MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE 3 TRIAL OF FULVESTRANT (FASLODEX®) WITH OR WITHOUT PD-0332991 (PALBOCICLIB) ± GOSERELIN IN WOMEN WITH HORMONE RECEPTOR-POSITIVE, HER2-NEGATIVE METASTATIC BREAST CANCER WHOSE DISEASE PROGRESSED AFTER PRIOR ENDOCRINE THERAPY

Compound:	PD-033,2991
Compound Name:	Palbociclib
United States Investigational New Drug Number:	69,324
European Clinical Trial Database (EudraCT) Number:	2013-002580-26
Protocol Number:	A5481023
Phase:	3

Document History

Document	Version Date	Summary of Changes
Amendment 3	20 October 2015	• Section 1.2.4.3: Added the section to clarify the rationale for Amendment 3. Upon approval, some of the safety and efficacy assessments will be reduced due to: 1) completion of efficacy analyses including interim and final analysis of primary endpoint and secondary endpoints; 2) additional analyses of safety conducted to comply with Health Authorities requirements; 3) at the time of amendment approval a smaller number of patients will be on study treatment and patients will remain under observation for a follow-up period of approximately 1 year and a half. • Protocol Summary-Background and Rationale/Section 1.2.1.8: Added data of interim analysis of present study. • Protocol Summary-Study Endpoints/Section 2.2: PRO endpoints have been better reworded. • Protocol Summary-Study Design/Schedule of Activities/Section 6.4/Section 7.2.1: Added clarification that tumor assessments will be conducted as per local practice after approval of Amendment 3. As a consequence, the requirement of conducting tumor assessment at the End of Treatment visit will not be mandatory any longer. • Protocol Summary-Study design/Section 7.2.3: Clarified that the third-party core imaging laboratory will not perform any longer blinded independent central review of PFS data. The investigators will stop sending the imaging studies to the central laboratory. • Protocol Summary-Schedule of Activities/Section 6.5.3/Section 7.2.4: Added clarification that survival follow-up visits will be conducted every 3 months after approval of Amendment 3.

Document	Version Date	Summary of Changes
		• Protocol Summary-Schedule of Activities: Added clarification that blood chemistry will be performed every 3 cycles (Day 1) after approval of Amendment 3. It was also clarified that, if an adverse event occurs that mandates blood chemistry to be performed (eg, hepatic function abnormality), the additional laboratory data will be recorded in the CRF. • Protocol Summary-Schedule of Activities: Clarified that hemoglobin A1c will be tested at the time of blood chemistry. • Protocol Summary-Schedule of Activities: Clarified that ophthalmology tests will continue to be collected. • Protocol Summary-Schedule of Activities/Section 5.3.3.1: Clarified that no time window is to be considered for treatment schedule of palbociclib/placebo and that hematology tests must meet retreatment criteria prior to administering palbociclib. • Protocol Summary-Tumor Assessment Requirements Flow Chart/Section 5.2: Clarified that, after approval of Amendment 3, tumor assessments will be conducted as per local practice, selection of imaging studies will depend on treating physician and radiologist as per local practice, and RECIST version 1.1 will not be mandatory any longer to evaluate imaging studies nor to confirm disease progression. • Section 5.5.1: Clarified that strong/moderate CYP3A inhibitors/inducers and proton pump inhibitors listed in the protocol are permitted for those patients who permanently discontinued palbociclib/placebo and continue on fulvestrant monotherapy only.

Document	Version Date	Summary of Changes
		• Section 6.5.4: The section was deleted as for patients who discontinued study treatment without an objectively documented progression, the tumor assessments showing progression of the disease will not be collected any more during follow-up. • Section 9: Clarified that the planned data analyses described in the protocol had been already conducted at the time of the interim analysis CCI [redacted] CCI [redacted] • Section 16: Added reference 41 related to interim analysis data of A5481023 study and deleted reference 60 to reflect changes made in the protocol.
Amendment 2	30 September 2014	• Schedule of Activities/Section 7.3.1 Laboratory Safety Assessments: Added prospective monitoring of hemoglobin A1c to characterize whether or not palbociclib affects glucose metabolism. • Schedule of Activities/Study design: Added clarification to the schedule of administration of fulvestrant and goserelin. • Schedule of Activities/Section 5.3.4.2.1/ Section 6: Language related to cycle delay further defined to clearly state that any new cycle may only start if blinded study treatment can be resumed. • Schedule of Activities/Section 7.3.3: Added clarification to the timing for physical examination/vital signs assessments. • Section 1.2.1.2. Human Pharmacokinetic Data: Updated section to add data findings to support: 1) administration of palbociclib with food; 2) prohibition of palbociclib administered concomitantly with proton-pump inhibitors;

Document	Version Date	Summary of Changes
		3) concomitant use of local antacids and H2-receptor antagonists; 4) prohibition of palbociclib administered concomitantly with strong/moderate CYP3A inducers/inhibitors; 5) palbociclib as a weak time-dependent inhibitor of CYP3A.  • Section 5.3.4.2.3: In Table 3, added language related to the criteria for treatment restart after the occurrence of toxicity to allow restart of palbociclib/placebo at the next lower dose level if uncomplicated Grade 3 neutropenia recurs in 2 consecutive cycles. • Section 5.5: Editorial changes made to differentiate between strong and moderate CYP3A inducers/inhibitors. Restriction on CYP3A substrate removed based on updated information indicating that palbociclib is a weak time-dependent inhibitor of CYP3A. Lastly, local antacids and H2-receptor antagonists were moved under the "Permitted Medications" Section 5.5.3 to reflect results from Study A5481038 showing that H2-receptor antagonists and local antacids given as defined per protocol did not impact the exposure of palbociclib. • Section 6.5: Added clarification of adverse events follow-up procedure (telephone contact) at 28 calendar days after treatment discontinuation. Additional editorial changes made to clarify follow-up procedures for patients who discontinue treatment for reasons other than disease progression and for patients who discontinue treatment due to disease progression.

Document	Version Date	Summary of Changes
		• Sections 9.6 and 9.7: Updated to report the analyses to be conducted on ocular events data and added clarification that the method of sample size re-estimation will be pre-specified in a separate technical document to be only shared with the E-DMC before the interim analysis. • Minor editorial changes made to correct inconsistencies or improve text clarity throughout the protocol.
Amendment 1	04 April 2014	• Schedule of Activities; Section 7.2.2. (Ocular Safety Assessments) – Added ocular safety assessment procedures to newly enrolled lens grading evaluable patients to assess the potential risk of palbociclib-associated lens changes. • Section 1.2.1.2 (Human Pharmacokinetic Data) – Included preliminary results from two clinical pharmacology studies of palbociclib supporting revisions of Sections 5.3.3.1 (Palbociclib/Placebo), 5.5.1 (Prohibited Medications), and 5.5.2 (Medications Not Recommended). CCI • Section 1.2.4. (Amendment Rationale): Added rationale for Amendment 1. • Section 4.1 (Inclusion Criteria) - Clarified inclusion criterion #6 and exclusion criteria #4, 5 and 6 to address frequent questions from investigational sites. • Section 5.3.3.1 (Palbociclib/Placebo) – Added recommendation to take palbociclib with food instead of under fasting conditions.

Document	Version Date	Summary of Changes
		• Section 5.3.4.2.3 (Retreatment Criteria), Table 3 – Specified time period of 7 days for delay of neutrophil recovery qualifying for further dose reduction to align with remainder of the protocol. • Section 5.5.1 (Prohibited Medications) – Added prohibition to take proton-pump inhibitors while receiving study drug. • Section 5.5.2 (Medications Not Recommended) – Added instructions about administration of local antacids and H2-receptor antagonist as alternative treatment for patients requiring gastroprotective treatment. • Section 6.6.1 (Active Treatment Phase Discontinuation) – Clarified that routine safety assessments must continue if patient continues study treatment despite progression of disease. • Appendix 4 (RECIST version 1.1 Guidelines) – Aligned terminology with RECIST version 1.1. • Appendix 8 Wisconsin Age-Related Eye Disease Study (AREDS) 2008 Clinical Lens Opacity Grading Procedure added. • Editorial changes to align language throughout the protocol, to clarify text considered confusing by investigational sites, and to reflect the sponsor's current protocol template.
Original protocol	24 July 2013	Not applicable.

This amendment incorporates all revisions to date.

PROTOCOL SUMMARY

Background and Rationale:

Palbociclib is an orally active pyridopyrimidine, first-in-class compound that is a potent and highly selective reversible inhibitor of Cyclin-Dependent Kinase (CDK) 4/6. The compound prevents cellular Deoxyribonucleic Acid (DNA) synthesis by prohibiting progression of the cell cycle from G1 into the S phase, as demonstrated both in laboratory models and in early clinical trials. There is a strong link between the action of estradiol and the G1-S phase transition, where it drives transcriptional activation of cyclin D1 leading to formation of the cyclin D1-CDK4/6-Rb complex which facilitates the G1 to S phase transition. Preclinical data, both Pfizer internal data and also from other laboratories, suggest that estrogen resistant models are exquisitely sensitive to the combination of palbociclib with antihormonal therapy or palbociclib alone.

Blockade of the Estrogen Receptor (ER) signaling pathway is synergistic with cell cycle arrest induction, as demonstrated by the more than doubling in median Progression Free Survival (PFS) observed to date in the ongoing trial evaluating ER+ metastatic breast cancer patients treated with the combination of an aromatase inhibitor (AI) and palbociclib compared with aromatase inhibitor alone. Overcoming resistance to endocrine therapy in breast cancer patients is a major challenge and there is a high unmet need for safe and efficacious treatment options in women resistant to endocrine therapy.

Postmenopausal women with hormone receptor (HR)+/ Human Epidermal Growth Factor Receptor 2(HER2)-negative breast cancer that have progressed after treatment with letrozole or anastrozole are now able to receive everolimus (Afinitor®) in combination with exemestane. However, despite promising efficacy recently demonstrated in the BOLERO-2 trial in ER+/HER2-negative patients (median PFS 6.9 months for the everolimus-exemestane combination vs. 2.8 months for exemestane alone per investigator's assessment), a high percentage of patients discontinued everolimus due to a challenging tolerability profile. The potential of everolimus to improve overall survival and clinical benefit in women with endocrine sensitive disease, or who present with advanced breast cancer in the pre- or perimenopausal status, is not yet known.

Data from the open-label Phase 2 study PALOMA-1 (A5481003) in a patient population of ER+/HER2-negative postmenopausal patients with newly diagnosed metastatic breast cancer indicate that the addition of palbociclib to letrozole significantly extends PFS with a tolerable safety profile. The results of two interim analyses showed a consistent trend of clinically meaningful improvements in PFS. In the first interim analysis (Part 1; N=66), the median PFS for the palbociclib plus letrozole arm was 18.2 months versus 5.7 months for the letrozole alone arm (Hazard Ratio (HR)=0.35; 95% confidence interval (CI): 0.17, 0.72; p=0.006). The second interim analysis (N=165) demonstrated a statistically significant improvement in PFS (26.1 vs. 7.5 months, respectively; HR=0.37; 95% CI: 0.21, 0.63; p <0.001).

While the study included patients whose disease had relapsed at various timepoints after prior endocrine therapy, there is limited clinical data on the activity of palbociclib in patients whose disease recurred on or early after antihormonal therapy - a population that may be less sensitive to re-treatment with antihormonal therapy. Such patients, who could be pre-, peri-, or postmenopausal, comprise a large high-risk population for whom more therapeutic options are needed.

Fulvestrant is a potent anti-estrogen drug that binds and degrades ER. Recent data with fulvestrant administered 500 mg monthly to patients with recurrent HR+/HER2-negative breast cancer indicate significant antitumor activity after both antiestogen and AI failure. In a Phase 2 study, the combination of fulvestrant and everolimus has shown efficacy in postmenopausal women after failure of AI treatment similar to that of the combination of tamoxifen with everolimus (median time to progression 7.4 months). Fulvestrant is currently indicated for the treatment of postmenopausal women with metastatic HR+ breast cancer following the failure of antiestrogen therapy. Despite its attractive mechanism of action, it has not been studied extensively in pre- or peri-menopausal women. However, it is expected to also add benefit to the treatment of pre- and peri-menopausal women if given concurrently with ovarian suppression/ablation.

Clinical experience demonstrates that ovarian ablation produces comparable outcomes to tamoxifen monotherapy and supports the use of goserelin (Luteinizing Hormone-Releasing Hormone [LHRH] agonist) concurrently with fulvestrant in premenopausal women with metastatic breast cancer. In fact, Phase 2 studies are currently underway evaluating the combination of fulvestrant with medical ovarian suppression in premenopausal women with breast cancer. The growing data about the activity of fulvestrant after antihormonal therapy failure, together with emerging efficacy data of palbociclib support their combined use in women with HR+, HER2-negative metastatic breast cancer whose disease has progressed after prior endocrine therapy. The present study will establish the degree of added benefit of palbociclib in HR+/HER2-negative recurrent breast cancer patients treated with fulvestrant versus fulvestrant alone.

The present study (PALOMA-3/A5481023) met its primary endpoint as per protocol at the interim analysis based on the recommendation of the external data monitoring committee. The addition of palbociclib to fulvestrant substantially improved PFS in pre/peri- and postmenopausal women with HR-positive, HER2-negative advanced breast cancer whose disease had progressed after prior endocrine therapy. The median PFS was 9.2 months (95% CI, 7.5 to not estimable) in the palbociclib-fulvestrant arm and 3.8 months (95% CI, 3.5 to 5.5) in the placebo-fulvestrant arm (HR=0.422; 95% CI, 0.318 to 0.560; 1-sided $P<0.000001$)..

In the open-label Phase 2 study PALOMA-1 (A5481003) in patients with ER-positive, HER2-negative metastatic breast cancer who had never received systemic therapy for their advanced disease, palbociclib in combination with letrozole improved PFS compared to letrozole alone, suggesting palbociclib has activity when combined with endocrine therapy in both endocrine-naive and -resistant settings.

In the present study, adverse events seen with palbociclib and fulvestrant were consistent with previously reported data. Overall, palbociclib was well tolerated, with a discontinuation rate due to adverse events similar to that seen with placebo, and manageable by dosing interruptions, dose reductions, and/or standard medical care. The majority of adverse events were mild to moderate in severity with the exception of hematological toxicties.

In addition, the patient-reported outcomes support the positive impact of palbociclib plus fulvestrant, maintaining global Quality of Life (QoL) on treatment and resulting in a statistically significantly higher on-treatment global QoL compared to placebo plus fulvestrant.

Double blinding of the present study will be maintained to allow ongoing collection of data for other pre-specified secondary endpoints including patient reported outcomes.

Study Design:

This is an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 clinical trial with the primary objective of demonstrating the superiority of palbociclib in combination with fulvestrant (Faslodex®) over fulvestrant alone in prolonging investigator-assessed PFS in women with HR+/HER2-negative metastatic breast cancer whose disease has progressed after prior endocrine therapy. The safety between the two treatment arms will also be compared.

Eligible patients must have histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of recurrent advanced (locally or metastatic) disease. Their breast cancer must have progressed during or within 12 months of completion of adjuvant therapy (with an AI, if postmenopausal, or with tamoxifen, if pre- or perimenopausal). Alternatively, it must have progressed while on, or within 1 month after the end of prior therapy for advanced/metastatic breast cancer (with an AI, if postmenopausal, or other prior endocrine treatment, if pre- or perimenopausal). One previous line of chemotherapy for metastatic disease is allowed. Patients must have measurable disease as per Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 or bone disease as their only site of disease. Tumor tissue is required for patient participation.

At least 417 patients will be randomized in a 2:1 ratio and stratified by documented sensitivity to prior hormonal therapy (yes vs. no), menopausal status at study entry (pre-/peri- vs. post menopausal), and presence of visceral metastases (yes vs. no).

Patients in Arm A (at least 278) will receive palbociclib 125 mg/day orally for 3 weeks followed by 1 week off plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, every 28 days (+/- 7 days) thereafter starting from Day 1 of Cycle 1.

Patients in Arm B (at least 139) will receive placebo orally daily for 3 weeks followed by 1 week off plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, every 28 days (+/- 7 days) thereafter starting from Day 1 of Cycle 1.

In both arms, pre- and peri-menopausal women will also receive the LHRH agonist goserelin (Zoladex® or generic).

At the time of approval of Amendment 3, patients will undergo tumor assessment according to local practice. .

Patients will continue to receive assigned treatment until objective Progressive Disease (PD), symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first. Crossover between treatment arms will not be allowed. Patients showing PD can continue with study treatment at the discretion of the investigator as long as that is considered to be in the best interest of the patient and 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.

In addition, should palbociclib/placebo related toxicity mandate palbociclib/placebo discontinuation, patients can continue to receive fulvestrant alone. Patients discontinuing the active treatment phase (ie, discontinuing both palbociclib/placebo and fulvestrant) will enter a follow-up phase during which survival and new anti-cancer therapy information will be collected, every 3 months from the last dose of study treatment going forward after approval of Amendment 3.

An external data monitoring committee (E-DMC) will perform an early review of safety data from approximately the first 40 randomized patients with sufficient pharmacokinetic (PK) sampling to confirm safety and tolerability of the combination. The early safety review by the E-DMC will also include Pharmacokinetic (PK) data from these initial approximately 40 patients to explore potential Drug-Drug-Interactions (DDIs) between fulvestrant, goserelin (if applicable) and palbociclib. The study will continue while these analyses and review are ongoing.

In addition, blood samples will be collected from all patients to assess trough concentrations of palbociclib for exposure/response analysis for safety and efficacy findings.

Patient Reported Outcomes (PRO) will be collected to evaluate health-related quality of life and health status.

The study will also include a molecular profiling component aimed at assessing the relationship between breast tumor sensitivity and resistance to palbociclib and the alteration of cell cycle pathway-related genes and proteins in tumor tissues.

Study Objectives:

Primary Objective:

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

Secondary Objectives:

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

Study Endpoints:

Primary Endpoint:

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

Secondary Endpoints:

- Overall Survival (OS).
- 1-year, 2-year, and 3-year survival probabilities.
- Objective Response (OR): Complete Response (CR) or Partial Response (PR).
- Duration of Response (DR).
- Clinical Benefit Response (CBR): CR or PR or Stable Disease (SD) ≥24 weeks.
- Type, incidence, severity (as graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.0), seriousness and relationship to study medications of Adverse Events (AEs) and any laboratory abnormalities.
- Trough plasma concentration of palbociclib, fulvestrant and goserelin (if applicable) in the subgroup of approximately 40 patients included in the initial safety review.

- PRO endpoints such as global quality of life symptoms and functioning assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Instrument (EORTC QLQ-C30) and European Organisation for Research and Treatment of Cancer Breast Cancer Module (EORTC QLQ-BR23) and Dimension Health State EuroQoL Score (EQ-5D)and time to deterioration (TTD) in pain endpoint.

- Tumor tissue biomarkers, including genes (eg, copy numbers of CCND1 and CDKN2A, PIK3CA mutations), proteins (eg, Ki67, pRb, CCNE1), and RNA expression (eg, cdk4, cdk6).

Statistical Methods:

The primary objective of this study is to demonstrate that the combination of palbociclib and fulvestrant (± goserelin) is superior to the combination of placebo and fulvestrant (± goserelin) in prolonging investigator-assessed PFS in women with HR+/HER2-negative metastatic breast cancer that has progressed on prior endocrine therapy, regardless of their menopausal status.

[redacted]

The study is designed to have one interim analysis. The interim analysis will be conducted to allow for early stopping of the study due to efficacy, or to potentially re-estimate the sample size of the trial based upon the primary endpoint of PFS. The safety of the combination will also be assessed at the interim analysis. The interim analysis of PFS will be performed after approximately 143 patients have documented PD or death (approximately 60% of the total events expected). The information fraction for the interim analysis may be adjusted if needed. The sample size of the study may also be adjusted as appropriate.

OS will be hierarchically tested for significance at the time of PFS analyses, provided the primary PFS endpoint is statistically significant at the interim and/or final PFS analyses.

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 patient.

