAA	US Food and Drug Administration Administration Amendments
FFPE	Formalin Fixed Paraffin Embedded
FIH	First in Human
FISH	Fluorescent In Situ hybridization
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
Hb	Hemoglobin
HDL	High Density Lipoprotein
HDPE	High Density Polyethylene
HER	Human Epidermal Growth Factor Receptor
hERG	Human Ether-à-Go-Go
HR	Heart Rate
IB	Investigator's Brochure
IC <sub>50</sub>	Concentration of 50% Inhibition
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IHC	Immunohistochemistry
IND	Investigational New Drug
INR	International Normalized Ratio
Internal DMC	Internal Data Monitoring Committee
IOP	Intraocular Pressure
IRB	Institutional Review Board
IRT	Interactive Randomization Technology
ITT	Intent-to-treat
LDL	Low Density Lipoprotein
LFT	Liver Function Test
LPD	Local Product Document
LSLV	Last Subject Last Visit
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model Repeated Measures
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose

N/A	Not Applicable
NCI	National Cancer Institute
OBU	Oncology Business Unit
OR	Objective Response
ORR	Objective Response Rate
OS	Overall Survival
PCD	Primary Outcome Completion Date
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response or Progesterone Receptor (depending on context)
PR	The PR interval is measured from the beginning of the P wave to the beginning of the QRS complex.
PS	Performance Status
PSC	Posterior Subcapsular Cataract
PRO	Patient Reported Outcome
PT	Prothrombin Time
QD	Quaque Die (once daily)
QRS	The QRS complex is a name for the combination of three of the graphical deflections seen on a typical electrocardiogram. The QRS complex reflects the rapid depolarization of the right and left ventricles.
QT	Time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QT <sub>c</sub>	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's fomula
QTcF	QT interval corrected for heart rate using Fridericia's fomula
RANKL	Receptor Activator of Nuclear Factor Kappa B Ligand
RB/Rb	Retinoblastoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
RR	The interval between an R wave and the next R wave
R <sub>ac</sub>	Accumulation Ratio
SABCS	San Antonio Breast Cancer Symposium
SAE	Serious Adverse Event
SD	Stable Disease or Standard Deviation (depending on context)
SPC	Summary of Product Characteristic
t <sub>½</sub>	Terminal Elimination Half-life
TdP	Torsade de Pointes
TEAE	Treatment Emergent Adverse Event
T <sub>max</sub>	Time for C <sub>max</sub>

ULN	Upper Limit of Normal
US	United States
VAS	Visual Analogue Scale
$V_z/F$	Apparent Volume of Distribution
WBC	White Blood Cell