Protocol Activity	**Screening**	**Active Treatment Phase[a] - One Cycle = 28 days**			**End of Treatment/Withdrawal[c]**	**Post-Treatment Follow-Up[d]**
		Cycles 1 and 2		**Cycles ≥3**		
Study Day	**Within 28 days prior to randomization unless specified otherwise**	**Day 1[b]**	**Day 15**	**Day 1**		
Visit Window		**±-2 days**	**±2 days**	**±7 days[a]**		**±7 days**
Informed Consent[e]	X					
Medical/Oncological History[f]	X					
Baseline Signs/Symptoms[g]		X[g]				
Physical Examination/Vital Signs[h]	X	X[b]		X	X	
Ophthalmic Examination[i]	X			X[i]	X	
ECOG Performance Status	X	X		X	X	
Laboratory Studies						
Hematology[j]	X	X[b]	X	X	X	
Blood Chemistry[j]	X	X[b]	X	X (upon approval of Amendment 3, assessed every 3 cycles)	X	
Pregnancy test, serum estradiol and FSH (if applicable)[j]	X					
12-Lead ECG (in triplicate)	X				X	
Disease Assessment						
CT/MRI Scans of Chest, Abdomen, Pelvis, any clinically indicated sites of disease, and of bone lesions; Clinical evaluation of superficial disease[k]	X	◄--►[k] Upon approval of Amendment 3, performed as per local practice (See tumor assessment requirements flowchart)			X	X
Radionuclide Bone Scan, Whole Body[l]	X	Upon approval of Amendment 3, performed as per local practice (See tumor assessment requirements flowchart)[l]			X	X
Other Clinical Assessments						
Adverse Event Reporting[m]	X	X	X	X	X	X

Protocol Activity	**Screening**	**Active Treatment Phase[a] - One Cycle = 28 days**			**End of Treatment/Withdrawal[c]**	**Post-Treatment Follow-Up[d]**
		Cycles 1 and 2		**Cycles ≥3**		
Study Day	**Within 28 days prior to randomization unless specified otherwise**	**Day 1[b]**	**Day 15**	**Day 1**		
Visit Window		**±-2 days**	**±2 days**	**±7 days[a]**		**±7 days**
Concomitant Medications/Treatments	◄--► Recorded from 28 days prior to the start of study treatment up to 28 days after the last dose of study treatment					
Pharmacokinetics (PK)[n]		First 40 patients: Sampling at pre-dose on Day 1 and Day 15 of Cycles 1 and 2, and Day 1 of Cycle 3; all other patients: Pre-dose sampling on Day 15 of Cycles 1 and 2				
[redacted]						
EuroQol-5D (EQ-5D)[r]		Pre-dose on Day 1 of Cycles 1, 2, 3, 4 and Day 1 of every other cycle thereafter starting with Cycle 6 (ie, Cycle 6,8, 10, etc)			X	
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ-C30)[r]					X	
European Organisation for Research and Treatment of Cancer Breast Cancer Module (EORTC-QLQ-BR23)[r]					X	
Survival Follow-up[s]						X
Study Treatment						
Randomization		X				
Fulvestrant (both treatment arms)[t]		◄--►[t] IM administration on Days 1 and 15 of Cycle 1, every 28 days (±7 days) thereafter starting from Day 1 of Cycle 1				
Palbociclib or placebo (Arm A only)[u]		◄--►[u] Orally once daily on Days 1 to 21of each Cycle followed by 7 days off treatment (visit windows not applicable to palbociclib/placebo dosing)				
For pre-/peri-menopausal patients only: Goserelin (both treatment arms, if applicable)[v]	SC administration at least 4 weeks before study treatment start[v]	◄--►[v] SC administration every 28 days				

a. **Active Treatment Phase:** Assessments should be performed prior to dosing on the visit day unless otherwise indicated. Acceptable time windows for performing each assessment are described in the column headers. No time window is to be considered for treatment schedule of palbociclib/placebo. One cycle consists of 28 days. A cycle could be longer than 28 days if persistent toxicity delays initiation of the subsequent cycle. **Day 1 of any cycle visit should coincide with the day the palbociclib/placebo treatment begins.** If there are delays due to toxicity, then the start of the next cycle visit will be delayed until the patient has recovered and can begin study treatment again. Fulvestrant injection will be given every 28 days (+/- 7 days) with the exception of Cycle 1 during which it will be administered on Days 1 and 15 (±2 days allowed according to the protocol visit time windows). Goserelin will be administered every 28 days (+/- number of days allowed according to the protocol visit time windows). The active treatment phase is ongoing as long as the patient is receiving both study drugs (ie, palbociclib/placebo and fulvestrant) or fulvestrant alone.
b. **Cycle 1/Day 1:** Blood chemistry, hematology, and physical examination not required if acceptable screening assessment is performed within 7 days prior to randomization.
c. **End of Treatment/Withdrawal:** Visit to be performed as soon as possible but no later than 4 weeks from the last dose of investigational products and prior to initiation of any new anticancer therapy. Obtain assessments if not completed during the previous 4 weeks on study.
d. **Post Treatment Follow-up:** Patients who discontinue study treatment should be contacted 28 calendar days (±7 days) after discontinuation of study treatment (palbociclib/placebo or fulvestrant) to assess if there have been any new adverse events and/or any change to any previously reported adverse events. This follow-up should occur 28 calendar days (±7 days) regardless of any new anti-cancer therapy that may have started. Telephone contact is acceptable. Follow-up visits to assess survival status will be conducted every 3 months going forward after approval of Amendment 3. See table footnote s (Survival Follow-up) below.
e. **Informed Consent:** Informed consent must be obtained prior to any protocol required assessments being performed (with the exception of certain imaging assessments if meeting the criteria defined in the Screening Section).
f. **Medical/Oncological History:** To include information on prior anticancer treatments.
g. **Baseline Signs/Symptoms:** Baseline tumor related signs and symptoms will be recorded at the Cycle 1 Day 1 visit prior to initiating treatment and then reported as adverse events during the trial if they worsen in severity or increase in frequency.
h. **Physical Examination/Vital signs:** A full physical examination including an examination of all major body systems and breasts, height (at screening only), weight, blood pressure and pulse rate, which may be performed by a physician, registered nurse or other qualified health care provider. Physical examinations will be carried out at Screening, Day 1 of every cycle and the End of Treatment/Withdrawal visit.

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

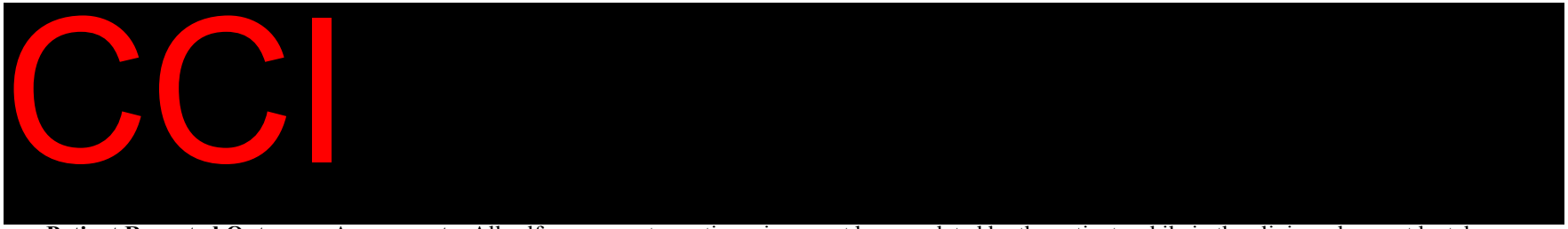
j. **Laboratory tests:** Hematology includes hemoglobin, WBC, absolute neutrophil count, platelet count. Hematology tests must meet retreatment criteria prior to administering palbociclib Blood chemistry includes AST/ALT, alkaline phosphatase, sodium, potassium, magnesium, total calcium, total bilirubin, blood urea nitrogen (BUN) (or urea), serum creatinine, and albumin. Additional hematology/chemistries panels may be performed as clinically indicated. Upon approval of Amendment 3, hemoglobin A1c will be measured in all patients every 3 cycles (Day 1) going forward (C7D1, C10D1, C13D1, etc) and at the End of Treatment/Withdrawal visit. Pregnancy test (serum) at screening only for women of childbearing potential. Test may be repeated as per request of IRB/IECs or if required by local regulations. Serum estradiol and Follicle stimulating hormone (FSH) levels are analysed at screening to confirm postmenopausal status of women <60 years old and who have been amenorrheic for at least 12 consecutive months. Upon approval of Amendment 3, blood chemistry will be performed every 3 cycles (Day 1) going forward (C7D1, C10D1, C13D1, etc) and at the End of Treatment/Withdrawal visit. Hemoglobin A1c will be tested at the time of blood chemistry. If an adverse event occurs that mandates blood chemistry to be performed (eg, hepatic function abnormality), the additional laboratory data will be recorded in the CRF.

k. **CT/MRI Scans of Chest, Abdomen, Pelvis:** Upon approval of Amendment 3, tumor assessments will be performed as per local practice. Refer to the tumor assessment requirement flowchart.

l. **Radionuclide Bone Scan, Whole Body:** Upon approval of Amendment 3, tumor assessments will be performed as per local practice. Refer to the tumor assessment requirement flowchart.

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

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



r. **Patient Reported Outcomes Assessments:** 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.

s. **Survival Follow-Up:** Upon approval of Amendment 3, for patients who discontinue study treatment, survival data will be collected every 3 months going forward. Telephone contact is acceptable. During follow-up visits the following data will be recorded in the CRF: 1) start, stop and type of new anticancer therapy; 2) tumor response of new anticancer therapy; 3) date of progression of the disease during or after the new antitumor agent; 4) survival status.

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

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

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

TUMOR ASSESSMENT REQUIREMENTS FLOWCHART

Method	Screening[a]	Treatment Period[b]	End of Treatment Visit[c]
CT or MRI of chest, abdomen, and pelvis	Required	Upon approval of Amendment 3, imaging studies will be conducted as per local practice.	Upon approval of Amendment 3, imaging studies will be conducted as per local practice.
CT or MRI of any other site of disease, as clinically indicated	Required	Upon approval of Amendment 3, imaging studies will be conducted as per local practice.	Upon approval of Amendment 3, imaging studies will be conducted as per local practice.
Radionuclide bone scan (whole body) and confirmatory imaging in case of any hot spots (CT, MRI or X-ray)	Required	Upon approval of Amendment 3, imaging studies will be conducted as per local practice.	Upon approval of Amendment 3, imaging studies will be conducted as per local practice.
Photographs of all superficial lesions as applicable	Required	Upon approval of Amendment 3, imaging studies will be conducted as per local practice.	Upon approval of Amendment 3, imaging studies will be conducted as per local practice.

a. Screening scans must occur within 4 weeks (ie, 28 days) prior to randomization unless otherwise specified.
b. During treatment period, upon approval of Amendment 3:
   - tumor assessment must be done according to local practice: if tumor assessments are scheduled as per the original protocol, upon approval of Amendment 3 they can be performed at a different schedule if this is common practice at that institution or it is recommended by the physician according to the patient's clinical conditions.
   - Selection of imaging studies will depend on treating physician and radiologist as per local practice.
   - Upon approval of Amendment 3, RECIST 1.1 may be used to evaluate imaging assessments but will not be mandatory. Evaluation of imaging studies will be conducted as per the practice at the institution.

TABLE OF CONTENTS

LIST OF TABLES

APPENDICES

1. INTRODUCTION

1.1. Indication

Women of any menopausal status with hormone receptor-positive (HR+), Human Epidermal Growth Factor Receptor 2 (HER2)-negative advanced/metastatic [1] breast cancer (BC) after failure of prior endocrine therapy.

1.2. Background and Rationale

HR+/HER2-negative breast cancer is the most common subset of breast cancer.[1] Most patients are diagnosed at an early stage and remain relapse-free if treated with a prolonged course of endocrine therapy. Unfortunately, not all patients respond to first-line endocrine therapy (primary or de novo resistance), and even patients who have a response will eventually relapse (acquired resistance). About one-third of all HR+/HER2-negative patients, diagnosed initially with early stage disease, experience disease recurrence.[2] As a result the HR+/HER2-negative subset is responsible for the majority of breast cancer related deaths. The fundamental problem is that endocrine agents are only partially effective, typically causing cell cycle arrest and tumor dormancy rather than true cure. As a result, secondary resistance to endocrine therapy is a major clinical challenge.

In postmenopausal patients with HR+/HER2-negative metastatic BC, aromatase inhibitors (AIs) have become the treatment of choice in first-line therapy.[3] On the contrary, most pre- or perimenopausal women with HR+ breast cancer present with early stage disease and are treated with the antiestrogen tamoxifen with or without ovarian ablation (by surgery, chemotherapy or luteinizing hormone-releasing hormone (LHRH)) in the adjuvant setting.[4] Upon initial presentation with metastatic disease during premenopause, the recommended approach is to suppress ovarian function (by ovarian ablation or luteinizing hormone-releasing hormone (LHRH) agonist therapy),[5] and then to concurrently follow post-menopausal treatment guidelines, switching treatment from tamoxifen to AIs or fulvestrant.[4] Thus, in clinical practice so called “pre/perimenopausal” patients with HR+ metastatic breast cancer will be rendered postmenopausal by the time of first line treatment for advanced disease.

Upon disease progression on hormonal therapy, historically the treatment options have been limited to a change in AIs (steroidal or nonsteroidal) or the use of the estrogen-receptor (ER) antagonists fulvestrant and tamoxifen.[6,7]

In the past few years the search for newer, non-endocrine related agents to treat recurrent metastatic ER+ breast cancers has expanded to include agents targeting the PI3K/mTOR pathway as well as cell cycle specific agents. Everolimus, recently approved in advanced, recurrent disease, is an example of the former,[8] and palbociclib, is an example of the latter.[9] In both cases, successful development of molecular patient selection criteria has so far proven to be elusive. More efficacious and safe therapeutic options are still needed,

1 The terms “advanced” and “metastatic” breast cancer are used interchangeably in this document.

particularly in molecularly selected patient populations. Thus, HR+/HER2-negative breast cancer patients who have tumor progression following endocrine therapies for metastatic disease, represent an important unmet medical need, regardless of their menopausal status.

1.2.1. Overview of Palbociclib

PD-0332991 (palbociclib), an orally active pyridopyrimidine, is a potent first-in-class, highly selective reversible inhibitor of CDK 4 and CDK6 (IC_{50} = 11 nM; Ki = 2 nM) with a molecular weight of 573.67. CCI [redacted] CCI [redacted]

The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase, as demonstrated both in laboratory models and in early clinical trials. CDK4 and CDK6 control G1 to S phase transit by binding to D-type cyclins.[10,11,12] The CDK4/6/Cyclin D1 complex phosphorylates the retinoblastoma susceptibility (RB1) gene product (Rb), releasing the E2F and DP transcription factors that drive expression from genes required for S-phase entry.[12] CDK activity and G1 progression is negatively regulated by Cip-Kip and INK4 family, typified by p16.[13,14,15,16,17] Overexpression of p16 in cells with normal Rb inhibits both CDK4-and CDK6-associated kinase activity and Rb phosphorylation, with subsequent cell cycle arrest.[18,19]

Preclinical data, both Pfizer internal data and also from other laboratories, suggest that estrogen resistant models are exquisitely sensitive to the combination of palbociclib with antihormonal therapy or palbociclib alone. Blockade of the ER signaling pathway is synergistic with cell cycle arrest, as demonstrated by the more than doubling in median PFS observed to date in the ongoing trial evaluating ER+ metastatic breast cancer patients treated with the combination of an aromatase inhibitor and palbociclib compared with aromatase inhibitor alone.[9] Overcoming resistance to endocrine therapy in breast cancer patients is a major challenge and there is a high unmet need for safe and efficacious treatment options in women resistant to endocrine therapy.

There is a strong link between the actions of estradiol and the G1-S phase transition, where the estradiol effector is the cyclin D1-CDK4/6-Rb complex.[20] Cyclin D1 is a direct transcriptional target of ER[21,22,23,24] and microinjection of antibodies to cyclin D1 inhibits estrogen-induced S-phase entry.[25,26,27,28,29] In addition, anti-estrogen-induced growth arrest of ER+ breast cancer cells is accompanied by decreased cyclin D1 expression[30] while endocrine resistance is associated with persistent cyclin D1 expression and Rb phosphorylation.[31] Consistent with the notion that the main function of cyclin D1 is to activate CDK4/6, its oncogenic activity is dependent on CDK4/6-associated kinase activity[32] and CDK4/6 inhibitors are most effective in tumors with gene amplification and overexpression of cyclin D1,[33,34,35] which is common in ER+ breast cancer. For example, palbociclib was most effective for ER+ breast cancer in a cell line panel,[36] including those that exhibited anti-estrogen resistance. Genetic aberrations leading to hyperactivation of cyclin D1-CDK4/6 is particularly common in ER+ breast cancer, consistent with its critical role in the tumorigenesis of this cancer subtype,[36] making CDK4/6 inhibitors particularly attractive agents for ER+ breast cancer.

1.2.1.2. Human Pharmacokinetic (PK) Data

To date, PK data have been collected in 8 clinical studies for a total of over 250 advanced cancer patients and 30 healthy volunteers (A5481001, A5481002, A5481003, A5481004, A5481008, A5481009, A5481010, and A5481011). In the first-in-human Study A5481001, the exposure ($AUC_{(0-10)}$ and C_{max}) 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 steady state, palbociclib was absorbed with a median T_{max} of ~4 hours. The mean palbociclib Vz/F was 2583 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 elimination half-life (t1⁄2) was 28.8 hours and the mean CL/F was 63.1 L/hour. Palbociclib accumulated following repeated dosing with a median R_{ac} of 2.4, which is consistent with the terminal half-life.

The effect of food on the bioavailability of palbociclib when administered as the commercial free base capsule, was investigated in Study A5481021. The administration of the free base formulation of palbociclib with food (including a high fat or a low fat meal given together with palbociclib, or moderate fat meals given 1 hour before and 2 hours after palbociclib) resulted in more uniform drug absorption and significantly reduced the intersubject variability in drug exposure when compared to the administration of free base formulation of palbociclib in a fasted state. The relative bioavailability of the commercial free base capsule administered with food and the isethionate capsule administered under overnight and minimal fasting conditions was investigated in Study A5481036. The two fasting conditions for administration of isethionate capsules represent the 2 extreme scenarios for compliant palbociclib dosing with regard to food intake in the pivotal Phase 1/2 efficacy trial, Study A5481003, in which patients were instructed to fast from 1 hour before until 2 hours after palbociclib dosing. The administration of palbociclib free base capsule formulation with food was found to be bioequivalent to palbociclib isethionate capsule formulation given under both the overnight and minimal fasting conditions. As a result of these findings, patients should be instructed to take palbociclib with food.

Study A5481018 showed that coadministration of palbociclib and QD doses of the proton-pump inhibitor (PPI) rabeprazole administered under fasted condition decreased single-dose palbociclib AUC_{inf} and C_{max} by 62% and 80%, respectively, when compared with those after a single dose of palbociclib administered alone. Another clinical trial (Study A5481038) showed that administration of palbociclib with famotidine and Mi-Acid Maximum Strength Liquid under fed conditions had no impact on the exposure of palbociclib. Coadministration of a single 125-mg palbociclib dose with multiple doses of the proton pump inhibitor (PPI) rabeprazole under fed conditions decreased palbociclib C_{max} by 41%, but it had limited impact on AUC_{inf} (13% decrease) compared with a single dose of palbociclib administered alone. The concomitant use of PPIs with palbociclib should be avoided.

Study A5481038, a Phase 1 study, was designed to investigate the effect of famotidine (an H_2-receptor antagonist) given 10 hours before and 2 hours after palbociclib; rabeprazole sodium (a PPI) given daily for 6 days before and 4 hours prior to palbociclib; mi-acid maximum strength liquid given 2 hours before palbociclib; mi-acid maximum strength liquid given 2 hours after palbociclib on the relative bioavailability of a single oral 125 mg of palbociclib commercial free base hard capsule formulation dose given under fed conditions in healthy volunteers. The results from this study showed that famotidine given 10 hours before and 2 hours after palbociclib or mi-acid maximum strength liquid (local antacid) given 2 hours before or 2 hours after palbociclib did not impact the exposure of palbociclib. Additionally, the results showed that coadministration of rabeprazole and palbociclib under fed conditions resulted in a decrease in palbociclib exposure less dramatic than the change in exposure observed in Study A5481018 where palbociblib was administered under fasted conditions. Palbociclib change in geometric mean C_{max} in combination with daily administration of rabeprazole decreased by 41% under fed conditions compared to the 80% decrease under fasted conditions. The change in AUC_{inf} of palbociclib when coadministered with rabeprazole under the fed conditions was approximately 13% compared to palbociclib given alone. Based upon these data, under fed conditions, the use of H_2-receptor antagonists

or local antacids is now permitted as defined in Section 5.5.3. As PPIs affect palbociclib Cmax and to a lesser extent AUC_{inf} their concomitant use will remain prohibited during the active treatment phase as outlined in Section 5.5.1.

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 Cytochrome P-450 (CYP) 3A4 enzymes. An exploratory evaluation of the circulating metabolites for palbociclib was conducted in plasma samples obtained from patients treated with palbociclib 200 mg QD (Schedule 2/1) in Study A5481001. Preliminary assessment of the pooled plasma samples on Day 14 of Cycle 1 indicated that the glucuronide conjugate of palbociclib and the lactam of palbociclib (PF-05089326) were the main metabolites present in plasma. Other metabolites observed were the glucuronide conjugates of hydroxylated palbociclib and the glucuronide conjugate of reduced palbociclib. 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.

Pharmacokinetic data are available from an itraconazole DDI study where the effect of multiple dosing of a potent CYP3A4 inhibitor, itraconazole (200 mg QD), on the single-dose PK of palbociclib (125 mg) was evaluated in 12 healthy fasted subjects (Study A5481016). Median palbociclib plasma concentrations were higher in the presence of itraconazole than those in the absence of itraconazole. Palbociclib mean plasma AUC from time 0 to infinity (AUC_{inf}) and C_{max} values increased approximately 87% and 34%, respectively, when administered in combination with itraconazole compared to when administered alone. Therefore, concomitant administration of agents known to be strong/moderate inhibitors of CYP3A isoenzymes (such as ketoconazole, miconazole, itraconazole, posaconazole, clarithromycin, erythromycin, telithromycin, nefazodone, diltiazem, verapamil, indinavir, saquinavir, ritonavir, nelfinavir, lopinavir, atazanavir, amprenavir, fosamprenavir, and grapefruit juice) should be avoided.

Pharmacokinetic data are available from a rifampin DDI study where the effect of multiple dosing of a potent CYP3A4 inducer, rifampin (600 mg QD), on the single-dose PK of palbociclib (125 mg) was evaluated in 15 healthy fasted subjects (Study A5481017). Median palbociclib plasma concentrations were substantially lower in the presence of rifampin than those in the absence of rifampin. Palbociclib mean plasma AUC from time 0 to infinity (AUC_{inf}) and C_{max} values decreased approximately 85% and 70%, respectively, when administered in combination with rifampin compared to when administered alone. Therefore, co-administration of palbociclib with strong/moderate CYP3A inducers (such as phenobarbital, rifampin, phenytoin, carbamazepine, rifabutin, rifapentin, and St. John's Wort) should be avoided.

Palbociclib and its metabolite PF-05089326 caused time-dependent inhibition of CYP3A in *in vitro* assays. Pharmacokinetic data are available from a midazolam DDI study where the effect of multiple dosing of palbociclib (125 mg QD) on the single-dose PK of a sensitive CYP3A4/5 probe substrate, oral midazolam (2 mg), was evaluated in 26 healthy women of non-childbearing potential (Study A5481012). When midazolam was administered with

palbociclib 125 mg QD at steady-state, the mean midazolam plasma C_{max} and AUC_{inf} values increased approximately 38% and 61%, respectively, as compared with those determined after administration of midazolam alone. These results indicated that palbociclib is a weak time-dependent inhibitor of CYP3A.

1.2.1.3. QT Interval Data

In vitro (hERG) and in vivo (dog telemetry) studies revealed a potential for QT prolongation at unbound concentrations ≥14-fold the unbound steady-state C_{max} associated with the clinical dose of 125 mg QD. A preliminary pharmacokinetic/pharmacodynamic analysis has been conducted to explore the QT/QTc and plasma palbociclib concentration relationship for Study A5481001 (First in Human 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 ≥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 (CI) of QTcF change from the baseline were 5.8 and 9.4 msec, respectively.

In order to achieve more extensive evaluation of the effect of palbociclib on QTc prolongation, time-matched Electrocardiogram (ECG) and PK data are being collected in a subset of at least 60 patients participating in Study A5481008.


CCI

1.2.1.5. 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 toxicities (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, anemia, diarrhea, constipation, vomiting and dyspnea, all with mild to moderate severity. A greater proportion of patients on the 2/1 schedule had treatment-related 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 (PR) 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. 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/day. This schedule and associated RP2D was further explored as a single agent and in combination with letrozole in the Phase 2 study and Phase ½ studies in patients with advanced breast cancer described below.

1.2.1.6. Phase 2 Trial of Palbociclib Alone in Women with Advanced Breast Cancer

A Phase 2 study is ongoing with single agent palbociclib in 36 women with advanced breast cancer. Preliminary results will be reported at the American Society of Clinical Oncology (ASCO) 2013 from 28 women who have completed Cycle 1. Palbociclib was given at 125 mg orally, Days 1- 21 of a 28-day cycle. Of the 28 women, 18 women are HR+/HER2-negative, 2 are HR+/HER2+ and 8 are HR-/HER2-negative. A total of 90% had prior chemotherapy for metastatic disease; 78% had prior hormonal therapy. Therapy with palbociclib alone was well-tolerated, and demonstrated tumor shrinkage and prolonged SD in patients with all subtypes of breast cancer and despite progression on prior hormonal- and chemotherapy. Clinical Benefit Response rates (PR+SD ≥6 months) were 4/18 (23%) in the HR+/HER2-negative cohort, 1/2 (50%) in the HR+/HER2+ cohort, and 1/8 (13%) in the HR-negative/HER2-negative cohort. Toxicities were consistent with those previously seen with palbociclib, ie, were mostly Grade 1/2, and Grade 3/4 toxicities were limited to transient neutropenia (50%) and thrombocytopenia (21%). Treatment was interrupted in 25% and dose was reduced in 46% of the patients for cytopenias. Translational studies examining molecular predictors of response are in progress.[38]

1.2.1.7. Data from Phase 1/2 Study of Palbociclib in Combination with Letrozole in Advanced Breast Cancer

A multicenter, randomized, controlled Phase 1/2 Study (A5481003) was designed to assess the efficacy, safety and PK 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-negative advanced breast cancer 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+ advanced breast cancer.

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-negative advanced breast cancer. 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[39] 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. PRs 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 ≥6 months and the clinical benefit rate (PR + SD ≥6 months) was 67%. Eight (8) patients discontinued from the study due to disease progression, including 2 patients with clinical progression, 1 patient withdrew consent, and 3 patients are still ongoing.

Two interim analyses for the Phase 2 portion of the study have been conducted. The results of the interim analyses showed consistent trend of clinically meaningful improvements in PFS (primary endpoint). In the first interim analysis (Part 1; N=66), the median PFS for the palbociclib plus letrozole arm was 18.2 months versus 5.7 months for the letrozole alone arm (HR=0.35; 95% CI: 0.17, 0.72; p=0.006). The second interim analysis (N=165) continued to demonstrate a statistically significant improvement in PFS (26.1 vs. 7.5 months, respectively; HR=0.37; 95% CI: 0.21, 0.63; p <0.001).[9, 40]

These results indicate that the combination of palbociclib with letrozole is well tolerated with a safety profile similar to that seen with palbociclib alone. The most frequently reported treatment-related adverse events included neutropenia, leukopenia, anemia, and fatigue. There were no cases of febrile neutropenia reported to date in this study. Overall, 8 patients in the combination arm were discontinued from the study treatment due to an adverse event, of which 5 were considered treatment-related (Grade 3 neutropenia [n=4] and ischemic colitis) and 1 patient from the letrozole alone arm. Additionally, the combination demonstrated antitumor activity which was consistent with the sensitivity of ER+ breast cancer observed in the preclinical models.

Complete information for palbociclib may be found in the Single Reference Safety Document for this compound which is the Investigator's Brochure (IB; November 2012).

1.2.1.8. Interim Analysis Data from Phase 3 Study A5481023 of Palbociclib in Combination with Fulvestrant

The present study A5481023 (PALOMA-3) met its primary endpoint at the preplanned interim analysis (data cutoff date of 05 December 2014) based on the recommendation of the external data monitoring committee. The addition of palbociclib to fulvestrant substantially improved PFS in pre/peri- and postmenopausal women with HR-positive, HER2-negative metastatic breast cancer whose disease had progressed after prior endocrine therapy. The median PFS was 9.2 months (95% CI, 7.5 to not estimable) on palbociclib-fulvestrant and 3.8 months (95% CI, 3.5 to 5.5) on placebo-fulvestrant (HR=0.422; 95% CI, 0.318 to 0.560; 1-sided P<0.000001). The random sample-based BICR audit approach has shown no investigator bias in favor of the palbociclib plus fulvestrant arm and the analysis results of BICR also corroborated the results of investigator-assessed PFS. Subgroup analyses for stratification factors and demographic/prognostic factors revealed consistent results. In particular, relative improvements in PFS for palbociclib were similar between pre/perimenopausal and postmenopausal patients (HR=0.435 versus 0.409, respectively, P=0.940 interaction test).[41]

In the present study, adverse events observed with palbociclib and fulvestrant were consistent with previously reported data. Overall, palbociclib was well tolerated, with a discontinuation rate due to adverse events similar to that seen with placebo, and manageable by dosing interruptions, dose reductions, and/or standard medical care. The majority of adverse events were mild to moderate in severity with the exception of hematological toxicties.

In the open-label Phase 2 study PALOMA-1 (A5481003) in patients with ER-positive, HER2-negative metastatic breast cancer who had never received systemic therapy for their advanced disease, palbociclib in combination with letrozole improved PFS compared to letrozole alone, suggesting palbociclib has activity when combined with endocrine therapy in both endocrine-naive and -resistant settings.

In addition, the patient-reported outcomes support the positive impact of palbociclib plus fulvestrant, maintaining global quality of life (QOL) on treatment and resulting in a statistically significantly higher on-treatment global QOL compared to placebo plus fulvestrant.

Double blinding of the present study will be maintained to allow ongoing collection of data for other pre-specified secondary endpoints including patient reported outcomes.

1.2.2. Overview of Fulvestrant (Faslodex®)

Approximately two thirds of breast cancers express ER[42] and the role for estrogens in breast cancer etiology and progression is well established. Modification of estrogen activity or synthesis represents the treatment of choice for women with hormone receptor-positive advanced breast cancer, particularly for those with slowly progressive disease (PD) and limited tumor-related symptoms.[43] Conversion of androgens to estrogens via aromatase enzyme action represents the main source of estrogens in postmenopausal women. Women with disease recurring early after AI or tamoxifen therapy are candidates to receive fulvestrant.

Fulvestrant (Faslodex®) is a competitive ER antagonist with an affinity comparable to estradiol. It blocks the trophic actions of estrogens without any partial agonist (estrogen-like) activity, and is currently indicated for the treatment of hormone receptor positive metastatic breast cancer in postmenopausal women with disease progression following antiestrogen therapy.[44]

The mechanism of action is associated with down-regulation of ER protein levels. Clinical trials in postmenopausal women with primary breast cancer have shown that fulvestrant significantly down-regulates ER protein in ER-positive tumours compared with placebo. There was also a significant decrease in progesterone receptor (PR) expression consistent with a lack of intrinsic estrogen agonist effects. It has also been shown that fulvestrant 500 mg/month downregulates ER and the proliferation marker Ki67 to a greater degree than fulvestrant 250 mg/month in breast tumours in postmenopausal neoadjuvant setting.[45]

Fulvestrant is comparable to AIs in terms of efficacy and tolerability for women who have progressed on prior tamoxifen therapy.[46] Past studies have found all AIs to be at least as good as tamoxifen in first-line metastatic therapy in postmenopausal women.[46]

Two Phase 3 clinical trials were completed in a total of 851 postmenopausal women with advanced breast cancer (77% of the women were ER+) who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. These trials compared the safety and efficacy of monthly administration of fulvestrant at the lower dose of 250 mg versus the daily administration of 1 mg of the AI anastrozole. Monthly 250 mg fulvestrant was at least as effective as anastrozole in terms of PFS, OR, and time to death. The combined data showed an objective response rate for fulvestrant 250 mg of 19.2% compared with 16.5% for anastrozole. The median time to death was 27.4 months for patients treated with fulvestrant and 27.6 months for patients treated with anastrozole. The hazard ratio of fulvestrant 250 mg to anastrozole for time to death was 1.01 (95% CI 0.86 to 1.19).[44]

However, there is evidence to suggest that doses of fulvestrant higher than 250 mg may have greater pharmacodynamic activity against the ER pathway. A Phase 3 clinical trial (CONFIRM) was completed in 736 postmenopausal women with advanced breast cancer who had disease recurrence on or after adjuvant endocrine therapy or progression following endocrine therapy for advanced disease. The study included 423 patients whose disease had recurred or progressed during anti-estrogen therapy (AE subgroup) and 313 patients whose disease had recurred or progressed during AI therapy (AI subgroup). This trial compared the efficacy and safety of fulvestrant 500 mg (n=362) with those of fulvestrat 250 mg (n=374). PFS for fulvestrant 500 mg was 6.5 months compared to 5.5 months for fulvestrant 250 mg. Overall survival data from the time of final analysis showed a median time to death of 26.4 months for fulvestrant 500 mg versus 22.3 months for fulvestrant 250 mg (HR (95%CI) 0.81 (0.69, 0.96), p-value 0.016).[47,48] Also, a pilot Japanese study showed fulvestrant 500 mg to have clinical activity in the treatment of advanced or recurrent breast cancer, to be well tolerated, and to result in plasma levels approximately double those seen with 250 mg fulvestrant.[49] Subsequently, a neoadjuvant study comparing fulvestrant 250 mg (low-dose) and 500 mg (high-dose) reported that significantly greater Ki67 and ER downregulation was achieved with the high-dose compared with the low-dose regimen and that both doses were well tolerated.[50]

A randomized Phase 2 trial assessed fulvestrant with or without dasatinib in postmenopausal patients with HR+ metastatic BC who have previously treated with an AI, a patient population similar to that included in the present study. In this trial, the median PFS for the fulvestrant alone arm was 5.3 months and the median PFS for the combination arm was 6.0 months, information used to determine the sample size in the present study. (See Sample Size Determination Section).[51]

The Single Reference Safety Document for the active comparator agent, fulvestrant (Faslodex®), is the IB.

1.2.3. Study Rationale

The present study is an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 clinical trial with the primary objective of demonstrating the superiority of palbociclib in combination with fulvestrant (Faslodex®) over fulvestrant alone in prolonging PFS in women with HR+, HER2-negative metastatic breast cancer whose disease has progressed after prior endocrine therapy. The safety between the two treatment arms will also be compared. Pre- and perimenopausal women must be receiving therapy with the LHRH agonist goserelin (Zoladex® or generic).

Palbociclib is an orally active pyridopyrimidine, first-in-class compound that is a potent and highly selective reversible inhibitor of Cyclin-Dependent Kinases 4 and 6 (CDK 4/6). The compound prevents cellular DNA synthesis by prohibiting progression of the cell cycle from G1 into the S phase, as demonstrated both in laboratory models and in early clinical trials. There is a strong link between the action of estradiol on the G1-S phase transition, where it drives transcriptional activation of cyclin D1 leading to formation of the cyclin D1-CDK4/6-Rb complex which facilitates the G1 to S phase transition. In non clinical experiments, palbociclib synergizes with antiestrogen to cause tumor regression in *in vitro* ER+ advanced breast cancer cell lines.

Preclinical data, both Pfizer internal data and also from other laboratories,[52] (unpublished data by L.Martin, Royal Marsden, London, UK) suggest that estrogen-resistant models are exquisitely sensitive to the combination of palbociclib with antihormonal therapy or palbociclib alone. Moreover, a small set of data in patients with HR+/HER2-negative recurrent breast cancer treated with monotherapy palbociclib suggests that about 25% of patients derive some degree of clinical benefit from monotherapy.[38]

Blockade of ER+ signaling pathway is synergistic with cell cycle arrest induction and results in significant clinical benefit as measured by PFS in patients with hormonal receptor positive metastatic breast cancer. Overcoming resistance to endocrine therapy in breast cancer is a major challenge and there still is an unmet need for safe and efficacious treatment options in women resistant to endocrine therapy.

Postmenopausal women with HR+/HER2-negative breast cancer that have progressed after treatment with letrozole or anastrozole are now able to receive everolimus (Afinitor®) in combination with exemestane. However, despite promising efficacy recently demonstrated in the BOLERO-2 trial in ER+/HER2-negative patients (median PFS 6.9 months for the everolimus-exemestane combination vs. 2.8 months for exemestane alone per investigator's assessment), a high percentage of patients discontinued everolimus due to a challenging tolerability profile. The potential of everolimus to improve overall survival and clinical benefit in women with endocrine sensitive disease, or who present with advanced breast cancer in the pre- or perimenopausal state, is not yet known.[53]

Data from the open-label Phase 2 study PALOMA-1 (A5481003) in a patient population of ER+/HER2-negative postmenopausal patients with newly diagnosed metastatic breast cancer indicate that addition of palbociclib to letrozole significantly extends PFS with a tolerable safety profile. While the study included patients whose disease had relapsed at various

timepoints after prior endocrine therapy, there is limited clinical data on the activity of palbociclib in patients whose disease recurred on or early after antihormonal therapy, a population that may be less sensitive to retreatment with antihormonal therapy. Such patients, who could be pre-, peri-, or postmenopausal, comprise a large high-risk population for whom more therapeutic options are needed.

Fulvestrant (see Section 1.2.1.8) is a potent anti-estrogen drug that binds and degrades ER. Recent data with fulvestrant administered at the dose of 500 mg/monthly to patients with recurrent HR+/HER2-negative breast cancer indicate significant antitumor activity after both antiestogen and aromatase inhibitor (AI) failures. In a Phase 2 study the combination of fulvestrant and everolimus has shown efficacy in postmenopausal women after failure of AI treatment similar to that of the combination of tamoxifen with everolimus (median time to progression 7.4 months).[54] Fulvestrant is currently indicated for the treatment of postmenopausal women with metastatic hormone receptor positive breast cancer following the failure of antiestrogen therapy. Despite its attractive mechanism of action, it has not been studied extensively in pre- or peri-menopausal women. However, it is expected to also add benefit to the treatment of pre- and peri-menopausal women if given concurrently with ovarian suppression/ablation. Clinical experience demonstrates that medical (or surgical) ovarian ablation produces comparable outcomes to tamoxifen monotherapy and support the use of goserelin (LHRH agonist) concurrently with fulvestrant in premenopausal women with metastatic breast cancer.[5,55] In fact, Phase 2 studies are currently underway evaluating the combination of fulvestrant with medical ovarian suppression in premenopausal women with breast cancer.[56]

The growing data about the activity of fulvestrant after antihormonal therapy failure[57] together with emerging efficacy data of palbociclib support their combined use in women with HR+, HER2-negative metastatic breast cancer whose disease has progressed after prior endocrine therapy. The present study will establish the degree of added benefit of palbociclib in HR+/HER2-negative recurrent breast cancer patients treated with fulvestrant versus fulvestrant alone.

Potential Drug-Drug-Interactions (DDIs)

The sponsor considers the potential for a clinically significant DDI between palbociclib and fulvestrant to be very low. The routes of elimination for fulvestrant include combinations of a number of possible biotransformation pathways analogous to those of endogenous steroids, including oxidation, aromatic hydroxylation, conjugation with glucuronic acid and/or sulphate. There are no known drug-drug interactions. Fulvestrant does not significantly inhibit any of the major CYP isoenzymes, including CYP 1A2, 2C9, 2C19, 2D6, and 3A4 *in vitro*, and studies of co-administration of fulvestrant with midazolam indicate that therapeutic doses of fulvestrant have no inhibitory effects on CYP 3A4 or alter blood levels of drug metabolized by that enzyme. Although fulvestrant is partly metabolized by CYP 3A4, a clinical study with rifampin, an inducer of CYP 3A4, showed no effect on the PK of fulvestrant. Also results from a healthy volunteer study with ketoconazole, a potent inhibitor of CYP3A4, indicated that ketoconazole had no effect on the PK of fulvestrant and dosage adjustment is not necessary in patients with co-prescribed CYP 3A4 inhibitors or inducers.[44]

Since palbociclib is not expected to affect the PK of fulvestrant, and based on the results of the CONFIRM study (see above)[47,48] the same dose regimen for fulvestrant (ie, 500 mg, intramuscularly on Days 1 and 15 of Cycle 1, and then on Day 1 of each subsequent 28 days Cycle) will be used in both treatment arms, ie, palbociclib plus fulvestrant and placebo plus fulvestrant.

Following fulvestrant monthly dosing with an additional dose on Day 15, steady-state concentration of fulvestrant will be achieved within the first month of study treatment.[43] Following monthly goserelin 3.6 mg SC depot (goserelin acetate implant), there is no significant evidence of drug accumulation.[56]

Likewise, the sponsor considers the potential for a clinically significant DDI between palbociclib and goserelin to be very low. Goserelin is a synthetic decapeptide analogue of gonadotropin releasing hormone whose primary route of elimination is the cleavage of C-terminal amino acids followed by renal excretion. No formal drug-drug interaction studies have been performed and no confirmed interactions have been reported between goserelin and other drugs.[58]

1.2.4. Amendment Rationale

1.2.4.1. Rationale for Changes in Amendment 1

Preliminary results from two clinical pharmacology studies A5481018 and A5481021 suggested that palbociclib taken with food results in more consistent drug absorption and exposure than in a fasted state, and palbociclib exposure may be decreased in a subgroup of patients taking palbociclib concomitantly with proton-pump inhibitors. Therefore, the protocol is being amended to revise the study drug administration instructions from administration in a fasted state to administration with food and to prohibit the concomitant use of proton-pump inhibitors.

Also, based on the limited pre-clinical and clinical data currently available, it is not known whether a clinical risk exists for palbociclib with regard to the development of cataracts. The protocol is therefore being amended to assess this potential risk by implementing prospective ophthalmic examinations in newly enrolled lens grading evaluable patients. Patients will be evaluated at baseline, during and at the end of study treatment. By adding these examinations the sponsor is addressing a request by the Food and Drug Administration (FDA) for the palbociclib program. The sponsor expects PALOMA-3 to contribute to this request ocular data from a minimum of 100 patients. The sponsor will inform sites as soon as these examinations are no longer required for this study. The results of the ophthalmic examinations will provide a better understanding of the potential risk of ocular adverse events.

Additional editorial changes are made to clarify inclusion criterion 6 and exclusion criteria #4, 5 and 6, to align language throughout the protocol, and to reflect the sponsor's current protocol template.

1.2.4.2. Rationale for Changes in Amendment 2

Given the observed nonclinical findings in rats and taking into account the limited laboratory glucose data in the current clinical dataset, the protocol was amended in order to prospectively characterize whether or not palbociclib affects glucose metabolism through monitoring of appropriate laboratory measurements.

In order to answer the many requests of clarifications from the clinical sites, the language related to cycle delay was further defined to clearly state that any new cycle may only start if blinded study treatment can be resumed. In addition, clarification to the schedule of administration of fulvestrant and goserelin was made. Language related to the criteria for treatment restart after the occurrence of toxicity was also added to allow restart palbociclib/placebo at the next lower dose level if uncomplicated Grade 3 neutropenia recurs in 2 consecutive cycles.

The section reporting Human Pharmacokinetic Data was updated. Data of clinical studies recently finalized have been added for the investigators to better clarify the reasons for 1) administration of palbociclib with food; 2) prohibition of palbociclib administered concomitantly with proton-pump inhibitors; 3) concomitant use of local antacids and H2-receptor antagonists; 4) prohibition of palbociclib administered concomitantly with strong/moderate CYP3A inducers/inhibitors; 5) palbociclib as a weak time-dependent inhibitor of CYP3A.

Further clarification was also added in the Concomitant Medications Section 5.5: editorial changes were made to differentiate between strong and moderate CYP3A inducers/inhibitors, restriction on CYP3A substrate was removed based on updated information indicating that palbociclib is a weak time-dependent inhibitor of CYP3A and local antacids and H_2-receptor antagonists were moved under the "Permitted Medications" Section 5.5.3 to reflect results from Study A5481038 showing that H_2-receptor antagonists and local antacids given as defined per protocol do not impact the exposure of palbociclib. "Human Pharmacokinetic Data" Section 1.2.1.2 was also updated to add data findings supporting the prohibition to concomitantly administer palbociclib with strong/moderate CYP3A inducers/inhibitors.

Clarification of adverse event follow-up procedure (telephone contact) at 28 calendar days after treatment discontinuation to assess if there have been any new adverse events and/or any change to any previously reported adverse events was added. Additional editorial changes were also made to clarify follow-up procedures for patients who discontinue treatment for reasons other than disease progression and for patients who discontinue treatment due to disease progression.

Clarification of timing for physical examination/vital signs assessments was provided.

Section 9 "Data Analysis/Statistical Methods" was updated to add the analyses to be conducted on ocular event data and clarify that the method of sample size re-estimation will be pre-specified in a separate technical document to be only shared with the E-DMC before the interim analysis.

In addition, minor editorial changes were made to correct inconsistencies or improve text clarity.

1.2.4.3. Rationale for Changes in Amendment 3

The scope of Amendment 3 will be to reduce efficacy and safety assessments mainly due to the following reasons: 1) the study met its primary endpoint of efficacy at the preplanned interim analysis; 2) additional efficacy analyses of the primary and secondary endpoints had been conducted upon request of Health Authorities (HAs); 3) additional analyses of safety had been conducted to comply with HAs requests. At the time of the amendment a smaller number of patients will be on study treatment and patients will remain under observation for a follow-up period of approximately 1 year and a half.

A summary of efficacy results at the time of interim analysis was added.

Main modification concerns the tumor assessments that will be conducted according to local practice at the institutions once this amendment is approved. The evaluation of the assessments as per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 will not be mandatory any longer. Tumor lesions and their measurements will not be recoreded in the case report form (CRF), nor will the RECIST assessments. Only the date of progression of disease will be recorded.

As a consequence of this modification, the tumor assessments showing progression of the disease will not be collected any more during follow-up for those patients who discontinued study treatment without an objectively documented progression.

Since the random sample-based BICR audit approach has shown no investigator bias in favor of the palbociclib plus fulvestrant arm and the analysis results of BICR also corroborated the results of investigator-assessed PFS, the third-party core imaging laboratory will no longer perform blinded independent central review of PFS data and the investigators will stop sending the imaging studies to the central laboratory.

Considering the safety profile of palbociclib as shown at the time of interim analysis and subsequent safety analyses, it was decided to perform blood chemistry only every 3 cycles (Day 1). However, when an adverse event occurs that mandates blood chemistry to be performed (eg, hepatic function abnormality), the additional laboratory data will be recorded in the CRF. Hemoglobin A1c must be tested at the time of blood chemistry collection. Ophtalomologic examination will continue.

It was also clarified that strong/moderate CYP3A inhibitors/inducers and proton pump inhibitors listed in the protocol are permitted for those patients who permanently discontinued palbociclib/placebo and continue on fulvestrant monotherapy only.

A modification of timing for survival follow-up was added. Survival follow-up visits will be conducted every 3 months from the last dose of study treatment after approval of Amendment 3.

In order to answer some requests of clarifications from the clinical sites, it was clarified that no time window is to be considered for treatment schedule of palbociclib/placebo.

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In addition, minor editorial changes were made to correct inconsistencies or improve text clarity.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objective:

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

Secondary Objectives:

- To compare measures of tumor control (including PFS, DR, CBR) between the treatment arms.
- To compare safety and tolerability between the treatment arms.
- To evaluate trough concentrations of palbociclib when given in combination with fulvestrant or fulvestrant plus goserelin compared to historical palbociclib data.
- To compare fulvestrant and goserelin trough concentrations when given in combination with palbociclib to those when given without palbociclib.
- To explore correlations between palbociclib exposures and efficacy/safety findings in this patient population.
- To compare Patient Reported Outcomes measures between treatment arms.
- To characterize alterations in genes, proteins, and RNAs relevant to the cell cycle, drug targets, tumor sensitivity and/or resistance.
- To conduct subgroup analysis for primary and secondary endpoints in stratified groups.

2.2. Endpoints

Primary Endpoint:

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

Secondary Endpoints:

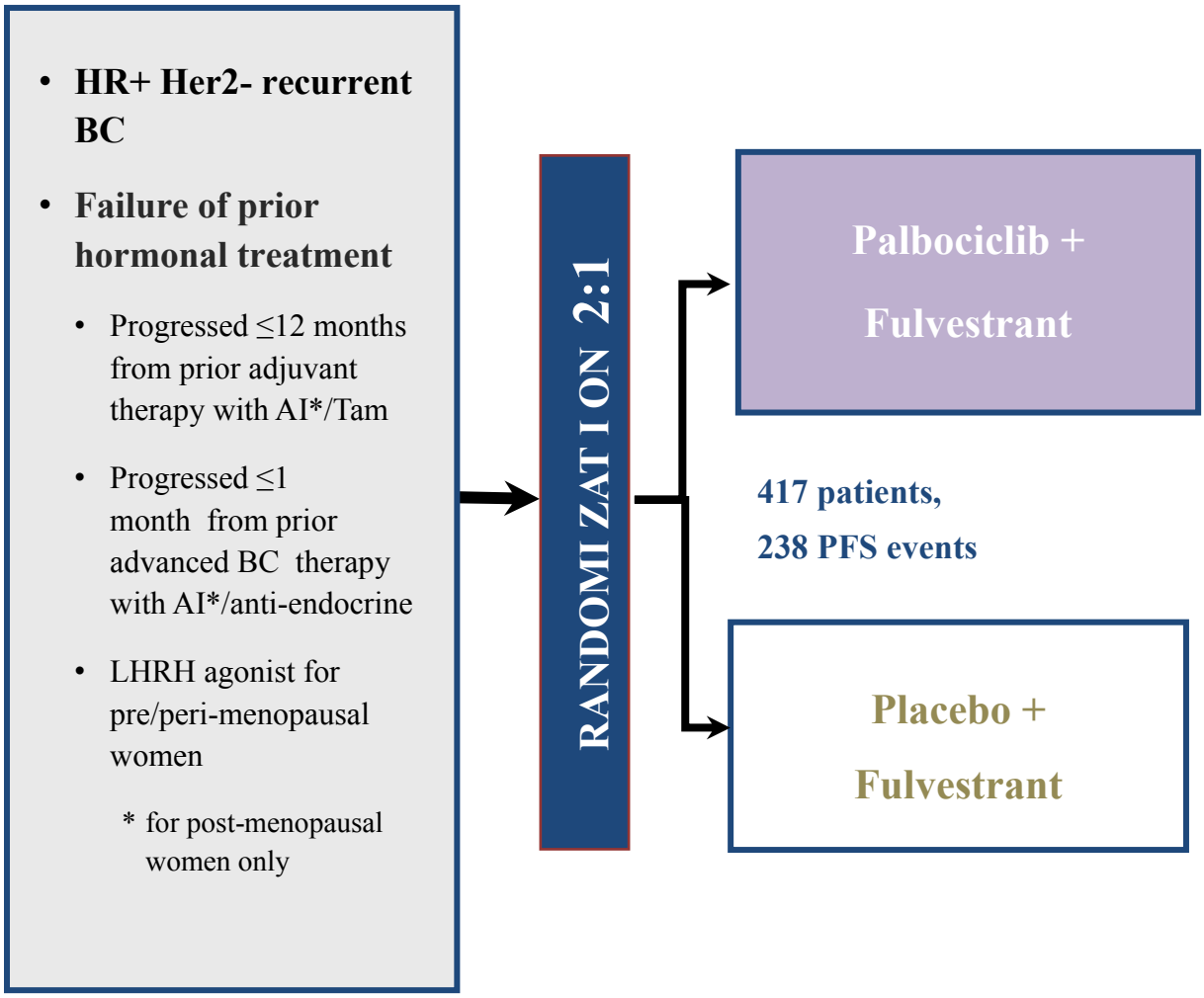
- Overall Survival (OS).
- 1-year, 2-year, and 3-year survival probabilities.
- Objective Response (OR: CR or PR).
- Duration of Response (DR).
- Clinical Benefit Response (CBR: CR or PR or SD ≥24 weeks).
- Type, incidence, severity (as graded by the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v4.0), seriousness and relationship to study medications of AEs and any laboratory abnormalities.
- Trough plasma concentration of palbociclib, fulvestrant and goserelin (if applicable) in the subgroup of approximately 40 patients included in the initial safety assessment.
- PRO endpoints such as global quality of life , symptoms and functioning assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Instrument (EORTC QLQ-C30) and European Organisation for Research and Treatment of Cancer Breast Cancer Module (EORTC QLQ-BR23) and Dimension Health State EuroQoL Score (EQ-5D) and time to deterioration (TTD) in pain endpoint.
- Tumor tissue biomarkers, including genes (eg, copy numbers of CCND1 and CDKN2A, PIK3CA mutations), proteins (eg, Ki67, pRb, CCNE1), and RNA expression (eg, cdk4, cdk6).

3. STUDY DESIGN

This is an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 clinical trial with the primary objective of demonstrating the superiority of palbociclib in combination with fulvestrant (Faslodex®) over fulvestrant alone in in women with HR+, HER2-negative metastatic breast cancer,regardless of their menopausal status, whose disease has progressed after prior endocrine therapy. The safety between the two treatment arms will also be compared. Pre- and perimenopausal women must receive therapy with the LHRH agonist goserelin (Zoladex® or generic).

Eligible patients must have histologically or cytologically proven diagnosis of adenocarcinoma of the breast with evidence of recurrent (locally or metastatic) disease. Their breast cancer must have progressed during or within 12 months of completion of adjuvant therapy (with an AI, if postmenopausal, or with tamoxifen, if pre- or perimenopausal). Alternatively, it must have progressed while on, or within 1 month after the end of prior therapy for advanced/metastatic breast cancer (with an AI, if postmenopausal, or other prior endocrine treatment, if pre- or perimenopausal). One previous line of chemo therapy for metastatic disease is allowed. Patients must have measurable disease as per RECIST v.1.1 (Appendix 4) or bone disease as their only site of disease. Tumor tissue is required for patient participation.

Approximately 417 women will be randomly assigned on a 2:1 basis to receive either palbociclib plus fulvestrant (at least 278 women; investigational arm), or placebo plus fulvestrant (at least 139 women; comparator arm). Pre- and peri-menopausal women continue receiving concurrent ovarian function suppression with goserelin.



Arm A (Investigational arm):

Palbociclib 125 mg/day orally for 3 weeks followed by 1 week off plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, every 28 days (+/- 7 days) thereafter starting from Day 1 of Cycle 1.

Arm B (Comparator arm):

Placebo orally daily for 3 weeks followed by 1 week off plus fulvestrant 500 mg intramuscularly on Days 1 and 15 of Cycle 1, every 28 days (+/- 7 days) thereafter starting from Day 1 of Cycle 1.

Details of palbociclib dose modifications for toxicity will be addressed in the STUDY TREATMENTS section. Dosages of fulvestrant will not be modified.

Pre- and peri-menopausal women must have commenced treatment with any LHRH agonist at least 4 weeks prior to randomization. If patients have not received goserelin as their LHRH agonist prior to study entry, they must switch to goserelin for the duration of the trial. Every effort should be made to administer goserelin (given every 28 days, see Zoladex® PI)[58] on site at the time of fulvestrant administration in order to minimize the number of clinic visits.

Randomization will be stratified by documented sensitivity to prior hormonal therapy (yes vs. no), by menopausal status at study entry (pre-/peri- vs. post menopausal), and by the presence of visceral metastases (yes vs. no).

Sensitivity to prior hormonal therapy is defined as either: (i) Documented clinical benefit (CR, PR, SD ≥24 weeks) to at least one prior hormonal therapy in the metastatic setting, OR (ii) At least 24 months of adjuvant hormonal therapy prior to recurrence. "Visceral" refers to lung, liver, brain, pleural and peritoneal involvement.

Patients will continue to receive assigned treatment until objective disease progression, symptomatic deterioration, unacceptable toxicity, death, or withdrawal of consent, whichever occurs first. Crossover between treatment arms is not allowed. However, patients may continue treatment as assigned at randomization beyond the time of 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. In this case, the patient would continue with routine safety relevant assessments as per the SCHEDULE OF ACTIVITIES for the active treatment period. In addition, should palbociclib/placebo related toxicity mandate palbociclib/placebo discontinuation, patients can continue to receive fulvestrant alone.

Upon approval of Amendment 3, patients discontinuing the active treatment phase will enter a follow-up period phase during which survival and new anti-cancer therapy information will be collected every 3 months from the last dose of study treatment going forward. Tumor response and progression to the subsequent therapy data will also be collected when applicable and available. The follow-up period will conclude at the time of the final OS analysis.

Upon the approval of Amendment 3, disease assessments will be performed and evaluated according to local practice.

Upon approval of Amendment 3, the third-party core imaging laboratory will no longer perform blinded independent central review (BICR) of PFS data of the subgroup of patients that was randomly selected. The investigators will stop sending the image studies to the core imaging laboratory.

Patients will undergo study-related safety and efficacy assessments as outlined in the relevant SCHEDULE OF ACTIVITIES located in the summary section.

A total of 238 PFS events will be required in the two treatment arms for the study to have a 90% power to detect an increase in PFS assuming a true HR of 0.64 (representing a 56% increase in median PFS from 6 to 9.38 months), if tested at a 1-sided significance level of α=0.025.

One interim analysis is planned to re-estimate the sample size, to assess patient safety and efficacy at 60% of the PFS events.

An external data monitoring committee (E-DMC) will perform an early review of safety data from approximately the first 40 randomized patients with sufficient PK sampling to confirm safety and tolerability of the combination. The early safety review by the E-DMC will also include PK data from these initial approximately 40 patients to explore potential Drug-Drug-Interactions (DDIs) between fulvestrant, goserelin (if applicable) and palbociclib. The study will continue while these analyses and review are ongoing.

In addition, trough concentrations of palbociclib will be collected from all patients and will be used for exposure/response analysis for safety and efficacy findings.

Patient Reported Outcomes (PRO) will be collected in this trial to evaluate the impact on quality of life, functioning, symptoms and general health status using the EuroQol-5D (EQ-5D), (Appendix 5) European Organisation for Research and Treatment of Cancer Quality of Life questionnaire (EORTC-QLQ-C30), (Appendix 6) and breast cancer (EORTC-QLQ-BR23) (Appendix 7).

The study will also include a molecular profiling component aimed at assessing the relationship between breast tumor sensitivity and resistance to palbociclib and the alteration of cell cycle pathway-related genes and proteins in tumor tissues.

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 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 appropriately qualified 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. Women 18 years of age or older, who are either:

    - Postmenopausal, as defined by at least one of the following criteria:

        - Age ≥60 years;
        - Age <60 years and cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause; and serum estradiol and FSH level within the laboratory's reference range for postmenopausal females;
        - Documented bilateral oophorectomy;
        - Medically confirmed ovarian failure.

    OR

    - Pre/peri-menopausal, ie, not meeting the criteria for being postmenopausal.

        - Pre/perimeopausal women can be enrolled if amenable to be treated with the LHRH agonist goserelin. Patients must have commenced treatment with goserelin or an alternative LHRH agonist at least 4 weeks prior to randomization. But, if patients have received an alternative LHRH agonist prior to study entry, they must switch to goserelin for the duration of the trial.

2. Histologically or cytologically proven diagnosis of breast cancer with evidence of metastatic or locally advanced disease, not amenable to resection or radiation therapy with curative intent.

3. Documentation of ER-positive and/or PR-positive tumor (≥1% positive stained cells) based on most recent tumor biopsy (unless bone-only disease, see below) utilizing an assay consistent with local standards.

4. Documented HER2-negative tumor based on local testing on most recent tumor biopsy: HER2-negative tumor is determined as immunohistochemistry score 0/1+ or negative *by in situ* hybridization (FISH/CISH/SISH/DISH) defined as a HER2/CEP17 ratio <2 or for single probe assessment a HER2 copy number <4.

5. Patients must satisfy the following criteria for prior therapy:

   - Progressed during treatment or within 12 months of completion of adjuvant therapy with an aromatase inhibitor if postmenopausal, or tamoxifen if pre- or perimenopausal.

   OR

   - Progressed while on or within 1 month after the end of prior aromatase inhibitor therapy for advanced/metastatic breast cancer if postmenopausal, or prior endocrine treatment for advanced/metastatic breast cancer if pre- or perimenopausal.

     One previous line of chemotherapy for advanced/metastatic disease is allowed in addition to endocrine therapy.

6. Except where prohibited by local regulations, all patients must agree to provide and have available a formalin-fixed paraffin embedded (FFPE) tissue biopsy sample taken at the time of presentation with recurrent or metastatic disease. A de novo biopsy is required if no archived tissue taken at the time of presentation with recurrent/metastatic disease is available. The sole exception is those patients with bone only disease for whom provision of previous archival tissue only is acceptable. Patients who had surgery within the last 3 years (but without neoadjuvant chemotherapy prior to surgery) and relapsed while receiving adjuvant therapy may provide a tumor specimen from that surgery.

7. Measurable disease as defined by RECIST version 1.1, or bone-only disease. Patients with bone-only metastatic cancer must have a lytic or mixed lytic-blastic lesion that can be accurately assessed by CT or MRI. Patients with bone-only disease and blastic-only metastasis are not eligible. Tumor lesions previously irradiated or subjected to other loco regional therapy will only be deemed measurable if progression at the treated site after completion of therapy is clearly documented.

8. Eastern Cooperative Oncology Group (ECOG) performance status 0-1.

9. Adequate organ and marrow function defined as follows:

   - ANC ≥1,500/mm3 (1.5 x 10^9/L);
   - Platelets ≥100,000/mm3 (100 x 10^9/L);
   - Hemoglobin ≥9 g/dL (90 g/L);
   - Serum creatinine ≤1.5 x ULN or estimated creatinine clearance ≥60 ml/min as calculated using the method standard for the institution;
   - Total serum bilirubin ≤1.5 x ULN (<3ULN if Gilbert's disease);
   - AST and/or ALT ≤3 x ULN (≤5.0 x ULN if liver metastases present);

- Alkaline phosphatase ≤2.5 x ULN (≤5 x ULN if bone or liver metastases present).

10. Resolution of all acute toxic effects of prior therapy or surgical procedures to National Cancer Institute (NCI) CTCAE Grade ≤1 (except alopecia).

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

12. Patients who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

4.2. Exclusion Criteria

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

1. Prior treatment with any CDK inhibitor, or fulvestrant, or with everolimus, or any agent whose mechanism of action is to inhibit the PI3K-mTOR pathway.

2. Patients with advanced/metastatic, 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 Central Nervous System (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 (eg, radiotherapy, stereotactic surgery) and are clinically stable off anticonvulsants and steroids for at least 4 weeks before randomization.

4. Current use of food or drugs known to be potent CYP3A4 inhibitors, drugs known to be potent CYP3A4 inducers (for examples, see the Prohibited Medications section), and drugs that are known to prolong the QT interval.

5. Major surgery, chemotherapy, radiotherapy, or other anti-cancer therapy within 2 weeks before randomization. Patients who received prior radiotherapy to ≥25% of bone marrow are not eligible independent of when it was received.

6. 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.

7. QTc interval >480 msec (based on the mean value of the triplicate ECGs), family or personal history of long or short QT syndrome, Brugada syndrome or known history of QTc prolongation or Torsade de Pointes.

8. Any of the following within 6 months of randomization: myocardial infarction, severe/unstable angina, ongoing cardiac dysrhythmias of NCI CTCAE Grade ≥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.

9. Impairment of gastro-intestinal (GI) function or GI disease that may significantly alter the absorption of palbociclib, such as history of GI surgery with may result in intestinal blind loops and patients with clinically significant gastroparesis, short bowel syndrome, unresolved nausea, vomiting, active inflammatory bowel disease or diarrhea of CTCAE Grade >1.

10. Prior hematopoietic stem cell or bone marrow transplantation.

11. Known abnormalities in coagulation such as bleeding diathesis, or treatment with anticoagulants precluding intramuscular injections of fulvestrant or goserelin (if applicable).

12. Known or possible hypersensitivity to fulvestrant, goserelin, any of their excipients or to any palbociclib/placebo excipients.

13. Known human immunodeficiency virus infection.

14. 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.

15. 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 patients who are Pfizer employees directly involved in the conduct of the trial.

16. Participation in other studies involving investigational drug(s) (Phases 1-4) within 4 weeks before randomization in the current study.

4.3. Randomization Criteria

- Patients will be randomized into the study provided they have satisfied all patient selection criteria.
- Prior to randomization, the site will complete a Pre-Randomization form which must be approved by the sponsor. On this form, information needed to stratify the patient must be identified and completed prior to randomizing the patient.

- The investigators or their pre-specified designee will randomize eligible patients by interactive randomization technology (IRT) as described in the Study Reference Manual.
- 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 within the site coordinator's manual.

To facilitate access to appropriately qualified medical personnel on study related medical questions or problems, patients 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 patients 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 patient directly and if a patient 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 and stratification factors, 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.

Eligible patients will be randomly assigned in a 2:1 ratio to either the experimental arm: palbociclib plus fulvestrant, or the control arm: placebo plus fulvestrant, stratified according to sensitivity to prior hormonal therapy, menopausal status at study entry, and presence of visceral metastases.

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

At the initiation of the trial, the trial site will be instructed on the method for breaking the blind. The method will be either a manual or electronic process. 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, 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 PD.

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 experimental drugs used in the course of this trial are palbociclib or placebo. In addition, all patients will receive fulvestrant (Faslodex®) administered at the study site. All three medications will be supplied by the sponsor. Goserelin is administered as per local standard of care and is not a study drug.

5.3.1. Formulation and Packaging

5.3.1.1. Palbociclib (PD-0332991)/Placebo

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).

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

Table 1. Palbociclib/Placebo Capsule Characteristics

Dosage	Capsule color
75 mg	Sunset Yellow
100 mg	Caramel/Sunset Yellow
125 mg	Caramel

5.3.1.2. Fulvestrant

Commercially available fulvestrant, 50mg/mL solution, will be supplied to sites by the sponsor. Complete information about fulvestrant formulation can be found in the local SPC for Faslodex.

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. Unused returned medication MUST NOT be re-dispensed to patients.

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 a single 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.

Patients will receive a drug diary to document palbociclib/placebo intake, and an administration card with information about storage and administration of palbociclib/placebo. The completed diary must be returned to the site at the next study visit.

5.3.2.2. Fulvestrant

Fulvestrant (Faslodex®) is supplied as two 5-mL clear neutral glass (Type 1) barrels, each containing 250 mg/5 mL of fulvestrant solution for intramuscular injection and fitted with a tamper evident closure. The syringes are presented in a tray with polystyrene plunger rod and safety needles (SafetyGlideTM) for connection to the barrel.

Refer to the local SPC for fulvestrant (Faslodex®) for instructions and steps necessary for drug preparation and administration. Drug preparation and administration will be performed at the site by a physician, registered nurse or other qualified health care provider.

Should goserelin be self-administered by the patient at home, patient will receive also a second drug diary to document goserelin injection. The completed diary must 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 the patient diary.

Patients should take palbociclib/placebo with food. Palbociclib/placebo will be administered orally once a day for 21 days followed by 7 days off treatment for each 28-day cycle. No time window is to be considered for treatment schedule of palbociclib/placebo. Prior palbociclib administration hematology tests must meet retreatment criteria (Section 5.3.4.2.2).

Patients experiencing investigational product related toxicity may have their dose modified according to the Dose Modification Section.

General rules for palbociclib/placebo administration:

- 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 the Medication Errors Section for further details on medication errors and overdose.

5.3.3.2. Fulvestrant

Fulvestrant 500 mg will be administered intramuscularly into the buttocks slowly (1-2 minutes per injection) as two 5 mL injections, one in each buttock. Drug preparation and administration will be performed at the site by a physician, registered nurse or other qualified health care provider. Refer to the local for Faslodex® for detailed administration instructions.

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 palbociclib/placebo may need to be adjusted as described in the following sections. Dose adjustment is permitted for palbociclib/placebo only. The fulvestrant dose cannot be adjusted; its dosing can only be delayed or interrupted.

Depending on the nature of the toxicity observed, treatment interruption may be required for 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.

The start of a cycle is defined as the day when palbociclib/placebo administration begins, starting with the first palbociclib/placebo dose at baseline (Cycle 1, Day 1). In case of palbociclib/placebo dose delays, administration of fulvestrant and goserelin will continue according to the pre-planned schedule.

Every effort should be made to synchronize Day 1 of palbociclib/placebo administration with the first injection of fulvestrant (and with the first on-study goserelin injection, if applicable and if administered at the study site) and other study related activities according to the SCHEDULE OF ACTIVITIES table.

5.3.4.1. Fulvestrant

No dose adjustment for fulvestrant is permitted. A single fulvestrant injection can be skipped in case of a fulvestrant-related toxicity or dosing can be delayed. Treatment delay for fulvestrant-related toxicities will be performed as per the investigator's best medical judgment, but by no more than 7 days. If delay of longer than 7 days is required then the dose should be skipped. In the event of a toxicity requiring dosing delay of palbociclib/placebo, fulvestrant can also be delayed by a maximum of 7 days.

Fulvestrant should not be administered if the platelet count is $<50{,}000/mm^3$.

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 followed by dose reduction, if required.

- Between cycles: next cycle administration may be delayed due to persisting toxicity when a new cycle is due to start.

- At start of the new 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 fulvestrant monotherapy as per the investigator's discretion.

5.3.4.2.1. Dosing Interruptions/Delays

Patients experiencing the following adverse events will have their treatment with palbociclib/placebo interrupted/delayed until criteria for retreatment are met:

- Uncomplicated Grade 3 or 4 neutropenia (ANC<1000/mm^3).

- Grade 3 or 4 neutropenia (ANC<1000/mm^3) associated with a documented infection or fever ≥38.5°C.

- Grade 3 or 4 thrombocytopenia (Platelet <50,000/mm^3).

- Non-hematologic toxicity persisting despite optimal medical treatment if either Grade 2 lasting more than 3 weeks, or Grade ≥3 (including, nausea, vomiting, and diarrhea). Patients should not hold or discontinue palbociclib/placebo for non-hematological side effects potentially or likely related to concomitant antihormonal therapy (eg, Grade 3 or long lasting Grade 2 joint pain) as per the investigator's judgment.

- Grade 3 QTc prolongation (QTc ≥501 msec on at least two separate ECGs).

- Concurrent >3x ULN ALT and 2x ULN Total Bilirubin. If those occur, the dose needs to be held while the cause is being investigated.

Doses should be held until toxicity resolution. Appropriate follow up assessments, as defined by the investigator, should be undertaken until adequate recovery occurs. Criteria required before treatment can resume are described in the Retreatment Criteria Section.

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 in the initiation of the subsequent cycle. A new cycle only starts when the retreatment criteria listed below are met and blinded study treatment may be administered, otherwise initiation of the new cycle must be delayed until such criteria are met.

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 treatment 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. In these cases, Day 1 procedures performed before the dose of palbociclib/placebo of the new cycle will be reported in the CRF at Day 1 of the new 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 the Dose Reductions Section unless an alternative plan is expressly agreed upon 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 >3 weeks, treatment resumption will be decided in consultation with the sponsor.

5.3.4.2.2. Retreatment Criteria

Retreatment with palbociclib/placebo 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 ≥50,000/mm^3.
- ANC ≥1000/mm^3 and no fever.
- Grade ≥3 non-hematologic AEs (including nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment), have recovered to Grade ≤1 or baseline.
- QTc ≤500 msec and potential reversible causes (eg, electrolyte imbalance, concomitant medications known to prolong QTc) corrected. If QTc remains above 480 msec, treatment may re-start but a cardiologist should be consulted and the ECG monitored more frequently as per the investigator's best medical judgement until QTc ≤480 msec.

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

If the retreatment parameters are met within 3 weeks of treatment interruption (which may include dose holding due do toxicity, the scheduled week off treatment and up to 7 days of cycle delay), palbociclib/placebo may be resumed. Refer to the Dose Reductions section below for adverse events requiring dose reduction at the time of treatment resumption.

If these parameters have not been met after 3 weeks of dosing interruption, the patient should permanently discontinue palbociclib/placebo treatment. Treatment resumption for patients recovering from treatment-related toxicity after >3 weeks of treatment interruption but deemed to be suitable for a trial of lower dose, is recommended but left at the investigator's discretion and upon discussion and agreement with the sponsor (see below for suggested dose adjustments).

5.3.4.2.3. Dose Reductions

No specific dose adjustments are recommended for Grade 1 or short lasting (<3 weeks) treatment-related Grade 2 toxicity. However, investigators should always manage their patients according to their medical judgment based on the individual clinical circumstances.

In case of a Grade 2 toxicity lasting for >3 weeks or a Grade ≥3 toxicity (both assessed in the presence of maximum supportive care as judged by the investigator), dose reduction is recommended for the subsequent cycles. Dose reduction of palbociclib/placebo by one, and, if needed, by two dose levels (Table 2) is recommended depending on type and severity of the toxicity. Patients requiring more than two dose reductions will be allowed to receive 75 mg/day for 2 weeks on followed by 2 weeks off study treatment (if, per the investigator's judgment, and in consulation with the sponsor, such a change in schedule is manageable and preferable to permanent palbociclib/placebo discontinuation and treatment continuation with fulvestrant only). 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)	Fulvestrant monthly dosing schedule
Starting dose	125 mg/d	2x 250 mg/injection
-1	100 mg/d	2x 250 mg/injection
-2	75 mg/d*	2x 250 mg/injection

* Palbociclib/placebo dose de-escalation below 75 mg/d is not allowed, but the schedule may be changed to 75 mg/day two weeks on followed by two weeks off (2/2 schedule).

Palbociclib/placebo dose modifications for treatment-related toxicities requiring treatment interruption/delay despite optimal medical treatment are described in Table 3.

Table 3. Palbociclib/Placebo Dose Modifications for Treatment-Related Toxicities

Toxicity	Palbociclib/Placebo Treatment at:
Uncomplicated Grade 3 neutropenia *(ANC ≥500 - <1000/mm^3)*	Same dose level; ↓ 1 dose level if neutrophil recovery is delayed beyond 7 days *, **
Grade 3 neutropenia (*ANC<1000/mm^3*) **associated with a documented infection or fever ≥38.5°C**	↓ 1 Dose Level; ↓ 2 dose levels*** if neutrophil recovery is delayed beyond 7 days *
Grade 4 neutropenia (*ANC<500/mm^3*)	↓ 1 Dose Level; ↓ 2 dose levels*** in case of recurrent grade 4 event *
Grade 3 or 4 thrombocytopenia (*Platelet count <50,000/mm^3*)	↓ 1 Dose Level; ↓ 2 dose levels*** in case of recurrent grade ≥3 event
Grade ≥3 non-hematologic toxicity (*including, nausea, vomiting, diarrhea, and hypertension only if persisting despite optimal medical treatment*)	↓ 1 Dose Level; ↓ 2 dose levels***, if repeated toxicity is seen in the next cycle or if recovery from grade 3 is delayed beyond 7 days *

* If recovery of neutrophils to ≥1000/*mm^3* or platelet count to ≥50,000/*mm^3* takes longer than 2 weeks (which may include dose holding due do toxicity, the scheduled week off treatment and up to 7 days of cycle delay), then reduce by 2 dose levels.

** If uncomplicated Grade 3 neutropenia recurs in 2 consecutive cycles, after recovery as per retreatment criteria (ANC ≥1000/mm3 and no fever), treatment may restart at the next lower dose level at investigator's discretion.

*** If no further dose reduction is possible (ie, patient is already receiving 75 mg/d according to schedule 3/1) consider changing the schedule to 75/mg/d 2 weeks on/2 weeks off), or discontinue palbociclib/placebo and continue with fulvestrant alone.

5.3.4.2.4. QTc prolongation management

In the event of QTc prolongation of >480 and ≤500 msec, possible 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 with the potential to prolong the QT interval [see Appendix 3]).

Dose modifications in the event of QTc prolongation are provided in Table 4.

Table 4. Palbociclib/Placebo Dose Modifications in the Event of QTc Prolongation

	Toxicity (NCI CTCAE Grade, Version 4.0)		
	Grade 2 QTc prolongation (>480 and ≤500 msec)	**Grade 3 QTc prolongation** (≥501 msec)	**Grade 4 QTc prolongation** (≥501 msec or >60 msec change from baseline AND life-threatening signs including Torsades de Pointes)
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 same dose level (1)	Treat reversible cause Withhold treatment until QTc ≤500 msec Resume treatment at the same dose level. Monitor ECG more frequently as per investigator's best medical judgment until QTc ≤480 msec.	Permanently discontinue palbociclib/placebo
No reversible cause identified	Consult cardiologist and initiate more frequent ECG monitoring according to investigator's best medical judgment until QTc ≤480 msec; Continue at the same dose level (1)	Withhold treatment until QTc ≤500 msec Resume treatment at the next lower dose level (2) Consult cardiology and monitor ECG more frequently as per investigator's best medical judgment until QTc ≤480 msec.	Permanently discontinue palbociclib/placebo

1. If the QTc remains >480 msec and ≤500 msec for 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 recurs after one dose reduction, further dose adjustment 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

Medication errors may result in this study from the administration or consumption of the wrong product, 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 CRF which is a specific version of the 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 is captured on the medication error version of the adverse event (AE) page, and if applicable, any associated AE(s) are captured on AE CRF page.

5.3.6. Compliance

Patients will be required to return all bottles of palbociclib/placebo 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 during the study. Dose adjustments must follow instructions provided in the dose adjustment guidelines section.

Fulvestrant will be administered by qualified study personnel at the site in accordance with the fulvestrant label. Fulvestrant administration will be documented on the corresponding study drug administration CRF.

5.4. Drug Storage and Drug Accountability

Storage conditions stated in the Single Reference Safety Document (ie, Investigator's Brochure (IB), United States Package Insert (USPI), Summary of Product Characteristics (SPC), or Local Product Document (LPD)) will 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. These include thermometers for both the room storage and refrigerator storage. Any temperature excursions must be reported to the sponsor. The investigational products 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 fulvestrant) must be quarantined and not used until the sponsor provides documentation of permission to use the investigational products.

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 Storage and Accountability

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.

5.4.1.1. Fulvestrant Storage and Accountability

Fulvestrant must be stored according to the instructions described in the local package insert.

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 products 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 fulvestrant (and goserelin for pre- and perimenopausal women) will be permitted during the active treatment phase. In general, any drugs containing "for the treatment of breast cancer" on the product label are not permitted on study.

- Potent (Strong/Moderate) 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 strong CYP3A inhibitors and inducers may change the plasma concentrations of palbociclib in humans. The concurrent use of the following compounds is not allowed in the study:

  - Strong CYP3A inhibitors, including, boceprevir, clarithromycin, conivaptan, delavirdine, indinavir, itraconazole, ketoconazole, lopinavir, mibefradil, miconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, suboxone, telaprevir, telithromycin, voriconazole, and grapefruit, grapefruit juice or any product containing grapefruit,

  - Strong CYP3A inducers, including carbamazepine, phenytoin, primidone, rifampin, rifapentin, and St. John's wort,

  - Only the following moderate CYP3A inhibitors**:** amprenavir, atazanavir, diltiazem, erythromycin, fosamprenavir, verapamil and moderate CYP3A inducers: felbamate, nevirapine, phenobarbital, rifabutin.

- Drugs known to cause QT interval prolongation are prohibited during the active treatment phase (refer to Appendix 3).

- 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.

- Anticoagulants: if patient is receiving anticoagulants, refer to the Faslodex® PI.[44]

- Proton-pump inhibitors (PPIs): The concomitant use of PPIs with palbociclib/placebo is prohibited, including but not limited to dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole. Should the use of PPIs be required for a given patient, please contact the Sponsor for an assessment of the best treatment choice. Alternative acid-reducing recommendations are provided in Section 5.5.3.

Strong/moderate CYP3A inhibitors/inducers and PPIs listed above, are now permitted ONLY for patients who permanently discontinued palbociclib/placebo and continue on fulvestrant monotherapy only.

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 one of the following treatments is deemed necessary, consultation and agreement with the sponsor is required prior to treatment initiation.

- The concurrent use of dexamethasone is not recommended.

- 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.

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 patient'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 ASCO guideline.[59] 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 a reasonable alternative.

- Erythropoietin may be used at the investigator's discretion for the supportive treatment of anemia.

- 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_2-receptor antagonists (including, but not limited to, cimetidine, famotidine, nizatidine, ranitidine); palbociclib/placebo treatment should occur at least 10 hours after H_2-receptor antagonist evening dose and 2 hours before H_2-receptor antagonist morning dose.

5.6. Concomitant Radiotherapy or Surgery

Any concurrent radiotherapy (except palliative radiotherapy as specified below) or cancer-related surgery is 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 the Screen Failure Section) 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.

One cycle consists of 28 days. A cycle could be longer than 28 days if persistent toxicity delays initiation of the subsequent cycle.

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); 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 SCHEDULE OF ACTIVITIES.

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.

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.

Any suspicious abnormalities (ie, hotspots) identified on the bone scans at baseline and on subsequent bone scans shall be confirmed by X-ray, CT or MRI to confirm its tumor-related malignancy. 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, Week 8 ±7 days from randomization) as for all other lesions. Areas that have received palliative radiotherapy cannot be used to assess response to study treatment.

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.

Once Amendment 1 is approved, a minimum of 100 lens grading evaluable, newly enrolled 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 - pupil dilated examination).

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 7.2.2. Ocular Safety Assessments for further details on these procedures. Sites and patients will be informed as soon as these ocular examinations are no longer required for the study.

For details on baseline procedures, see the SCHEDULE OF ACTIVITIES.

6.2. Screen Failure

Patients who completed the informed consent process but do not meet one or more eligibility criteria and therefore are not randomized will be considered as screen failures.

For all screen failures, clinical sites must provide the following information using the appropriate CRFs: screening number, demographic data as well as the final patient summary including the reason for failing the screening process.

Ineligible patients are allowed to be re-screened a single time only. When re-screened they must be reconsented and will be assigned a new study patient identification (ID).

6.3. Active Treatment Phase

For details on procedures during the active treatment phase, see the SCHEDULE OF ACTIVITIES tables.

6.4. End of Treatment Visit

The end of treatment visit will be performed as soon as possible but no later than 4 weeks from last dose of investigational products and prior to the initiation of any new anticancer therapy.

Obtain these assessments if not completed during the previous 4 weeks on study.

For details on procedures to be performed at the End of Treatment visit, see the SCHEDULE OF ACTIVITIES tables.

6.5. Follow-up Visits

6.5.1. 28-day Post-treatment Follow-up

Patients who discontinue study treatment should be contacted 28 calendar days (+/- 7 days) after discontinuation of investigational product (palbociclib/placebo or fulvestrant) to assess if there have been any new adverse events and any change to any previously reported adverse events. This follow-up should occur 28 calendar days (±7 days) regardless of any new anti-cancer therapy that may have started. Telephone contact is acceptable. The telephone contact will be documented in the patient's file.

6.5.2. Survival Follow-up

After discontinuation of study treatment, post-study survival status (including start, stop and type of post study anticancer therapies, tumor response and date of progression of the disease during or after the subsequent anticancer therapy) will be collected every 3 months from the last dose of study treatment going forward after approval of Amendment 3 Telephone contact is acceptable.

For details on follow-up visit procedures, see the SCHEDULE OF ACTIVITIES tables.

6.6. Patient Withdrawal

6.6.1. 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, ie, discontinues treatment of palbociclib/placebo AND fulvestrant. 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);
- Symptomatic deterioration (ie, global deterioration of health status without objective evidence of disease progression);
- Need for new or additional anticancer therapy not specified in the protocol;
- Unacceptable toxicity;
- Investigator's conclusion that discontinuing therapy is in the patient's best interest;
- Lost to follow-up;

- Patient choice to withdraw from treatment (follow-up permitted by patient);
- Withdrawal of patient consent (cessation of follow-up);
- Death.

* Patients may continue treatment as assigned at randomization beyond the time of 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. In this case, the patient would continue with routine safety-relevant assessments as per the SCHEDULE OF ACTIVITIES during the treatment period.

Patients 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 products 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.

6.6.2. 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 patient consent (ie, refuses tumor assessments or follow-up on survival status after the 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 returns all unused investigational product(s), request the patient returns for a final visit, if aplicable, and follow-up with the patient regarding any unresolved AEs.

Data to be collected for the end of study treatment/withdrawal are described in the SCHEDULE OF ACTIVITIES.

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 footnotes to the SCHEDULE OF ACTIVITIES.

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. Pregnancy Testing

For women of childbearing potential, a serum pregnancy test, with a sensitivity of at least 25 mIU/mL will be performed before starting investigational products at screening and repeated at the baseline visit. A negative pregnancy result is required before the patient may receive the study treatment.

No routine pregnancy test will be carried out after baseline as patients will be rendered postmenopausal by the administration of goserelin and fulvestrant. However, pregnancy tests will also be done whenever a potential pregnancy is suspected. In the case of a positive hCG test, the patient will be withdrawn from study medication but may remain on study for survival follow up. Pregnancy tests may also be repeated as per request of Institutional Review Board (IRB)/IECs or if required by local regulations.

In this protocol, a woman is defined of childbearing potential if pre- or perimenopausal at the time of consenting to study enrollment (see Inclusion Criterion n.1 for details).

Additionally, for women who are <60 years old and have been amenorrheic for at least 12 consecutive months, serum estradiol and FSH levels will be analysed pre-dose at baseline to confirm postmenopausal status.

7.2. Efficacy Assessments

7.2.1. Tumor Assessments

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:

- CT or MRI scan of the chest, abdomen, and pelvis.

- 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 as only site of disease 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 the Screening Section for further details on timing allowance for baseline brain and bone scans.

Post-baseline tumor assessments. Upon approval of Amendment 3, tumor assessments/imaging studies will be performed according to local practice.

If tumor assessments are scheduled as per the original protocol, upon approval of Amendment 3, they can be performed at a different schedule if this is common practice at that institution or it is recommended by the physician according to the patient's clinical conditions.

Upon approval of Amendment 3, selection of imaging studies will depend on treating physician and radiologist as per local practice. RECIST 1.1 may be used to evaluate imaging assessments but will not be mandatory. Evaluation of imaging studies will be conducted as per the practice at the institution.

Tumor lesions [ie, target lesion(s), non-target lesion(s) and target lymph node(s)] will no longer be recoreded in the CRF, nor will the RECIST assessments. Only the date of progression of disease will be recorded.

7.2.2. Ocular Safety Assessments

Amendment 3 will not affect ocular safety assessments which will continue to be collected as per the SCHEDULE OF ACTIVITIES.

7.2.2.1. 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 +/– 1.25 diopters compared with the screening examination will be reported as an adverse event.

7.2.2.2. 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).

7.2.2.3. 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[a]	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[a]	No cells	1 to 5 cells	6 to 10 cells	11 to 20 cells	>20 cells

[a] Evaluation of Anterior Chamber Inflammation (modified from Hogen et al.)[60]:

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 45o to the plane of the iris.

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

7.2.2.4. Lens Grading

When doing lens grading, graders must be aware of their bias, either conscious or unconscious, 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.[61] (Appendix 8). 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 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.

7.2.2.5. 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.

7.2.3. Independent Review of Disease Assessments

Upon approval of Amendment 3, the third-party core imaging laboratory will stop performing blinded independent central review (BICR) of PFS data of the subgroup of patients that was randomly selected. The investigators will stop sending the image studies to the core imaging laboratory.

7.2.4. Overall Survival

Upon approval of Amendment 3, after the End of Treatment visit, survival status will be collected in all patients (telephone contact is acceptable) every 3 months from the last dose of study treatment going forward. Information on start, stop and type of subsequent anticancer therapy as well as the date of disease progression during or after the anticancer therapy will also be collected.

7.3. Safety Assessments

Safety assessment will consist of monitoring of all AEs, including SAEs, regular monitoring of hematology, serum chemistry, and routine monitoring of ECGs, physical examinations, vital signs, and ECOG performance status.

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

Baseline cancer 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.

7.3.1. Laboratory Safety Assessments

Blood tests include the following:

Hematology Panel		Blood Chemistry Panel		Hormonal Status (if applicable)	
1	Hemoglobin	**1**	ALT	**1**	Serum Beta-HCG*
2	Platelets	**2**	AST	**2**	Serum estradiol**
3	WBC	**3**	Alkaline Phosphatase	**3**	FSH**
4	Absolute Neutrophil Count	**4**	Sodium		
		5	Potassium		
		6	Total Calcium		
		7	Magnesium		
		8	Total Bilirubin		
		9	BUN or Urea		
		10	Serum Creatinine		
		11	Albumin		
		12	Hemoglobin A1c		

* For women of childbearing potential.
** For postmenopausal status confirmation of women <60 years old who have been amenorrheic for at least 12 consecutive months.

Blood tests will be drawn at the time points described in the SCHEDULE OF ACTIVITIES table, and analyzed at local laboratories.

Hematology tests must meet retreatment criteria prior to administering palbociclib/placebo.

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.

7.3.2. Electrocardiogram

All Electrocardiograms (ECGs) will be performed using a 12-lead (with a 10-second rhythm strip) tracing. ECG measurements will include PR interval, QT interval, RR interval, and QRS complex. It is preferable that the machine used has a capacity to calculate the standard intervals automatically.

ECG interval readings by the ECG recorder's algorithm will be read and interpreted at the investigational site for eligibility determination and patient safety monitoring and documentation stored in the source documents.

Additional ECGs may be performed as clinically indicated at any time.

For the purpose of the study, triplicate ECGs are defined as three consecutive ECGs performed approximately 2 minutes apart at the protocol specified timepoints (see SCHEDULE OF ACTIVITIES table for details) to determine the mean QTc interval.

Refer to the Dose Modification Section for details on dose management in case of abnormal ECGs considered related to investigational product.

7.3.3. Other Safety Assessments

A full physical examination including an examination of all major body systems and breasts, height (at screening only), weight, blood pressure and pulse rate which may be performed by a physician, registered nurse or other qualified health care provider, will be required at screening, Day 1 of every cycle and End of Treatment/Withdrawal visit.

Symptom directed physical examinations, blood pressure and pulse rate may be performed at interim cycle visits at the Investigator's discretion.

Performance Status: The ECOG performance status scale will be used (see Appendix 2).

7.4. Pharmacokinetic Assessments

In the initial approximately 40 patients included in the early safety review, plasma PK samples will be drawn at predose on Day 1 and Day 15 of Cycle 1 and Cycle 2, and Day 1 of Cycle 3 for DDI assessments.

Review of the PK data will be done by the E-DMC once all planned PK samples from theseapproximately 40 patients have been analyzed. The study will continue while PK analysis and data review are ongoing. Details of the analysis (along with other safety data included in the early safety review) will be provided in the E-DMC charter.

For patients who receive palbociclib and fulvestrant, PK samples will be analyzed for palbociclib and fulvestrant concentrations. For patients who receive fulvestrant and placebo, PK samples will be analyzed for fulvestrant. For pre- and perimenopausal women also receiving goserelin, PK samples will be analyzed for palbociclib, fulvestrant AND goserelin concentrations. For patients who receive fulvestrant, goserelin and placebo, PK samples will be analyzed for fulvestrant and goserelin. Concentrations of fulvestrant and Goserelin will be compared between the palbociclib and placebo subgroups. The concentrations of palbociclib will be compared with historical data.

In these approximately 40 patients, two (combinations without goserelin) or three (combinations with goserelin) 3 mL samples of venous blood will be collected in appropriately labeled collection tubes for assessment of palbociclib, fulvestrant, and/or goserelin levels at the protocol-specified times, as described above.

In all other patients (not participating the early safety review), plasma concentrations will be drawn on Day 15 of Cycle 1 and Cycle 2 for palbociclib determination. These trough concentrations will be used for exposure/response analysis for safety and efficacy findings. From those patients, one 3 mL sample of venous blood will be collected in appropriately labeled collection tubes for assessment of palbociclib. Samples will be analyzed using validated analytical methods in compliance with Pfizer standard operating procedures.

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 son 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 assessessments (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 missing dose should also be recorded in the CRF.

Additional PK blood samples for palbociclib and fulvestrant (and goserelin if applicable) may be collected 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.

7.5. Patient Reported Outcomes

Patient reported outcomes of health-related quality of life and health status will be assessed using the EQ-5D instrument, the EORTC QLQ-C30, and EORTC QLQ-BR23 (Appendix 5, Appendix 6, Appendix 7, respectively).

Patients will complete each instrument at pre-dose on Day 1 of Cycles 1-4, then on Day 1 of every other subsequent Cycle starting with Cycle 6 (eg, Cycles 6, 8, 10, 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 instruments will be given to the patient in the appropriate language for the site.

7.5.1. EuroQol Health Utilities Index EQ-5D

The EuroQol-5D (EQ-5D) (version 3L) (see Appendix 5) 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.

7.5.2. EORTC QLQ-C30

The EORTC-QLQ-C30 (see Appendix 6) is a 30-item questionnaire composed of five multi-item functional subscales (physical, role, cognitive emotional, and social functioning), three multi-item symptom scales (fatigue, nausea/vomiting, and pain), a global health/quality of life (QOL) subscale, and six single items assessing other cancer-related symptoms (dyspnea, sleep disturbance, appetite, diarrhea, constipation, and the financial impact of cancer). The questionnaire employs 28 4-point Likert scales with responses from "not at all" to "very much" and two 7-point Likert scales for global health and overall QOL. For functional and global QOL scales, higher scores represent a better level of functioning and are converted to a 0 to 100 scale. For symptom-oriented scales, a higher score represents more severe symptoms.

7.5.3. EORTC QLQ-BR23

The EORTC-QLQ-BR23 (see Appendix 7) is a 23-item breast cancer-specific companion module to the EORTC-QLQ-C30 and consists of two functional scales (body image and sexuality); three symptom subscales (arm/hand, breast, and systemic side effects) and single items covering sexual enjoyment, distress at hair loss, and future perspective.

7.6. Biomarker Assessments

Tumor tissues are required from all patients for study participation.

HR and HER2 status for eligibility will be based on local results utilizing an assay consistent with local standards for entry into the trial and for reporting of the efficacy endpoints. Central assessment of ER, PR, and HER2 on suitable samples will be performed retrospectively at a qualified central laboratory.

A biomarker will be nominated as the primary marker for analysis using data external to the current study. The interaction between this primary marker (eg, pRb or other from a set of biomarkers to be analyzed) and benefit from palbociclib in terms of prolongation of PFS will be examined. In addition, other tumor tissue biomarkers, including DNA, RNA and protein analytes, will be analyzed to investigate possible associations with resistance/sensitivity to treatment with palbociclib. 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 are not limited to, CCND1 and CDKN2A gene copy number, cdk4 and cdk6 RNA expression, and Ki67, pRb, cyclin E and p16 protein expression. The relationship between centrally reported ER/PR and HER2 status and resistance/sensitivity to treatment with palbociclib will also be assessed.

All patients with archived samples need to provide a FFPE tissue blocks of adequate size to allow for three 0.6 mm diameter x 5 mm deep core punchesthat will be used to generate a tissue microarray. If FFPE tissue block cannot be provided, a minimum of 12 unbacked glass slides each containing an unstained 5-micron FFPE tissue section, will be required for patient participation. Archived FFPE specimen from the metastatic or recurrent tumor tissue will be collected and sent to the sponsor-designated central laboratories for assessment of biomarkers potentially associated with sensitivity and/or resistance to palbociclib (eg, Ki67, p16/CDKN2A, pRb, PIK3CA, CCNE1).

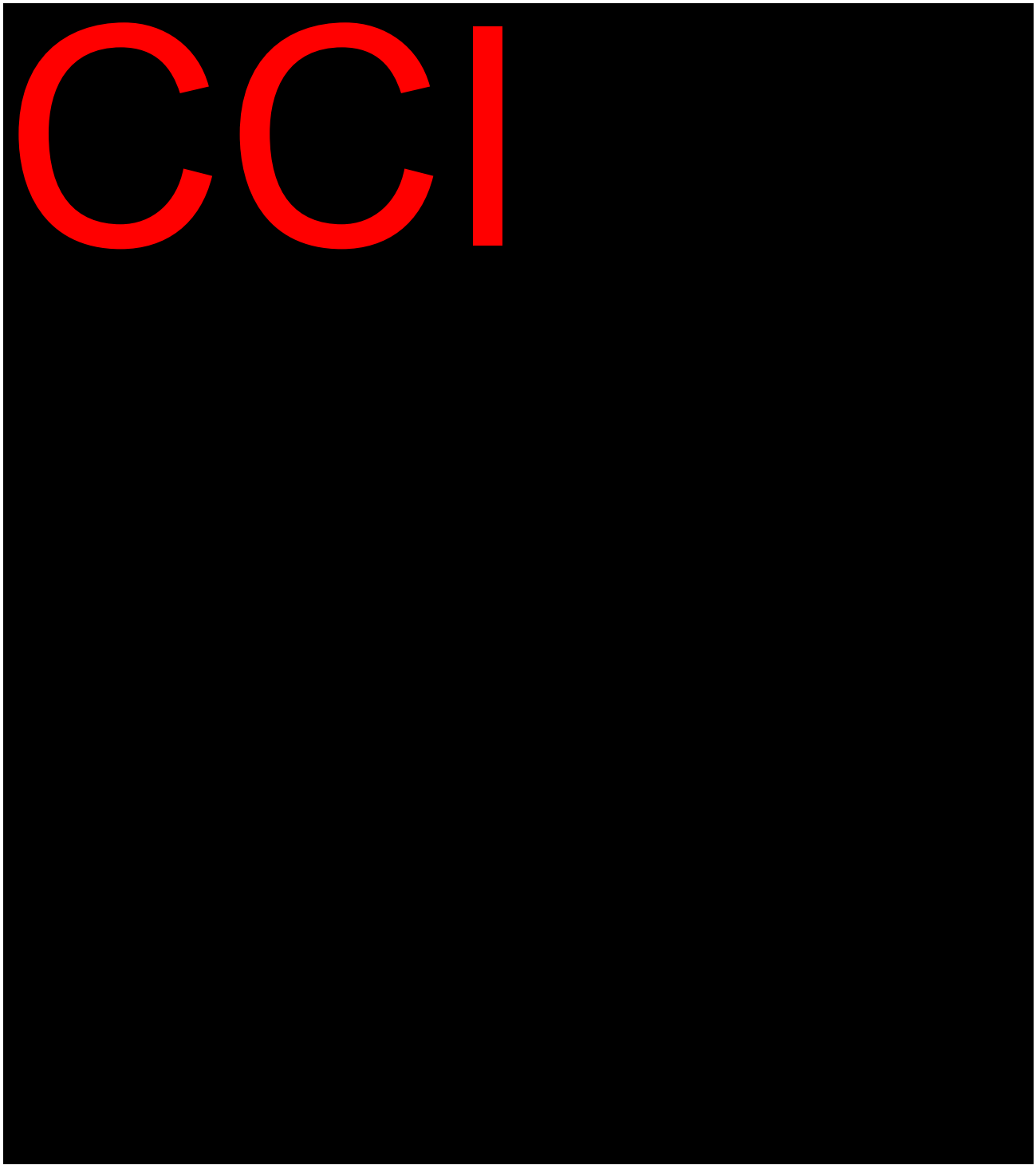
Plasma samples will be collected for analyses of circulating free DNA or RNA, and the relationship with resistance/sensitivity to treatment with Palbociclib/placebo.

If archived FFPE tissue from a recurrent tumor or distant metastasis is unavailable, a de novo biopsy is required for patient participation, except those with bone metastasis only, when, in the investigator's judgment, such biopsy is feasible and can be safely performed. Original diagnostic tumor tissue will be used for biomarker analyses in the event that patients have bone disease only. Patients who had surgery (but without neoadjuvant chemotherapy prior to surgery) within the last 3 years and relapsed while receiving adjuvant therapy may provide tissue from that surgery. Provision of de novo metastatic tissue in these cases is strongly encouraged but not mandated.

Detailed information about biomarker sample collection, preparation, storage, labeling, and shipment is indicated in the central laboratory manual.

7.6.1. Optional Tumor Tissue Biopsy for Molecular Profiling

An optional *de novo* 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.

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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 an 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 patient 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 the patient's last 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 breastfeeding;
- 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 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 for Adverse Events (CTCAE) 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 patient 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 the Section on Serious Adverse Event Reporting Requirements).

8.5.2. Potential Cases of Drug-Induced Liver Injury

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal 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 (potential 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 ≥3 times the upper limit of normal (X ULN) concurrent with a total bilirubin ≥2 X ULN with no evidence of hemolysis and an alkaline phosphatase ≤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 ≥2 times the baseline values and ≥3 X ULN, or ≥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 ≥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. For oncology studies 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, 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 infection and liver imaging (eg, biliary tract) may be warranted. 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 of 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 lab abnormality);
- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly physical exam);
- 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

GRADE	Clinical Description of Severity
0	No Change from Normal or Reference Range (This grade is not included in the Version 4.0 CTCAE 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 the 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 both unapproved/unlicensed products and for marketed products, an exposure during pregnancy occurs if:

1. 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).

2. A male 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 or study patient's partner 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 (SAE) Form and Exposure in Utero (EIU) Supplemental Form, regardless of whether an SAE has occurred. 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 EDP 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 the 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 the drug safety unit within 24 hours of the 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 investigator site file.

8.11. Withdrawal Due to Adverse Events (See also the Section on 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, 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 have been documented in a Statistical Analysis Plan (SAP), which have been 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. The planned data analysis in this section was performed when the study A5481023 (PALOMA-3) met its primary endpoint at the preplanned interim analysis from the data with the cutoff date of 05 December 2014. With the ongoing data collection of overall survival (OS) information, the planned OS interim analysis and final analysis will be performed based on the detailed plan described in the SAP.

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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/placebo or fulvestrant), 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

Efficacy analyses will be based on ITT population. Analysis of DR will be based upon the responders (CR or PR) from ITT population. All analyses will be performed by using SAS® Version 9.1.3 or higher.

All primary and secondary endpoints based on radiological (and photographical where applicable) assessments of tumor burden (ie, PFS, OR, DR, CBR) will be derived using the local radiologist's/investigator's assessment. Radiographic images (approximately 40%, randomly collected) and clinical information collected on-study will also be reviewed by a blinded independent third-party core imaging laboratory to verify investigator reported tumor assessments. This information will be used for supportive analyses.

In addition to analyses driven by the study objectives, subset analyses may be conducted, for example, by age, regions, race, performance status, line of therapy in metastatic setting, biomarkers, and others as deemed appropriate.

All of the above secondary analyses will be conducted at a one-sided 0.025 level of significance. Additional sensitivity analyses will be outlined in the SAP.

9.3.1. Analysis of Primary Endpoint

The primary endpoint is PFS 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 the duration of one 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. Patients with documentation of PD or death after an unacceptably long interval (ie, 2 or more incomplete or non-evaluable assessments) since the last tumor assessment will be censored at the time of last objective assessment that did not show PD.

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 factors used to conduct the stratified log-rank test for the primary analysis 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. CIs for the 25^{th}, 50^{th} and 75^{th} 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 and the stratified long-rank test (one-sided, α=0.025) will be used.

9.3.2. Analysis of Secondary Endpoints

Overall Survival (OS)

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. OS will be hierarchically tested for significance at the time of PFS analysis, provided the primary PFS endpoint is statistically significant at the interim and/or final analyses. 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 treatment 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% CI.

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 using the Greenwood's formula, and then back transformed to give a CI for the 1-year survival probability itself.

The 2-year and 3-year survival probabilities will be estimated similarly.

Objective Response (OR)

OR is defined as a complete response (CR) or partial response (PR) according to RECIST v.1.1 (Appendix 4) 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 CR or 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 OR (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 of 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. Refer to the end of Appendix 4 for definitions of Best Overall Response based upon RECIST v. 1.1.

Duration of Response (DR)

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 OR. 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.

Clinical Benefit Response (CBR)

CBR is defined as CR or PR or SD ≥24 weeks according to the RECIST version 1.1 (Appendix 4) recorded in the time period between randomization and disease progression or death of any cause.

The CBR rate on each randomized treatment arm will be estimated by dividing the number of patients with CR, PR, or SD ≥24 weeks by the number of patients randomized to the treatment arm. A 95% CI for the CBR rates will be provided. CBR 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 CBR 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.

Patient Reported Outcomes (PRO)

Breast cancer-specific quality of life scores and change from baseline scores will be compared between the treatment arms using a mixed model repeated measures 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.

In addition to the above analyses, an examination of the time to deterioration (TTD) composite endpoint will be carried out using survival analysis methods. A composite definition for deterioration based on death, tumor progression, and/or breast cancer-specific quality of life subscale MIDs may be used.

9.5. Analysis of Other Endpoints

Pharmacokinetic Analysis

For approximately the initial 40 patients included in the early safety review, the concentration data of palbociclib, fulvestrant and goserelin will be listed by analyte, patient, collection time and day and treatment arm (combination). Summary statistics will be provided for concentrations by analyte, collection time and day, and treatment arms (combination).

For all patients on the palbociclib treatment arm, palbociclib trough concentrations will be listed by patient, collection time and day, and unique combination. Summary statistics will be provided by collection time and day, and unique combination. If fulvestrant or goserelin does not have an effect on the palbociclib PK, an average of the two trough concentrations of palbociclib will be listed by patient for the corresponding combination, and summary statistics will be provided. If both fulvestrant and goserelin has no effect on palbociclib PK, summary statistics will be provided including average trough concentration from all patients

across combinations. The relationship between trough concentration and potential covariates will 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. Refer to Statistical Analysis Plan for details of the analyses.

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 SAP for details of the analyses. The results of these modeling analyses may be reported separately from the clinical study report.

Biomarker Analysis

For baseline continuous endpoint data, descriptive statistics, including the mean, standard deviation, median, minimum, and maximum values, will be provided by treatment arm.

For baseline categorical data, the number and percentage of patients in each category will be provided by treatment arm.

Appropriate statistical methods may be used to investigate any possible relationship of biomarker levels with palbociclib plus fulvestrant anti-tumor efficacy.

9.6. 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 v. 15.1) 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.

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.

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.

9.7. Interim Analysis

The study is designed to have one interim analysis. The interim analysis will be conducted to allow for early stopping of the study due to efficacy, and to allow for potential re-estimating the sample size of the trial based upon the primary endpoint of PFS. The safety of the combination will also be assessed at the interim analysis. The efficacy boundary of PFS will also be pre-specified. The Haybittle-Peto boundary[63,64] will be used (alpha=0.00135 is to be spent at interim analysis) in developing the efficacy boundary of the interim analysis of PFS. The total Type I error rate will be well preserved. Specific details regarding the efficacy boundary will be described in the SAP.

The interim analysis of PFS will be performed after approximately the first 143 patients have documented PD or death (approximately 60% of the total events expected). The information fraction (60% currently) for the interim analysis may be adjusted if needed. As appropriate, the sample size of the study may be adjusted using the method outlined by Cui, Hung, and Wang[65] and applied to the PFS endpoint. The technical details of sample size re-estimation approach will be pre-specified in a separate technical document that is to be shared only with the E-DMC before the interim analysis.

OS will be hierarchically tested for significance at the time of PFS analyses, provided the primary PFS endpoint is statistically significant at the interim and/or final PFS analyses.

Further details, along with a table of nominal alpha for the interim and final PFS analysis and for OS will be included in the SAP.

9.8. Data Monitoring Committee

The study will use an External Data Monitoring Committee (E-DMC). The E-DMC membership and governance is outlined in a separate charter.

The E-DMC will be responsible for ongoing monitoring of the efficacy and safety of patients in the study according to the Charter. The E-DMC will make a recommendation as to whether or not the trial should continue based on ongoing reviews of safety data. In addition,

the E-DMC will also evaluate interim efficacy data and make a recommendation regarding study continuation based on observed results of the study. 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, which may include summaries of aggregate analyses of endpoint events and of safety data which are not endpoints, to regulatory authorities, as appropriate. The sponsor will designate a biostatistician not affiliated with the project to prepare data for E-DMC review. Only if action or consultation with Health Authorities is required will other sponsor staff be involved. 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 agent 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 IRB/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 Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 and 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.

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, or his/her legal representative, 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 (ClinicalTrials.gov), 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

Pfizer posts clinical trial Basic Results on 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, Food and Drug Administration (FDA)-approved products, Pfizer posts results within one year of the primary completion date. For studies involving products approved in any country, but not FDA approved, Pfizer posts results one year from last patient, last visit:

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

Pfizer posts clinical trial results on 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 last subject last visit (LSLV) on or after 27-Sep-2007 for which Basic Results were posted on 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 Drug. 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, Institution 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. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010; 60: 277-300.

2. EBCTCG. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005; 365: 1687-1717.

3. Smith IE, Dowsett M. Aromatase inhibitors in breast cancer. N Engl J Med, 2003;348:2431-42.

4. National Comprehensive Cancer Network. Guidelines for patients: Breast Cancer. http://www.nccn.com/cancer-guidelines.html

5. Taylor CW, Green S, Dalton WS, et al. Multicenter randomized clinical trial of goserelin versus surgical ovariectomy in premenopausal patients with receptor positive metastatic breast cancer: An Intergroup study. Journal of Clinical Oncology 16:994-999, 1998.

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. Baselga J, Campone M, Piccart M, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. The New England journal of medicine 2012; 366: 520-529.

9. Finn RS, Crown JP, Boer K, et al. 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 (BC). Abstract# 100O, Annals of Oncology 23 (Supplement 2): ii43–ii45, 2012.

10. Sherr CJ, Roberts JM. CDK inhibitors: positive and negative regulators of G1-phase progression. Genes Dev. 1999; 13:1501-1512.

11. Van den Heuvel S, Harlow E. Distinct roles for cyclin-dependent kinases in cell cycle control. Science 1993; 262:2050-2054.

12. Weinberg, RA. The retinoblastoma protein and cell cycle control. Cell 1995; 81:323-330.

13. Harper JW, Adami GR, Wei N, et al. The p21 Cdk-interacting protein Cip1 is a potent inhibitor of G1 cyclin-dependent kinases. Cell 1993;75:805-16.

14. Koff A, Ohtsuki M, Polyak K, et al. Negative regulation of G1 in mammalian cells: inhibition of cyclin E-dependent kinase by TGF-beta. Science 1993; 260: 536-9.

15. Polyak K, Kato JY, Solomon MJ, et al. p27Kip1, a cyclin-Cdk inhibitor, links transforming growth factor-beta and contact inhibition to cell cycle arrest. Genes & development 1994;8:9-22.

16. Sherr CJ. D-type cyclins. Trends in biochemical sciences 1995;20:187-190.

17. Toyoshima H, Hunter T. p27, a novel inhibitor of G1 cyclin-Cdk protein kinase activity, is related to p21. Cell 1994;78:67-74.

18. Lukas J, Parry D, Aagaard L, et al. Retinoblastoma-protein-dependent cell-cycle inhibition by the tumour suppressor p16. Nature 1995;375:503-6.

19. Medema RH, Herrera RE, Lam F, Weinberg RA. Growth suppression by p16ink4 requires functional retinoblastoma protein. Proceedings of the National Academy of Sciences of the United States of America 1995;92:6289-93.

20. Butt AJ, McNeil CM, Musgrove EA, Sutherland RL. Downstream targets of growth factor and oestrogen signalling and endocrine resistance: the potential roles of c-Myc, cyclin D1 and cyclin E. Endocrine-related cancer 2005; 12 Suppl 1: S47-59.

21. Altucci L, Addeo R, Cicatiello L, et al. 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.

22. 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; 46:450-45.

23. 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.

24. 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.

25. Altucci L, Addeo R, Cicatiello L, et al. 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.

26. Foster JS, Wimalasena J. Estrogen regulates activity of cyclin-dependent kinases and retinoblastoma protein phosphorylation in breast cancer cells. Molecular endocrinology 1996; 10: 488-498.

27. Planas-Silva MD, Weinberg RA. Estrogen-dependent cyclin E-cdk2 activation through p21 redistribution. Molecular and cellular biology. 1997;17:4059-4069.

28. Prall OW, Sarcevic B, Musgrove EA, et al. 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. The Journal of biological chemistry. 1997; 272:10882-10894.

29. 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. Molecular and cellular biology 1996;16:6917-6925.

30. Watts CK, Brady A, Sarcevic B, et al. Antiestrogen inhibition of cell cycle progression in breast cancer cells in associated with inhibition of cyclin-dependent kinase activity and decreased retinoblastoma protein phosphorylation. Molecular endocrinology 1995;9:1804-1813.

31. Thangavel C, Dean JL, Ertel A, et al. Therapeutically activating RB: reestablishing cell cycle control in endocrine therapy-resistant breast cancer. Endocrine-related cancer 2011;18: 333-345.

32. Yu Q, Sicinska E, Geng Y, et al. Requirement for CDK4 kinase function in breast cancer. Cancer cell. 2006; 9: 23-32.

33. Konecny GE, Winterhoff B, Kolarova T, et al. Expression of p16 and retinoblastoma determines response to CDK4/6 inhibition in ovarian cancer. Clinical cancer research: an official journal of the American Association for Cancer Research 2011; 17: 1591-1602.

34. Fry DW, Harvey PJ, Keller PR, et al. Specific inhibition of cyclin-dependent kinase 4/6 by PD 0332991 and associated antitumor activity in human tumor xenografts. Molecular cancer therapeutics. 2004; 3: 1427-1438.

35. Cen L, Carlson BL, Schroeder MA, et al. p16-Cdk4-Rb axis controls sensitivity to a cyclin-dependent kinase inhibitor PD0332991 in glioblastoma xenograft cells. Neuro-Oncology 2012; 14: 870-881.

36. Finn RS, Dering J, Conklin D, et al. PD-0332991, 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.

37. 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.

38. DeMichele A, Clark A, Tan KS, et al. A phase II trial of the CDK 4/6 inhibitor PD0332991 in advanced breast cancer. ASCO 2013, Abstract 519.

39. Slamon DJ, Hurvitz SA, Applebaum S, et al. Phase I study of PD-0332991, 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).

40. Finn RS, Crown JP, Boer K, et al. Preliminary results of a randomized Phase 2 Study of PD 0332991, a Cyclin-Dependent Kinase 4/6 inhibitor, in combination with letrozole for first line treatment of patients with postmenopausal, ER-positive, HER2-negative advanced breast cancer. Poster; SABCS; Dec 6-10, 2011; San Antonio, Texas.

41. Turner NC, Ro J, Andre F, et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. The New England journal of medicine; online publication Jun 01, 2015.

42. Harvey JM, Clark GM, Osborne CK, Allred DC. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicitng response to adjvuant endocrine therapy in breast cancer. J Clin Oncol. 1999 Vol 17, No5, pp 1474-11481.

43. Wood WC, Muss HB, Solin LJ, et al. Malignant tumors of the breast. In: DeVita VT, Hellman S, Rosenberg SA, editor(s). Cancer: principles and practice of oncology. Philadelphia (PA): Lippincott-Williams & Wilkins; 2005. p. 1415-77.

44. Product Information: Faslodex®, fulvestrant (injection). AstraZeneca Pharmaceuticals, Wilmington, Delaware, (PI revised 07/2002) reviewed 12/2002.

45. Kuter I, Sapunar F and McCormack P. Pharmacokinetic profile of fulvestrant 500 mg vs 250 mg: Results from the NEWEST study. J Clin Oncol. 2008 ASCO Procedings, Vol 26, No 15S (May 20 Supplement), 2008:579.

46. Robertson JF et al. Activity of fulvestrant 500 mg versus anastrozole 1 mg as first-line treatment for advanced breast cancer: Results from the FIRST study. J Clin Oncol. 2009 Sep 20;27(27):4530-5. doi: 10.1200/JCO.2008.21.1136. Epub 2009 Aug 24.

47. Di Leo A, Jerusalem G, Petruzelka L, et al. Results of the CONFIRM Phase III trial comparing fulvestrant 250 mg with fulvestrant 500 mg in postmenopausal women with estrogen receptor-positive advanced breast cancer. J Clin Oncol. 2010 Oct 20; 28(30): 4594-600.

48. Di Leo A, Jerusalem G, Petruzelka L, et al. Final analysis of overall survival for the Phase III CONFIRM trial: fulvestrant 500 mg versus 250 mg. General Session Presentation S 1-4, SABCS 2012.

49. Fujiwara Y, Ohno S, Iwata H, et al. Tolerability of fulvestrant high-dose (HD) in postmenopausal Japanese women with hormone receptor-positive (HR+) advanced (ABC) or recurrent breast cancer (RBC). 2007 ASCO Breast Cancer Symposium: Abstract 192.

50. Kuter I, Sapunar F, McCormack P. Pharmacokinetic profile of fulvestrant 500 mg vs 250 mg: Results from the NEWEST study. J Clin Oncol 26: 2008 (May 20 suppl; abstr 579).

51. Wright GL, Blum J, Krekow LK, et al. Randomized Phase II Trial of Fulvestrant with or without Dasatinib in Postmenopausal Patients with Hormone Receptor-Positive Metastatic Breast Cancer Previously Treated with an Aromatase Inhibitor. Cancer Research: December 15, 2011; Volume 71, Issue 24, Supplement 3 doi: 10.1158/0008-5472.SABCS11-PD01-01.

52. Miller TW, Balko JM, EM Fox, Ghazoui Z, et al. Erα-Dependent E2F Transcription can mediate resistance to estrogen deprivation in human breast cancer. Cancer Discovery 2011; 1:338-351.

53. Prescribing information: Everolimus (Afinitor®) http://www.pharma.us.novartis.com/product/pi/pdf/afinitor.pdf

54. Croley J, Black EP, Romond E, et al. A Phase II study of combined fulvestrant and RAD001 (everolimus) in metastatic estrogen receptor (ER) positive breast cancer after Aromatase inhibitor (AI) failure. Cancer Research: Dec 15, 2012; Vol 72, Issue 24, Supplement 3; doi: 10.1158/0008-5472.SABCS12-P2-14-05.

55. Prowell TM, Davidson NE. What is the role of ovarian ablation in the management of primary and metastatic breast cancer today? The Oncologist. Breast Cancer. 2004; 9:507-517.

56. Randomized Phase II Study OF Goserelin (G) Plus Fulvestrant (F) vs. G Plus Anastrozole (A) vs. G Alone for HR+, Tamoxifen Pretreated, Premenopausal Woman (ongoing) http://www.clinicaltrial.gov/ct2/show/NCT01266213?term=fulvestrant&rank=13

57. Bartsch R, Bago-Horvath Z, et al. Ovarian function suppression and fulvestrant as endocrine therapy in premenopausal women with metastatic breast cancer. European Journal of Cancer 48: 1932–1938, 2012.

58. Prescribing information: Goserelin (Zoladex®): http://www1.astrazeneca-us.com/pi/zoladex3_6.pdf

59. 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.

60. Hogan MJ, Kimura SJ, Thygeson P: Signs and symptoms of uveitis: I. Anterior uveitis. Am J Ophthalmol 1959;47:155-70.

61. 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.

62. Dodd E L, Korn L E, Freidlin B, Gray R, Bhattacharya S. An audit strategy for progression-free survival. Biometrics, Vol 67, Issue 3; 1092-99, 2011.

63. Haybittle JL. Repeated assessment of results in clinical trials of cancer treatment. Brit. J. Radiology 1971; 44:793-797.

64. Peto, R., Pike, M. C., Armitage, P., Breslow, N.E., Cox, D.R., Howard, S.V., Mantel, N., McPherson, K., Peto, J., Smith, P.G. Design and Analysis of Randomized Clinical Trials Requiring Prolonged Observation of Each Patient: I. Introduction and Design. Brit. J. Cancer 1976; 34:585–612.

65. Cui L, Hung HMJ, Wang S, et al. Modification of sample size in group-sequential clinical trials. Biometrics 1999; 55: 853-857

Appendix 1. List of Abbreviations

AE	Adverse Event
ALT	Alanine Aminotransferases
AI	Aromatase Inhibitor
ANC	Absolute Neutrophil Count
AREDS	Age-Related Eye Disease Study
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferases
AUC	Area under the concentration curve
BICR	Blinded Independent Central Review
BUN	Blood Urea Nitrogen
CBR	Clinical Benefit Response
CCND1	Cyclin D1
CDK	Cyclin-Dependent Kinase
CI	Confidence Interval
CISH	Chromogenic In Situ Hybridization
Cmax	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
DD	Differential discordance
DICOM	Digital Imaging and Communications in Medicine
DISH	Dual in situ hybridization
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic Acid
DR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
E-DMC	External Data Monitoring Committee
EDR	Early discrepancy rate
EDTA	Ethylenediaminetetraacetic acid
EIU	Exposure In Utero
EORTC-QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC-QLQ-BR23	European Organisation for Research and Treatment of Cancer breast cancer module

EQ-5D	Dimension Health State EuroQoL Score
ER	Estrogen Receptor
FDA	US Food and Drug Administration
FDAAA	US Food and Drug Administration Administration Amendments
FFPE	Formalin Fixed Paraffin Embedded
FISH	Fluorescent In Situ hybridization
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
G-CSF	Granulocyte Colony Stimulating Factor
GM-CSF	Granulocyte Macrophage Colony Stimulating Factor
HDPE	High Density Polyethylene
HER	Human Epidermal Growth Factor Receptor
hERG	Human Ether-à-Go-Go
HR	Hazard Ratio
IB	Investigator's Brochure
IC50	Concentration of 50% Inhibition
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identification
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Randomization Technology
ITT	Intent-to-treat
LDR	Late discrepancy rate
LFT	Liver Function Test
LHRH	Luteinizing Hormone-Releasing Hormone
LPD	Local Product Document
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response or Progesterone Receptor (depending on context)
PR interval (in context of ECG)	The PR interval is measured from the beginning of the P wave to the beginning of the QRS complex.
PRO	Patient Reported Outcome
PSC	Posterior Subcapsular Cataract

PT	Prothrombin Time
RR interval (in the context of ECG)	The PR interval is measured from the peak of one QRS complex to the peak of the next QRS complex.
QD	Quaque Die (once daily)
QOL	Quality of Life
QRS	Name for the combination of three of the graphical deflections seen on a typical electrocardiogram
QT	Time between the start of the Q wave and the end of the T wave in the heart's electrical cycle
QTc	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
Rac	Accumulation Ratio
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
SPC	Summary of Product Characteristic
t½	Terminal Elimination Half-life
Tmax	Time for Cmax
TTD	Time to deterioration
ULN	Upper Limit of Normal
USPI	United States Package Insert
Vz/F	Apparent Volume of Distribution
WBC	White Blood Cells

Appendix 2. Eastern Cooperative Oncology Group (ECOG) Performance Status

Description	Grade
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 3. List of Drugs Known to Predispose to Torsade de Pointes

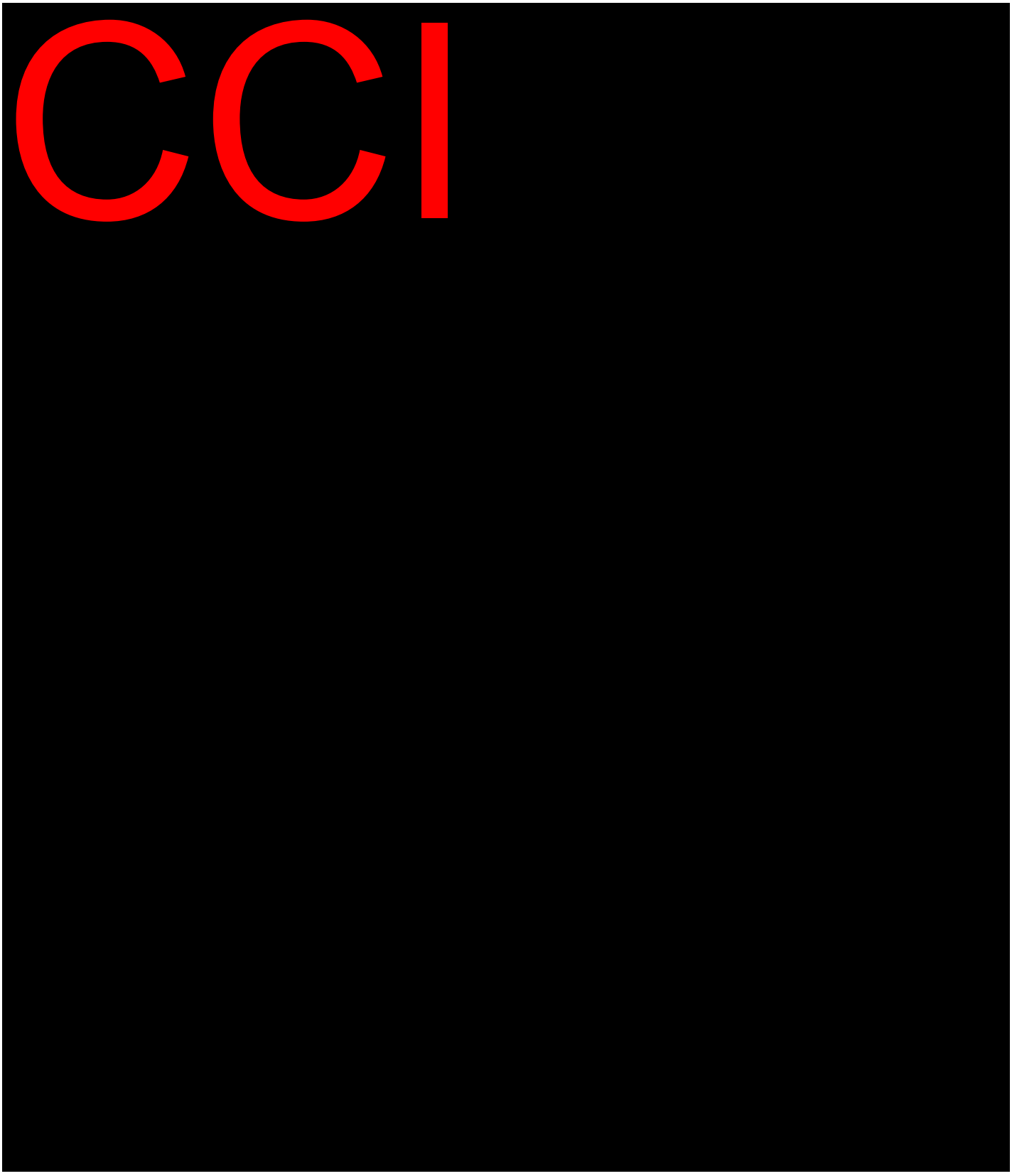
Generic Name	Brand Name(s)
Amiodarone	Cordarone®, Pacerone®
Arsenic trioxide	Trisenox®
Astemizole	Hismanal®
Azithromycin	Zithromax®
Bepridil	Vascor®
Chloroquine	Aralen®
Chlorpromazine	Thorazine®
Cisapride	Propulsid®
Citalopram	Celexa®
Clarithromycin	Biaxin®
Disopyramide	Norpace®
Dofetilide	Tikosyn®
Domperidone	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.azcert.org/medical-pros/drug-lists/bycategory.cfm#. This list is not meant to be considered all inclusive. See website for current list.

Appendix 4. 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*

Upon approval of Amendment 3, RECIST version 1.1 will no longer be mandatory to evaluate tumor assessments.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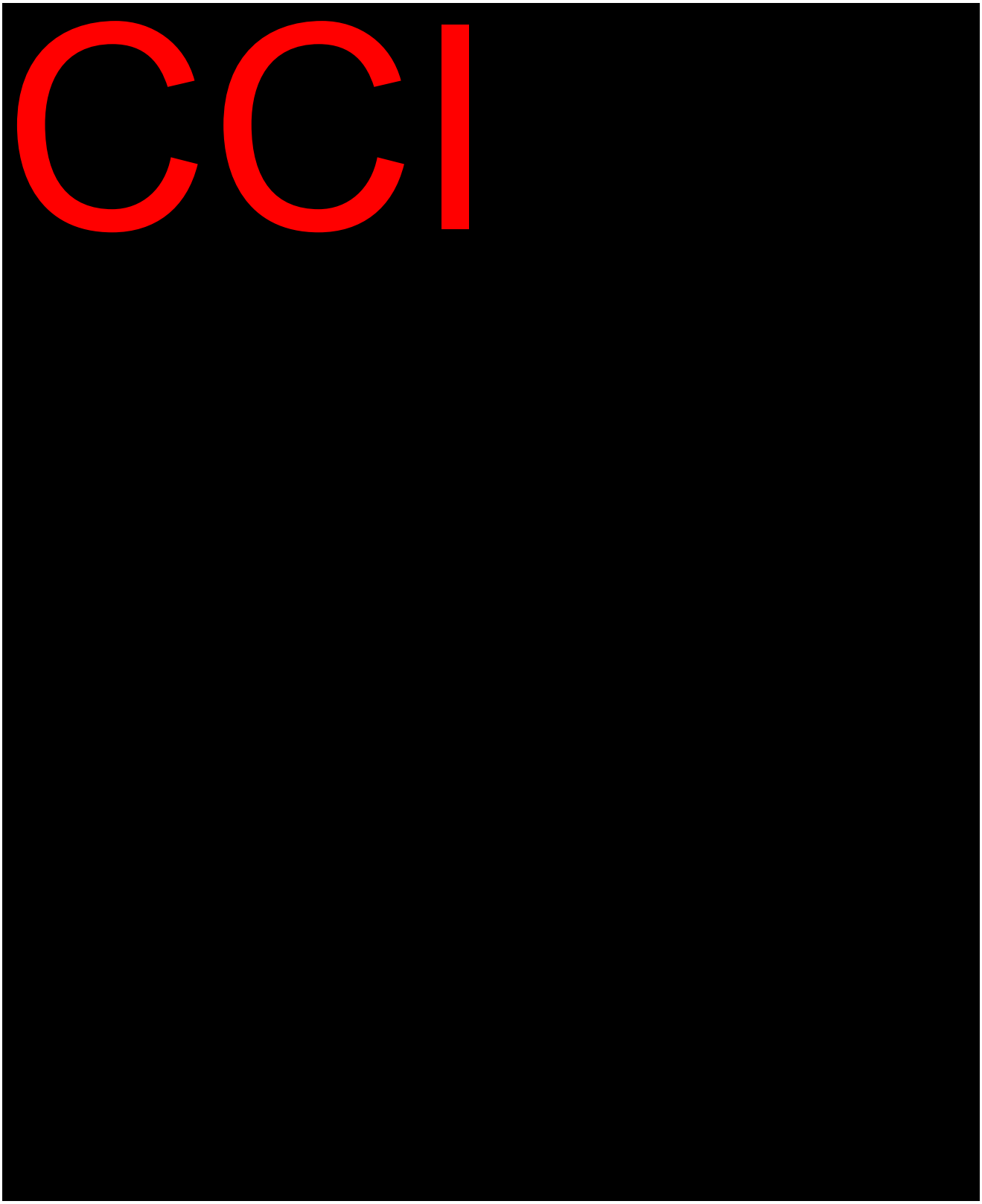
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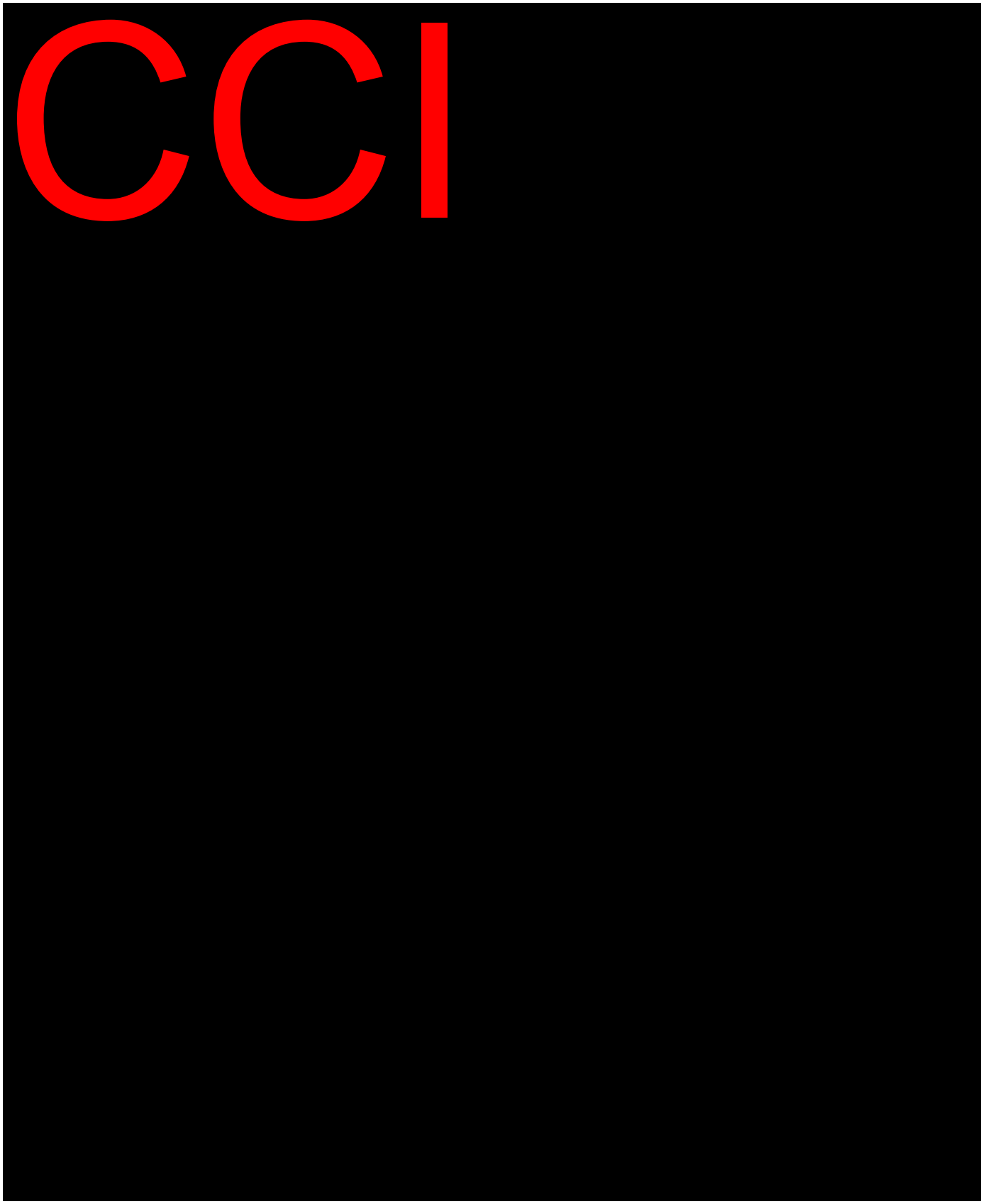
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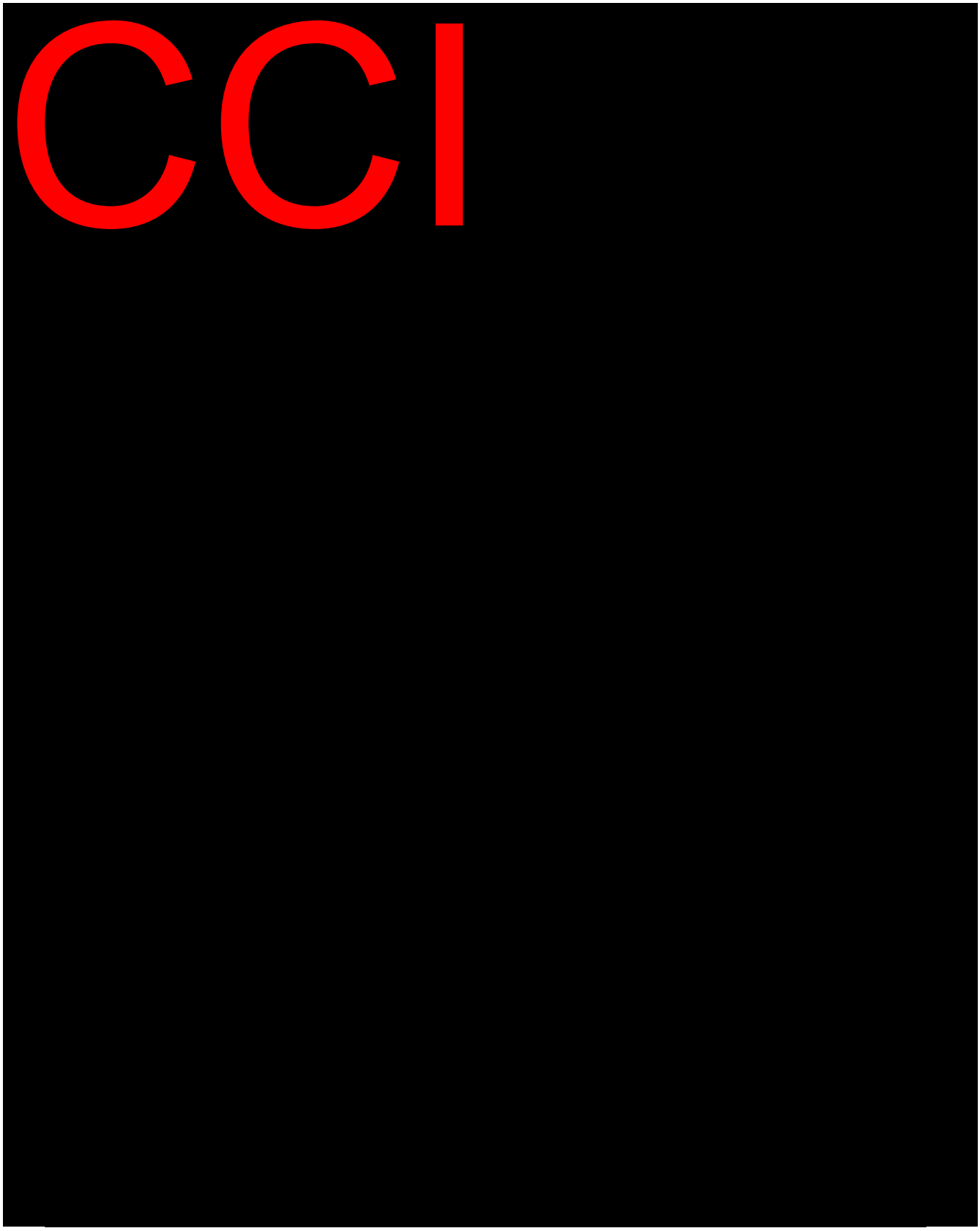
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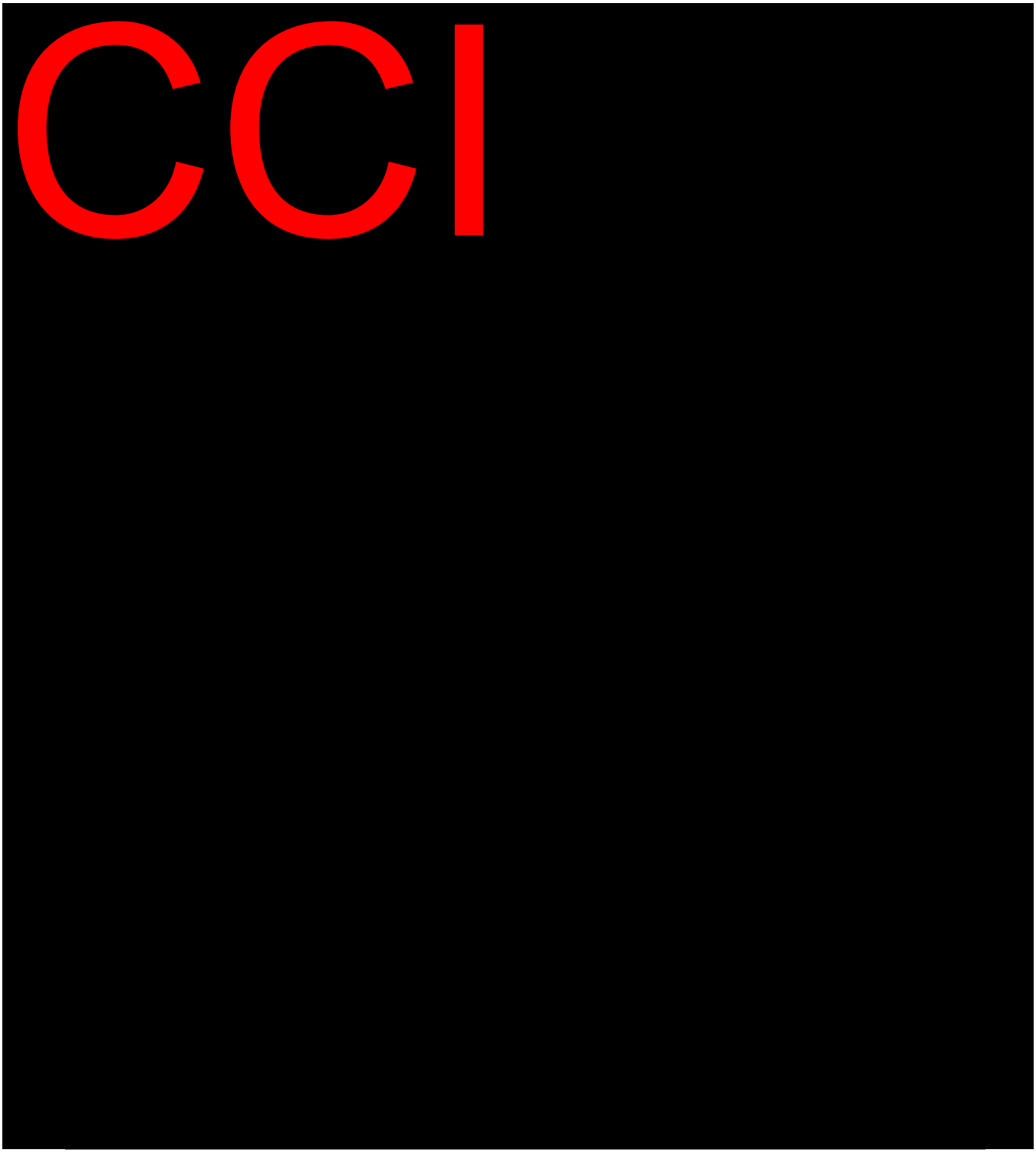
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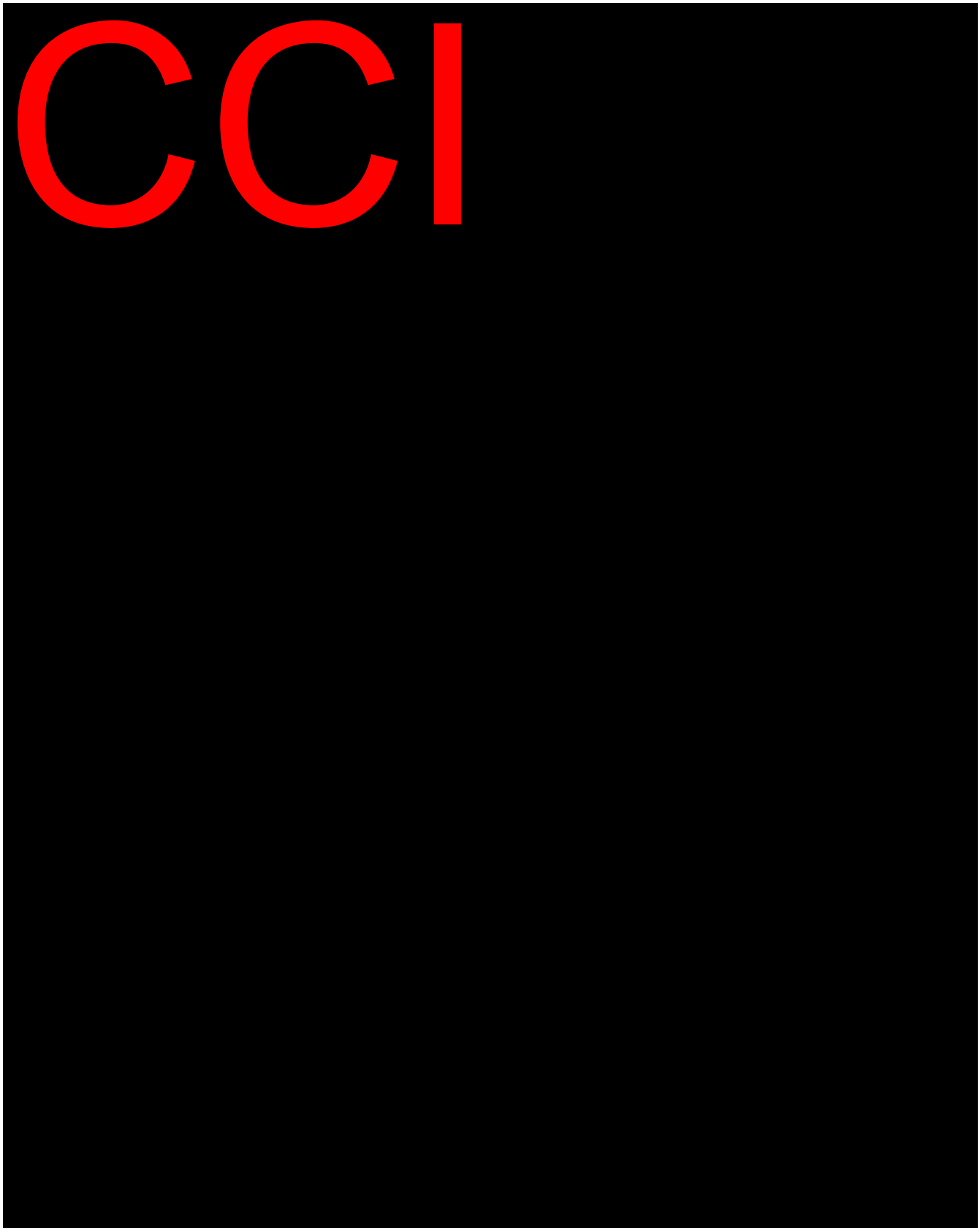
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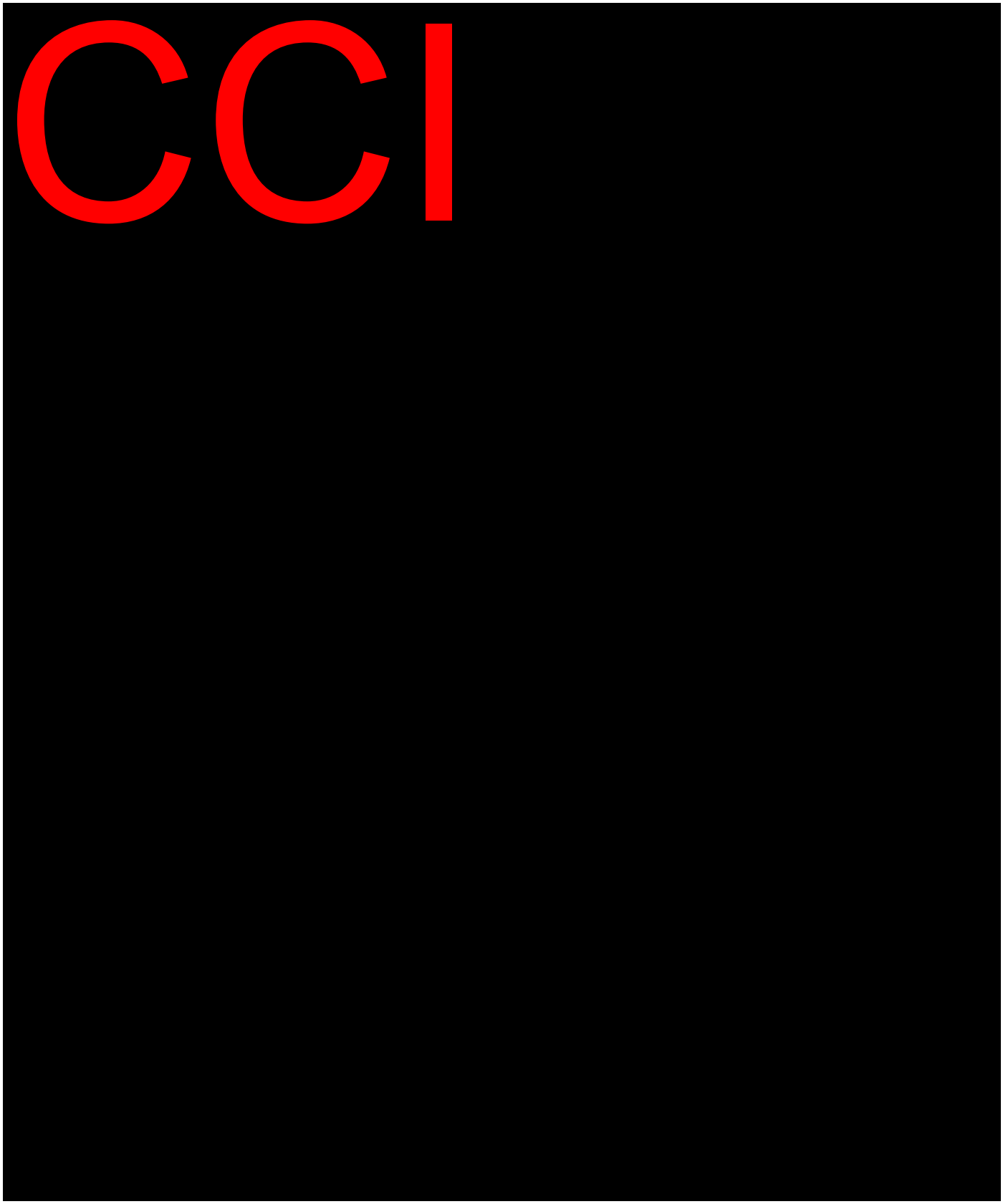
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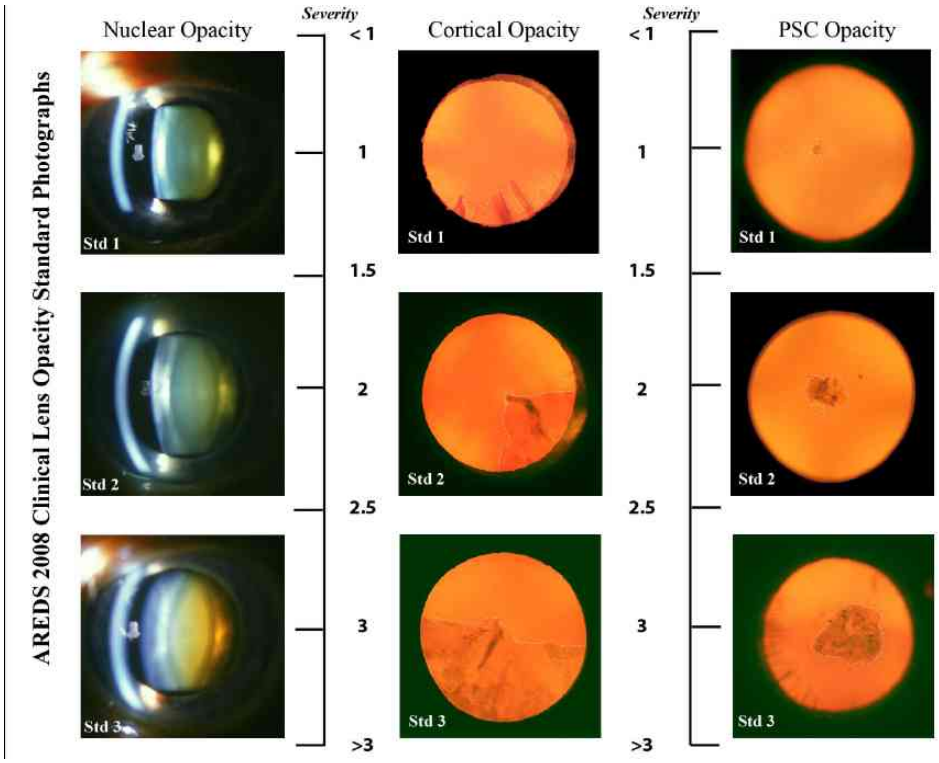
Appendix 8. Wisconsin Age-Related Eye Disease Study (AREDS) 2008 Clinical Lens Opacity Grading Procedure

- 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.


AREDS 2008 Clinical Lens Opacity Standard Photographs
Nuclear Opacity
Severity
< 1
1
1.5
2
2.5
3
>3
Cortical Opacity
Severity
< 1
1
1.5
2
2.5
3
>3
PSC Opacity
Std 1
Std 2
Std 3
Std 1
Std 2
Std 3
Std 1
Std 2
Std 3